

REVIEW

Silymarin in type 2 diabetes–Targeting adipose tissue dysfunction and pancreatic β -cell damage: A review

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Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and progressive pancreatic β -cell dysfunction, processes strongly influenced by adipose tissue inflammation, oxidative stress, and dysregulated lipid metabolism. Silymarin, a flavonolignan complex derived from *Silybum marianum*, has attracted interest as a potential adjunctive agent because of its antioxidant, anti-inflammatory, and metabolic regulatory properties. This review summarizes experimental and clinical evidence on the effects of silymarin and its major bioactive constituent, silibinin, on adipose tissue dysfunction and pancreatic β -cell injury in T2DM. Available evidence was narratively synthesized with emphasis on adipogenesis, lipid accumulation, inflammatory signaling, insulin signaling, oxidative stress, and β -cell survival. Experimental studies indicate that silymarin may reduce adipogenesis and lipid accumulation through modulation of adipogenic transcription factors, including peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT/enhancer-binding protein alpha (C/EBP α), and activation of AMP-activated protein kinase (AMPK). Silymarin may also attenuate pro-inflammatory cytokine production, enhance antioxidant defenses, and protect pancreatic β -cells from glucotoxicity-, lipotoxicity-, and cytokine-induced apoptosis. Limited clinical data suggest potential improvements in glycemic control, insulin resistance, lipid parameters, and systemic inflammation. Overall, silymarin shows promise as an adjunctive strategy for metabolic dysfunction in T2DM; however, standardized formulations and well-designed randomized clinical trials are needed to confirm its efficacy, safety, and clinical relevance.

Keywords: Silymarin, pancreatic β -cells, adipose tissue, insulin resistance, oxidative stress, type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder globally, posing a significant public health challenge. It is characterized by chronic hyperglycemia, resulting from a combination of insulin resistance and progressive pancreatic β -cell dysfunction [1–3]. Its development is influenced by several metabolic and environmental factors, including obesity, sedentary lifestyle, genetic predisposition, and chronic inflammation [4].

Adipose tissue is central to systemic metabolic regulation. Once considered merely an energy storage organ, it is now recognized as an active endocrine organ that secretes numerous bioactive molecules known as adipokines [5]. These molecules, including leptin, adiponectin, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6), influence insulin sensitivity, inflammation, and energy balance [6]. In obesity, adipose tissue becomes dysfunctional, leading to excessive production of inflammatory cytokines and the development of insulin resistance [7].

Oxidative stress is another major contributor to metabolic disorders. Excessive production of reactive oxygen species (ROS) can damage cellular proteins, lipids, and DNA, leading to impaired insulin signaling and β -cell dysfunction [8]. Pancreatic β -cells are particularly susceptible to oxidative damage due to their relatively low antioxidant capacity [9].

Natural compounds derived from medicinal plants have garnered increasing attention as potential therapeutic agents for metabolic diseases. Among these, silymarin, an extract obtained from the seeds of *Silybum marianum*, has been extensively investigated for its antioxidant and anti-inflammatory properties [10–12]. Silymarin comprises several flavonolignans, including silibinin (also known as silybin), isosilibinin, silychristin, and silydianin, with silibinin considered the most biologically active component [13].

Recent studies suggest that silymarin may influence glucose metabolism, lipid homeostasis, and cellular defense mechanisms, thereby offering potential benefits for metabolic disorders such as obesity and T2DM [14–16]. This review focuses

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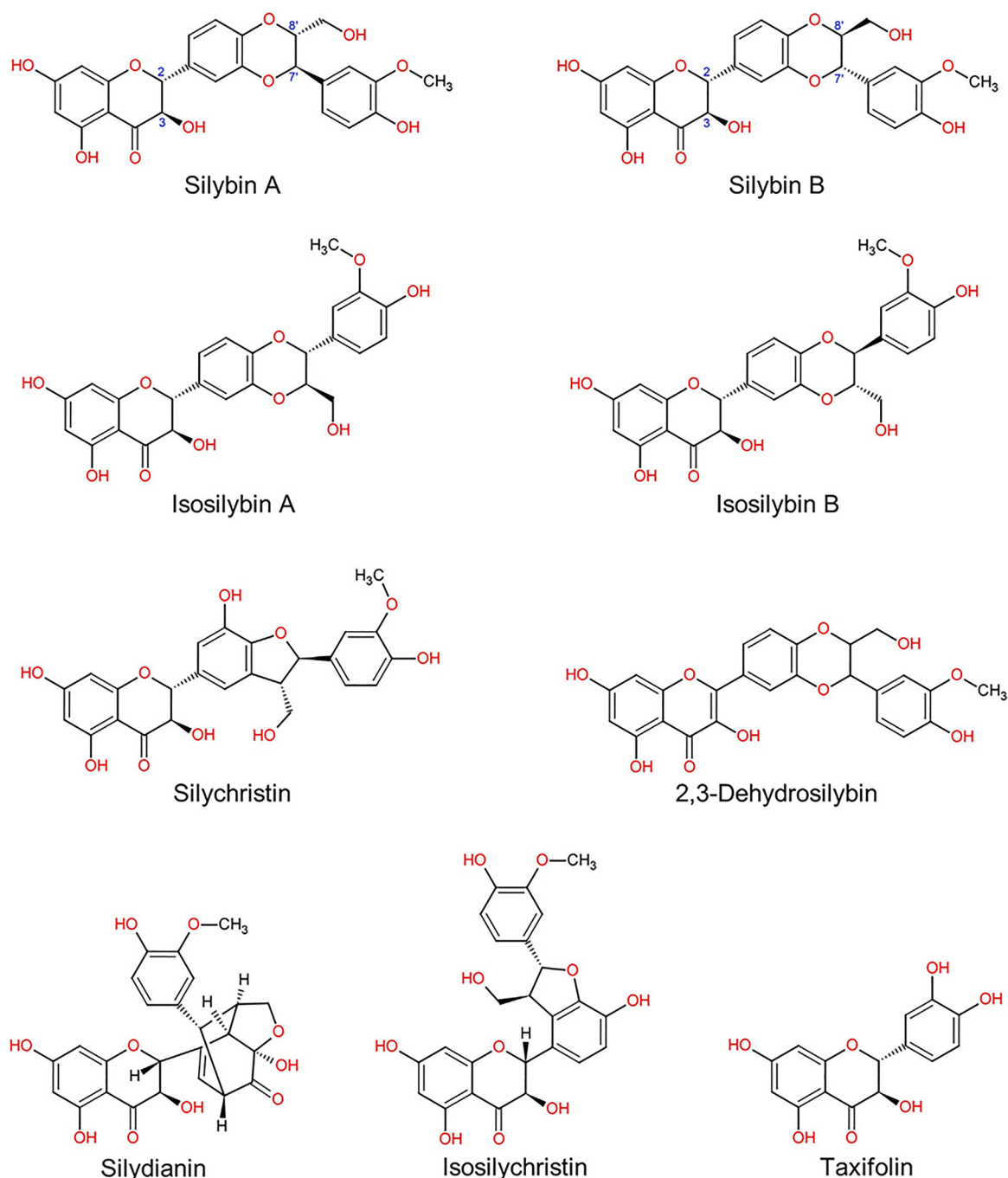


Figure 1. Chemical structures of the principal constituents of silymarin derived from *Silybum marianum* seeds. The figure shows the major flavonolignans present in the silymarin complex, including silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin, and 2,3-dehydrosilybin, as well as taxifolin, a flavonoid component. Silybin A and silybin B together form silybin, also known as silibinin, which represents approximately 40%–60% of the silymarin complex and is considered its main biologically active constituent [20].

on the effects of silymarin on adipose tissue metabolism and pancreatic β -cell protection.

Chemical composition and pharmacological properties of silymarin

Silymarin is a standardized extract derived from the fruits and seeds of *Silybum marianum*, commonly known as

milk thistle [17]. The extract is primarily composed of flavonolignans, including silibinin (also known as silybin), isosilibinin, silychristin, and silydianin. Other compounds, such as taxifolin (a flavonoid), are also present. Among these components, silibinin constitutes approximately 40%–60% of the silymarin complex and is responsible for most of its biological activities [18, 19] (Figure 1).

Milk thistle has a long history of use in traditional medicine for various conditions, including jaundice and kidney stones. Modern research later identified silymarin as the main active extract, which is widely studied and utilized for its potent hepatoprotective effects in liver disorders [20]. Silymarin acts by stabilizing cellular membranes, enhancing protein synthesis, and promoting hepatocyte regeneration [21].

Silymarin exerts its hepatoprotective effects primarily through robust antioxidant and anti-inflammatory actions. These include inhibiting lipid peroxidation, reducing leukotriene and prostaglandin synthesis, and stabilizing inflammatory cells in the liver. It also enhances hepatocyte regeneration by stimulating ribosomal RNA polymerase and protein synthesis, supports detoxification and glutathione preservation, limits fibrosis by inhibiting hepatic stellate cell activation, and exhibits immunomodulatory and anticancer properties [22]. Through these mechanisms, silymarin helps reduce oxidative stress and protect cells from damage [23].

Beyond its established liver-protective effects, silymarin—particularly through its main bioactive compound, silibinin—plays a significant role in regulating metabolism within adipose tissue and pancreatic β -cells. Research indicates that silibinin suppresses adipogenesis and lipid accumulation by influencing key transcription factors involved in fat cell formation, including peroxisome proliferator-activated receptor gamma (PPAR γ) and sterol regulatory element-binding protein 1c (SREBP1c), while also activating metabolic regulators like AMP-activated protein kinase (AMPK). These mechanisms lead to reduced lipid synthesis, improved lipid processing, and diminished inflammation in adipose tissue. Furthermore, silymarin and its active components help safeguard pancreatic β -cells by mitigating oxidative damage, bolstering antioxidant defenses, and maintaining insulin secretion during high-glucose conditions [24–26].

Role of adipose tissue in metabolic regulation

Adipose tissue is an essential regulator of energy homeostasis and metabolic balance. It stores excess energy as triglycerides and releases fatty acids during periods of energy demand [27]. Additionally, adipose tissue secretes a variety of adipokines that regulate appetite, insulin sensitivity, and inflammatory responses [28].

In obesity, adipocytes undergo hypertrophy and become metabolically dysfunctional. This leads to increased infiltration of immune cells, particularly macrophages, which produce inflammatory cytokines such as TNF- α and IL-6 [29]. These inflammatory mediators interfere with insulin signaling pathways and contribute to the development of insulin resistance [30].

Chronic inflammation in adipose tissue is now recognized as a major contributor to metabolic disorders, including T2DM and cardiovascular disease. In obesity, this inflammatory state is largely driven by the infiltration and activation of immune cells—particularly macrophages—which adopt a pro-inflammatory phenotype and release cytokines that impair insulin signaling and promote insulin resistance. Consequently,

adipose tissue inflammation represents an important therapeutic target [31, 32].

Effects of silymarin on adipose tissue

Experimental studies suggest that silymarin can modulate adipocyte differentiation and lipid metabolism. Silibinin has been shown to inhibit adipogenesis by downregulating transcription factors such as PPAR γ and CCAAT/enhancer-binding protein alpha (C/EBP α), which are essential for adipocyte development [33, 34].

Silymarin has also been reported to reduce lipid accumulation in adipocytes by suppressing the expression of key lipogenic enzymes and regulating genes involved in lipid metabolism. Furthermore, silibinin can stimulate fatty-acid oxidation and improve metabolic balance, thereby limiting fat storage and contributing to enhanced adipocyte function [35].

Silymarin exerts potent anti-inflammatory effects by modulating cytokine signaling, reducing the production of pro-inflammatory mediators such as TNF- α , IL-1 β , and IL-6 while enhancing anti-inflammatory cytokines. Through this regulation of inflammatory pathways, silymarin may contribute to improved insulin sensitivity and better metabolic homeostasis [36].

Another important mechanism involves the activation of the AMPK pathway, a key regulator of cellular energy homeostasis. Experimental studies have shown that silibinin and silymarin can activate AMPK signaling, which promotes fatty-acid oxidation and suppresses lipogenesis, thereby contributing to improved metabolic homeostasis and reduced lipid accumulation in metabolic tissues [37]. Additionally, silymarin exhibits several complementary mechanisms that may contribute to the management of metabolic syndrome. These include antidyslipidemic effects mediated by its antioxidant properties and reduced intestinal cholesterol absorption, antihypertensive activity partially attributed to inhibition of the angiotensin II type-1 (AT1) receptor, and antidiabetic and anti-obesity actions characterized by decreased adipogenesis and lipid accumulation, regulation of adipokine secretion (reduced leptin and resistin with increased adiponectin), attenuation of inflammation, promotion of pancreatic β -cell regeneration, and inhibition of hepatic gluconeogenesis. Collectively, these effects contribute to improved metabolic regulation [37, 38] (Figure 2).

Protective effects of silymarin on pancreatic β -cells

Pancreatic β -cells play a central role in maintaining glucose homeostasis through the synthesis and secretion of insulin. In T2DM, persistent insulin resistance places an increased functional demand on β -cells, which over time contributes to their progressive dysfunction and loss [39–41].

Chronic hyperglycemia and elevated circulating lipids promote glucotoxicity and lipotoxicity, leading to excessive production of ROS and the activation of inflammatory pathways. Because pancreatic β -cells naturally express relatively low levels of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, they are particularly

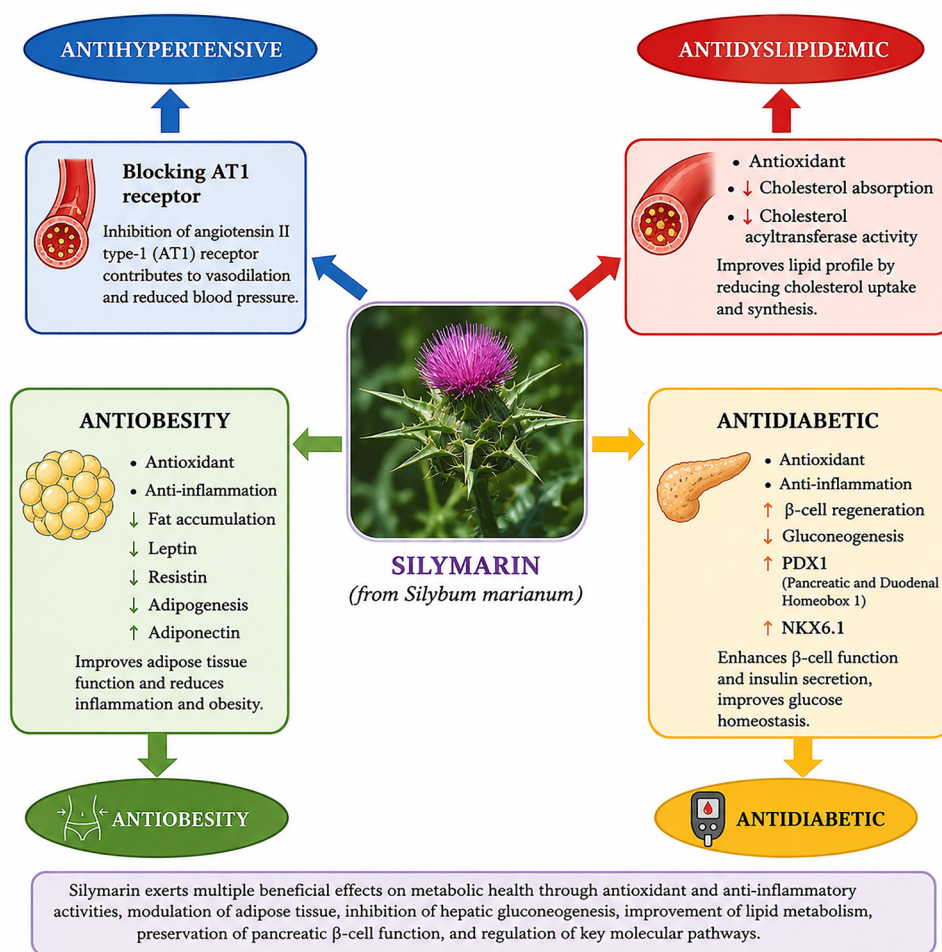


Figure 2. Proposed mechanisms underlying the beneficial metabolic effects of silymarin in metabolic disorders. The schematic summarizes the pleiotropic actions of silymarin, derived from *Silybum marianum*, on key components of metabolic dysfunction. Silymarin may exert antihypertensive effects by inhibiting the angiotensin II type 1 receptor, thereby promoting vasodilation and lowering blood pressure. Its antidyslipidemic activity is associated with antioxidant effects, reduced intestinal cholesterol absorption, and decreased cholesterol acyltransferase activity, contributing to an improved lipid profile. In adipose tissue, silymarin may exert anti-obesity effects by reducing oxidative stress, inflammation, fat accumulation, and adipogenesis, while decreasing leptin and resistin levels and increasing adiponectin, thereby improving adipose tissue function. In addition, silymarin may exert antidiabetic effects by attenuating oxidative stress and inflammation, inhibiting hepatic gluconeogenesis, promoting pancreatic β-cell regeneration, and upregulating pancreatic and duodenal homeobox 1 and NK6 homeobox 1, which support β-cell function and insulin secretion. Overall, these mechanisms suggest that silymarin may improve metabolic homeostasis through coordinated effects on lipid metabolism, adipose tissue dysfunction, and pancreatic β-cell preservation. The figure was created by the authors based on evidence synthesized from the literature [37, 38, 46, 50]. **Abbreviations:** AT1, angiotensin II type 1; NKX6.1, NK6 homeobox 1; PDX1, pancreatic and duodenal homeobox 1.

vulnerable to oxidative stress-induced damage. This oxidative and inflammatory environment ultimately impairs insulin secretion and promotes β-cell apoptosis, contributing to the progressive deterioration of glycemic control characteristic of T2DM [42].

Silymarin has demonstrated protective effects on β-cells, mitigating oxidative stress and inflammatory damage. Its antioxidant properties reduce ROS production, thereby preventing oxidative injury to cellular components [43, 44]. Furthermore, silymarin modulates inflammatory pathways implicated in β-cell destruction. By inhibiting nuclear factor kappa B (NF-κB) activation and reducing cytokine production, it helps preserve β-cell viability and insulin secretory function [45–47].

Additionally, silymarin and its primary constituent, silibinin, exhibit anti-apoptotic and cytoprotective properties, safeguarding β-cells from glucotoxicity- and cytokine-induced damage while supporting their survival and function [48, 49]. Silymarin promotes pancreatic recovery and metabolic homeostasis in diabetic models by upregulating key β-cell transcription factors, such as pancreatic and duodenal homeobox 1 (Pdx1) and NK6 homeobox 1 (Nkx6.1). This upregulation enhances insulin expression, stimulates β-cell neogenesis, and restores normoglycemia. Silymarin also improves glucose metabolism and insulin sensitivity by reducing oxidative stress and modulating inflammatory pathways, ultimately contributing to the normalization of serum insulin, glucose, and glycated hemoglobin A1c (HbA1c) levels [50] (Figure 3).

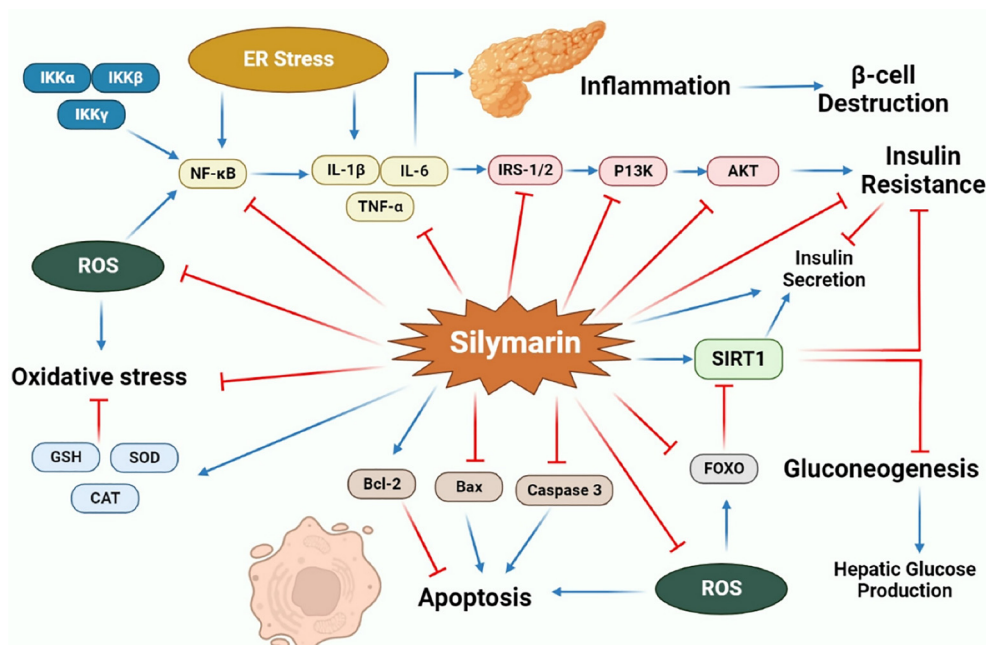


Figure 3. Proposed molecular mechanisms underlying the antidiabetic actions of silymarin. The schematic illustrates how silymarin may modulate interconnected oxidative, inflammatory, apoptotic, and insulin-signaling pathways relevant to pancreatic β -cell injury and insulin resistance. Silymarin appears to attenuate reactive oxygen species generation and oxidative stress while enhancing endogenous antioxidant defenses, including glutathione, superoxide dismutase, and catalase. It may also suppress inflammatory signaling by inhibiting I κ B kinase/NF- κ B activation and reducing the production of pro-inflammatory mediators, including tumor necrosis factor- α , interleukin-1 β , and interleukin-6, thereby limiting endoplasmic reticulum stress, inflammation, and β -cell destruction. In parallel, silymarin may improve insulin signaling through modulation of the insulin receptor substrate 1/2-phosphoinositide 3-kinase–Akt pathway, support insulin secretion, and reduce insulin resistance. The figure also indicates anti-apoptotic effects, characterized by increased Bcl-2 signaling and suppression of Bax- and caspase 3-associated apoptosis. In addition, regulation of the sirtuin 1/forkhead box O axis may contribute to reduced gluconeogenesis and lower hepatic glucose production. Overall, these mechanisms support a potential role for silymarin in preserving pancreatic β -cell function and improving metabolic homeostasis. Blue arrows indicate activation or stimulation, whereas red blunt-ended lines indicate inhibition or suppression [46]. **Abbreviations:** Akt, protein kinase B; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CAT, catalase; ER, endoplasmic reticulum; FOXO, forkhead box O; GSH, glutathione; IKK, I κ B kinase; IL, interleukin; IRS-1/2, insulin receptor substrate 1/2; NF- κ B, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF- α , tumor necrosis factor- α .

Brief results of clinical and experimental studies and therapeutic perspectives

Clinical studies

Clinical evidence supporting the metabolic benefits of silymarin is limited but encouraging. In a randomized, double-blind, placebo-controlled trial, **Huseini et al.** administered silymarin (200 mg three times daily) to patients with T2DM for four months. This intervention resulted in significant reductions in fasting blood glucose, HbA1c, total cholesterol, and LDL cholesterol compared with placebo [49]. More recently, **MacDonald-Ramos et al.** reported that silymarin supplementation improved insulin resistance and reduced systemic inflammatory markers in women with obesity without diabetes [16]. Although these findings suggest potential metabolic benefits, the available clinical studies are few, involve limited sample sizes, and feature short intervention periods.

Experimental studies

Experimental studies provide stronger mechanistic evidence for silymarin's therapeutic potential. In animal models of obesity and high-fat diet feeding, silymarin reduced adipose tissue inflammation, decreased adipocyte hypertrophy,

improved lipid metabolism, and preserved pancreatic β -cell mass [14, 24, 25]. Cellular studies further demonstrated that silibinin inhibits adipogenesis through the downregulation of PPAR γ and C/EBP α while activating AMPK signaling, thereby reducing lipid accumulation and improving metabolic homeostasis [33–35]. In pancreatic β -cells, silymarin attenuated oxidative stress, inhibited NF- κ B-mediated inflammation, reduced apoptosis, and preserved insulin secretory function under glucotoxic and inflammatory conditions [47, 48] (Table 1).

Therapeutic perspectives

Despite these promising findings, several challenges remain before silymarin can be routinely incorporated into clinical practice. A principal limitation is its poor oral bioavailability, which has stimulated the development of novel delivery systems such as liposomal, phospholipid-complex, and nanoparticle formulations to improve systemic absorption and therapeutic efficacy [47]. Future multicenter randomized clinical trials with standardized formulations, optimized dosing regimens, and longer follow-up periods are warranted to establish the long-term efficacy and safety of silymarin in obesity and T2DM.

Table 1. Summary of clinical and preclinical studies on silymarin's effects in metabolic disorders

Reference	Study model / population	Silymarin intervention	Duration	Main outcomes	Limitations
Feng et al. [14]	High-fat diet-induced obese mice	Silymarin	Experimental study	Improved lipid metabolism, enhanced mitochondrial biogenesis, and reduced inflammation	Animal study; findings require clinical validation
MacDonald-Ramos et al. [16]	Women with obesity (non-diabetic)	Oral silymarin supplementation	Several weeks	↓ Insulin resistance; ↓ inflammatory markers	Limited to non-diabetic women; relatively short intervention
Wang et al. [25]	Obese mice	Silibinin	Experimental study	Improved adipose tissue protein expression and adipocyte metabolism	Preclinical animal study
Barbagallo et al. [33]	Human adipocytes	Silibinin	Cell culture	↓ Lipid accumulation; modulation of adipocyte differentiation	<i>In vitro</i> study
Ka et al. [34]	3T3-L1 preadipocytes	Silibinin	Cell culture	Inhibited adipogenesis through activation of the Insig pathway	<i>In vitro</i> study
Matsuda et al. [47]	Pancreatic β -cells	Silymarin	Cell culture	Reduced cytokine-induced toxicity and apoptosis; preserved β -cell viability	<i>In vitro</i> study
Chen et al. [48]	Pancreatic β -cell model	Silibinin	Cell culture	Protected β -cells against glucotoxicity through regulation of the Insig-1/SREBP-1c pathway	<i>In vitro</i> study
Huseini et al. [49]	Patients with type 2 diabetes ($n = 25$ silymarin; $n = 26$ placebo)	Silymarin 200 mg orally, three times daily	4 months	↓ FBG; ↓ HbA1c; ↓ total cholesterol; ↓ LDL-C; ↓ triglycerides; ↓ AST (SGOT); ↓ ALT (SGPT); improved glycemic control	Small sample size; single-center study; relatively short follow-up

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol.

In addition to its well-documented antioxidant and anti-inflammatory activities, accumulating evidence suggests that silymarin may regulate the expression of genes involved in metabolic homeostasis through the modulation of transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2), NF- κ B, forkhead box O1 (FOXO1), PPAR γ , and sirtuin 1 (SIRT1). Through these regulatory networks, silymarin may influence oxidative stress, inflammatory responses, glucose metabolism, lipid homeostasis, and pancreatic β -cell survival. However, the precise transcriptional and epigenetic mechanisms underlying these effects remain incompletely understood. Future studies integrating transcriptomic, proteomic, metabolomic, and epigenetic approaches are needed to further elucidate these molecular mechanisms and clarify the specific contributions of individual silymarin constituents.

Beyond its potential role in metabolic disorders, silymarin has demonstrated a broad spectrum of biological activities across diverse pathological conditions, particularly in oncology. Accumulating evidence indicates that silymarin exerts antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, antiangiogenic, and antimetastatic effects through the modulation of multiple molecular signaling pathways, including NF- κ B, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription 3 (STAT3). These pleiotropic mechanisms have been investigated in several malignancies, including cervical, breast, prostate, colorectal, and hepatocellular cancers, highlighting silymarin's

capacity to regulate oxidative stress, inflammatory signaling, cell-cycle progression, apoptosis, and cellular homeostasis. Furthermore, combination strategies involving silymarin and other bioactive phytochemicals, such as berberine, chlorogenic acid, genistein, malvidin, morin, and p-coumaric acid, have demonstrated synergistic effects on energy metabolism, fatty acid β -oxidation, lipogenesis, autophagy, and gut-liver axis signaling in experimental models. Although these findings extend beyond the primary scope of the present review, they further underscore the pleiotropic pharmacological actions of silymarin and support future investigations exploring its therapeutic potential in multimodal strategies for metabolic diseases and related chronic disorders [38, 51].

Ethical statement

This review article does not involve original research with human subjects or animal experimentation. All studies cited herein were conducted in accordance with relevant ethical guidelines as reported in the original publications.

Limitations and future directions

Despite accumulating evidence suggesting silymarin's multifaceted biological effects pertinent to obesity, insulin resistance, and T2DM, several limitations warrant acknowledgment. The majority of current evidence stems from *in vitro* studies and animal models. While these provide valuable mechanistic insights, they cannot fully replicate the intricate complexity of human metabolic disorders. Furthermore, existing clinical

evidence is limited and heterogeneous, exhibiting variations in study design, sample size, treatment duration, patient populations, and the specific formulations and dosages of silymarin employed.

A significant limitation arises from the difficulty in comparing studies that evaluate whole silymarin extracts with those investigating individual constituents, particularly silibinin, given their potentially differing pharmacological properties. Additionally, silymarin's relatively low oral bioavailability presents a challenge, although several novel delivery systems have demonstrated improved pharmacokinetic characteristics in experimental studies.

Future research should prioritize large-scale, rigorously designed randomized controlled trials utilizing standardized silymarin formulations, clearly defined dosing regimens, and extended follow-up periods to conclusively establish efficacy and safety. Further mechanistic investigations are imperative to elucidate the specific contributions of individual silymarin constituents and to delineate the molecular pathways underlying their effects on adipose tissue dysfunction, insulin signaling, and pancreatic β -cell preservation. Such studies are essential for determining the clinical relevance of promising findings observed in experimental models.

Conclusion

Silymarin, a flavonolignan complex extracted from *Silybum marianum* seeds, exhibits diverse biological activities relevant to the pathophysiology of insulin resistance and T2DM. Available experimental and emerging clinical evidence indicates that this natural extract possesses antioxidant, anti-inflammatory, and metabolic regulatory properties, which may influence various pathways involved in glucose homeostasis and metabolic dysfunction.

At the cellular level, preclinical studies demonstrate silymarin's contribution to redox balance maintenance by reducing ROS production and enhancing endogenous antioxidant defenses. These effects are particularly pertinent to pancreatic β -cells, which are highly susceptible to oxidative damage. Experimental evidence further suggests that silymarin can attenuate oxidative stress and modulate apoptotic signaling pathways, thereby contributing to the preservation of β -cell viability and insulin secretory capacity.

Furthermore, experimental studies indicate that silibinin, silymarin's primary bioactive constituent, may modulate inflammatory signaling and enhance insulin receptor signaling via the insulin receptor substrate 1 (IRS-1)/PI3K/Akt pathway. Through these mechanisms, silymarin has demonstrated improved insulin sensitivity and glucose metabolism in pre-clinical models. However, confirmation of these mechanisms in human subjects remains limited.

Evidence also suggests that silymarin may influence adipose tissue function by reducing inflammation and oxidative stress, potentially mitigating the chronic low-grade inflammatory state associated with obesity-related insulin resistance. Nevertheless, these findings are predominantly derived from experimental models and necessitate further clinical validation.

Overall, the available evidence supports the concept that silymarin exerts pleiotropic biological effects through antioxidant activity, modulation of inflammatory responses, improvement of insulin signaling, and protection of pancreatic β -cell function. While these findings highlight its potential as an adjunctive strategy for metabolic disorders associated with insulin resistance, current clinical evidence remains limited and heterogeneous. Consequently, silymarin's therapeutic role should be considered promising but remains investigational. Future well-designed randomized controlled trials employing standardized formulations, optimized dosing regimens, and long-term follow-up are essential to confirm its efficacy, establish its safety profile, and define its definitive role in the management of obesity-associated insulin resistance and T2DM.

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