Reprint from The Review of DIABETIC STUDIES Vol 21 No 1 2025

The Review of DIABETIC STUDIES

RESEARCH

Modulation of Glycemic, Lipid, and Hepatorenal Biomarkers by Silymarin Supplementation in Type 2 Diabetes Mellitus

Ali M. Muhammed Ali[1]*, Ehsan HT. Al Dabbagh[1], Omar M. Yahya[1]

[1]*Department of Biochemistry, College of Medicine, University of Mosul, Mosul, Iraq.Address correspondence to: Ali M. Muhammed Ali, Email: ali.23hmp29@student.uomosul.edu.iq*

Manuscript Submitted September 30, 2024; Resubmitted December 24, 2024; Accepted January 06, 2025

■ Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a worldwide metabolic disorder. Diabetes is often linked with microvascular complications as well as macrovascular complications. Silymarin (SLM) is a phytochemical extracted from the plant Silybum marianum. It has been employed for treating various liver-related ailments for over two millennia. Owing to its antioxidant and anti-inflammatory characteristics, it is proposed as a promising option for the management of diabetes and its consequences objective: Assess the effectiveness of SLM as an adjunct remedy to conventional oral hypoglycemic drugs on glycemic indices, lipid profile, serum urea and creatinine levels, and hepatic enzymes (ALT, AST, and ALP) in comparison to conventional therapy solely in individuals with type 2 DM. **Methods:** The study included 70 patients who were allocated to one of two groups: the Silymarin group, which received 140 mg silymarin capsules twice daily along with their standard oral anti-diabetic medications for 60 days, and the Control group, which received only their standard medication. All patients received comprehensive history and clinical evaluation at baseline. Blood samples were collected following a 12-hour fasting. to assess the subsequent variables at a starting point and after treatment completion for determining treatment outcomes: Fasting Blood Glucose (FBG), Glycated Hemoglobin (HbA1c), Total Cholesterol (TC), Triglycerides (TG), HDL-C, LDL-C, VLDL-C, Serum Urea, Serum Creatinine, and Liver Enzymes, specifically ALT, AST and ALP. **Results:** The Silymarin group revealed significant differences in FBG, HbA1c, TC, TG, VLDL-C, S.urea, S.Cr, and hepatic enzymes in comparison to the control group following two months (p value < 0.05). HDL and LDL cholesterol values changed similarly in both groups. **Conclusion:** Supplementation with 140 mg of silymarin twice daily with conventional hypoglycemic medications for 60 days showed superiority over conventional treatment alone.

Keywords: Silymarin, Diabetes Mellitus, Liver Enzymes, Lipid Profile, Glycemic Status.

1. Introduction

Diabetes mellitus (DM) is a complex and chronic metabolic illness that affects a substantial worldwide population [1]. The disorder is defined by elevated glucose levels in the blood, known as hyperglycemia. This arises from inadequate insulin production by the body and/or insufficient use of the insulin produced [2]. It was predicted that around 10% of the global population, or around 573 million individuals, were affected by diabetes. If current trends persist, the anticipated number of individuals impacted by diabetes is forecast to reach 700 million by 2045. This number underscores the considerable worldwide health burden posed by diabetes, which has extensive repercussions for healthcare systems, the economy, and the general quality of life [3]. Diabetes mellitus is primarily classified into two categories: Type 1 and Type 2. Every classification possesses distinct pathophysiology underpinnings, risk determinants, and clinical presentations [4]. Type 2 Diabetes Mellitus (T2DM) is a widespread metabolic condition primarily caused by two main factors: diminished insulin secretion by pancreatic beta cells and a decreased sensitivity of insulin-responsive tissues to insulin [5].

The liver, skeletal muscle, adipose tissue, GIT, brain, and kidney are all involved in the pathogenesis of diabetes mellitus. Decreased insulin sensitivity in hepatic, muscular, and adipose tissues, coupled with a gradual deterioration in pancreatic beta-cell function resulting in compromised insulin secretion, ultimately leads to hyperglycemia, the defining characteristic of Type 2 DM [6]. Diabetes is a condition frequently linked with both microvascular and macrovascular complications, such as retinopathy, nephropathy, and neuropathy (microvascular), as well as ischemic heart disease, peripheral vascular disease, and cerebrovascular

 DOI 10.1900/RDS.2025.21.01

disease (macrovascular), leading to organ and tissue damage [7].

Given that inflammation and oxidative stress are implicated in insulin resistance, lipid peroxidation, and cardiovascular illnesses, mitigating inflammatory biomarkers, oxidative stress indicators, and hyperlipidemia may enhance diabetes management [8]. The prevailing norm of care for people suffering from diabetes mellitus encompasses non-pharmacological interventions (low-calorie diet and exercise) and pharmacological therapies (antidiabetic medications) [9].

Silymarin (SLM) is a phytochemical derived from the plant Silybum marianum, commonly recognized as milk thistle. It has been utilized for managing numerous liver-related disorders for over two thousand years [10]. Recent years have witnessed an increase in literature addressing the application of SLM for the management of diverse medical conditions. The radical scavenging and anti-inflammatory capabilities of SLM [11], coupled with its capacity to modulate cellular signalling pathways, are key aspects contributing to SLM's therapeutic potential and its extensive application in treating neurological and metabolic disorders [12]. The research suggests that SLM can work as a beneficial treatment for chronic metabolic liver disease and other chronic metabolic illnesses, including obesity and T2DM [13]. This study aimed to assess the usefulness of silymarin as a complement remedy to conventional oral antidiabetic medications on glycemic management, lipid profile, renal function biomarkers, and hepatic enzymes, in comparison to conventional oral antidiabetic medications alone in patients with T2DM.

2. Materials and Methods

2.1. Study Settings

Following the acquisition of ethical permission from the Ethics Committees of the College of Medicine, University of Mosul and of the Nineveh Health Directorate in Mosul, Iraq. A randomized clinical trial was performed in Mosul City from August 2024 to November 2024. A total of 70 participants in this study were patients with type 2 DM and were diagnosed according to the criteria of ADA (American Diabetes Association), from all sectors of Mosul city, including visitors to health institutes and private clinics. Participants were interviewed regarding the study's purpose and instructed to comply with the medication therapy. Participants were managed by The Declaration of Helsinki (1975) asserts that the principal objective of medical research involving volunteers is to comprehend the etiology, progression, and consequences of diseases, as well as to devise preventive, diagnostic, and therapeutic measures.

2.2. Patients

The inclusion criteria included: Adults aged 31 to 75 years, having been diagnosed with T2DM for a minimum of 6 months, and still on oral hypoglycemic medications only. The exclusion criteria included type 2 DM who are receiving any kind of insulin as anti-diabetic medication, chronic hepatic illness, ischemic heart disease, renal insufficiency (SCr > 2 mg/dl), severe heart dysfunction (NYHA class III or higher), psychological disorders, allergy to any kind of herbal products, steroid usage, and severe infections. Individuals consuming multivitamins and multi-mineral supplements were likewise eliminated. Pregnant and breastfeeding females were explicitly excluded. Patients who experienced alterations in their medications at the time of the study interval are also excluded. Patients and control are using the same ordinary food and moderate lifestyle of exercise and activity.

2.3. Methods

The study comprised 70 patients who were randomly allocated to one of two groups: the Silymarin group, consisting of 35 patients administered 140 mg SLM capsule (Legalon® MEDA Pharma GmbH, Homburg–Germany) twice a day alongside their conventional oral anti-diabetic medications for 60 days, and the Control group, which included 35 patients receiving only their standard oral antidiabetic medication for the same duration.

In the beginning, all participants had comprehensive history taking and clinical evaluation. Blood specimens were obtained following a 12-hour fasting period to assess the subsequent parameters at baseline and after treatment, utilized for evaluating treatment outcomes: fasting blood glucose (FBG), glycated haemoglobin (HbA1c), total cholesterol (TC), Triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), serum urea, serum creatinine, and liver enzymes, specifically alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

A dry chemistry analyzer (Dri-Chem NX500: Fujifilm, Japan) was employed to quantify FBG, TC, TG, HDL, S. urea, S. creatinine, ALT, AST, and ALP.

LDL and VLDL were calculated using the subsequent formulas [14]:

LDL = Total cholesterol – HDL - (TGs/5).

VLDL=TGs/5.

Glycated haemoglobin (HbA1C) was quantified with a fully automated analyzer. Cobas® 6000 c501, Roche Molecular Systems, Inc.: USA, utilizing the TINIA colorimetric approach.

Data processing and evaluation were performed utilizing SPSS version 21. A p-value less than 0.05 is considered significant.

3. Results

3.1. Demographic Parameters

A total of 70 participants, comprising 42 males and 28 females, were enrolled and allocated into

two groups as follows: the Control group included 20 male and 15 female patients, while the Silymarin group involved 22 male and 13 female. The ages of the participants ranged from 31 to 75 years. We observed no significant differences concerning age, gender, and family history between the two groups (p-value>0.05) (Table 1). After statistical analysis (Fisher's exact test) was performed on the medication regimens of both groups, it was determined that there was no significant difference between them.

Table 1: Initial Variables and Demographic Variables.

Variables		Control Group (N=35)	Study Group (N=35)	*p*-value
Gender	Male	20	22	0.625 [a]
	Female	15	13	
Family History of T2DM	Positive	24	21	0.454 [a]
	Negative	11	14	
Age		Mean Rank = (38.20) Range (32 – 72) years	Mean Rank = (32.80) Range (31 – 75) years	0.266 [b]

n = number of subjects.
Statistical test: a: Chi-square test.
b: Mann-Whitney test.
Statistical significance was established at p ≤ 0.05.
Control group: obtaining conventional oral anti-diabetic medications only.
Study group: obtaining conventional oral anti-diabetic medications plus SLM capsule.

3.2. Laboratory Parameters

Regarding Glycemic Control: A notable difference in fasting blood sugar (FBS) was observed in the silymarin group after two months of including silymarin in the conventional oral antidiabetic medications (p-value < 0.05), but no significant change occurred in the control group. A significant difference in HbA1c was seen between the two groups (p-value < 0.05), with a large effect of oral antidiabetic medications (OAM) in the silymarin group, contrasted with a moderate effect in the control group (Table 2).

Table 2: Comparing the Glycemic Indices at the Starting Point and Following Two Months between the Research Groups.

Parameter	Group	Timing	Mean Rank	*P*-value	E.S	E.S
FBS	Control	Before	14.08	0.583	0.093	Small
		After	23.23			
	Study	Before	18.44	0.0001*	0.864	Large
		After	3			
HbA1c	Control	Before	19.34	0.028*	0.37	Medium
		After	14.13			
	Study	Before	19	0.0001*	0.866	Large
		After	1.5			

Statistical Test: Wilcoxon Signed Rank test.
*: A significant difference was established at p ≤ 0.05.
E.S : < 0.3 = Small, 0.3 < 0.5 = Medium, ≥ 0.50 = Large
Control group: obtaining conventional anti-diabetic medications.
Study group: obtaining conventional anti-diabetic medications and silymarin.

Table 3: Comparing the Lipid Profile at the Starting Point and Following Two Months between the Research Groups.

Parameter	Group	Timing	Mean Rank	*P*-value	E.S	E.S
Total Cholesterol	Control	Before	14.00	0.014*	0.414	Medium
		After	19.17			
	Study	Before	20.17	0.001*	0.580	Large
		After	11.72			
Triglyceride	Control	Before	20.38	0.606	0.087	Small
		After	15.75			
	Study	Before	20.54	0.000*	0.720	Large
		After	7.86			
HDL	Control	Before	16.89	0.674	0.071	Small
		After	17.13			
	Study	Before	17.82	0.281	0.182	Small
		After	18.12			
LDL	Control	Before	13.29	0.011*	0.431	Medium
		After	20.46			
	Study	Before	18.24	0.037*	0.353	Medium
		After	15.95			

Parameter	Group	Timing	Mean Rank	*P*-value	E.S	E.S
VLDL	Control	Before	20.56	0.571	0.096	Small
		After	15.58			
	Study	Before	19.46	0.000*	0.716	Large
		After	8.33			

Statistical Test: Wilcoxon Signed Rank test.
*: A significant difference was established at p ≤ 0.05.
E.S : < 0.30 = Small / 0.30 < 0.50 = Medium / ≥ 0.50 = Large
Control group: obtaining conventional anti-diabetic medications.
Study group: obtaining conventional anti-diabetic medications and silymarin.

Regarding Lipid Profile: The total cholesterol levels of the two groups are significantly different (p-value < 0.05). In contrast to the control group, which exhibited an increase in total cholesterol, the silymarin group showed an improvement. Triglyceride levels decreased significantly just in the silymarin group. In both groups, HDL-C remained unchanged significantly. LDL-C exhibited a similar rhythm of total cholesterol in both groups. Since there was a statistically significant change in TG level alone in the silymarin group, there was a corresponding change in VLDL-C levels in the silymarin group as well (Table 3).

Regarding Renal Biomarkers: The findings of both groups unexpectedly indicated a significant change (p-value < 0.05) in serum urea; however, the control group exhibited an adverse shift, with urea levels increasing instead of decreasing as shown in the silymarin group. The serum creatinine levels of both groups dropped significantly, although the silymarin group's improvement was more pronounced (Table 4).

Table 4: Comparing the Serum urea and Creatinine at the Starting Point and Following Two Months between the Research Groups.

Parameter	Group	Timing	Mean Rank	*P*-value	E.S	E.S
S. Urea	Control	Before	11.39	0.0001*	0.588	Large
		After	20.29			
	Study	Before	19	0.0001*	0.707	Large
		After	12			
S. Creatinine	Control	Before	16.14	0.034*	0.358	Medium
		After	13.95			
	Study	Before	16.89	0.0001*	0.825	Large
		After	4.5			

Statistical Test: Wilcoxon Signed Rank test.
*: A significant difference was established at p ≤ 0.05.
E.S : < 0.30 = Small / 0.30 < 0.50 = Medium / ≥ 0.50 = Large
Control group: obtaining conventional oral anti-diabetic medications.
Study group: obtaining conventional oral anti-diabetic medications and silymarin.

Table 5: Comparing the Hepatic Enzymes at the Starting point and Following Two Months between the Research Groups.

Parameter	Group	Timing	Mean Rank	*P*-value	E.S	E.S
ALT	Control	Before	17.8	0.085	0.291	Small
		After	14.33			
	Study	Before	19.45	0.0001*	0.69	Large
		After	11			
AST	Control	Before	19.14	0.613	0.086	Small
		After	16.35			
	Study	Before	19.23	0.0001*	0.698	Large
		After	9.42			
ALP	Control	Before	18.59	0.07	0.306	Medium
		After	17.73			
	Study	Before	19.19	0.001*	0.562	Large
		After	14			

Statistical Test: Wilcoxon Signed Rank test.
*: A significant difference was established at p ≤ 0.05.
E.S : < 0.30 = Small / 0.30 < 0.50 = Medium / ≥ 0.50 = Large
Control group: obtaining conventional anti-diabetic medications.
Study group: obtaining conventional anti-diabetic medications and silymarin.

Regarding Hepatic Enzymes: As anticipated, ALT, AST, and ALP exhibited significant modifications (p-value < 0.05) in the study group, indicating a substantial impact of silymarin supplementation on these

enzymes. The control group demonstrated a decrease in hepatic enzyme levels; however, this is insufficient to induce a significant alteration (Table 5). The overall findings including glycemic, lipid and hepatorenal indices are summarized in Figure (1).

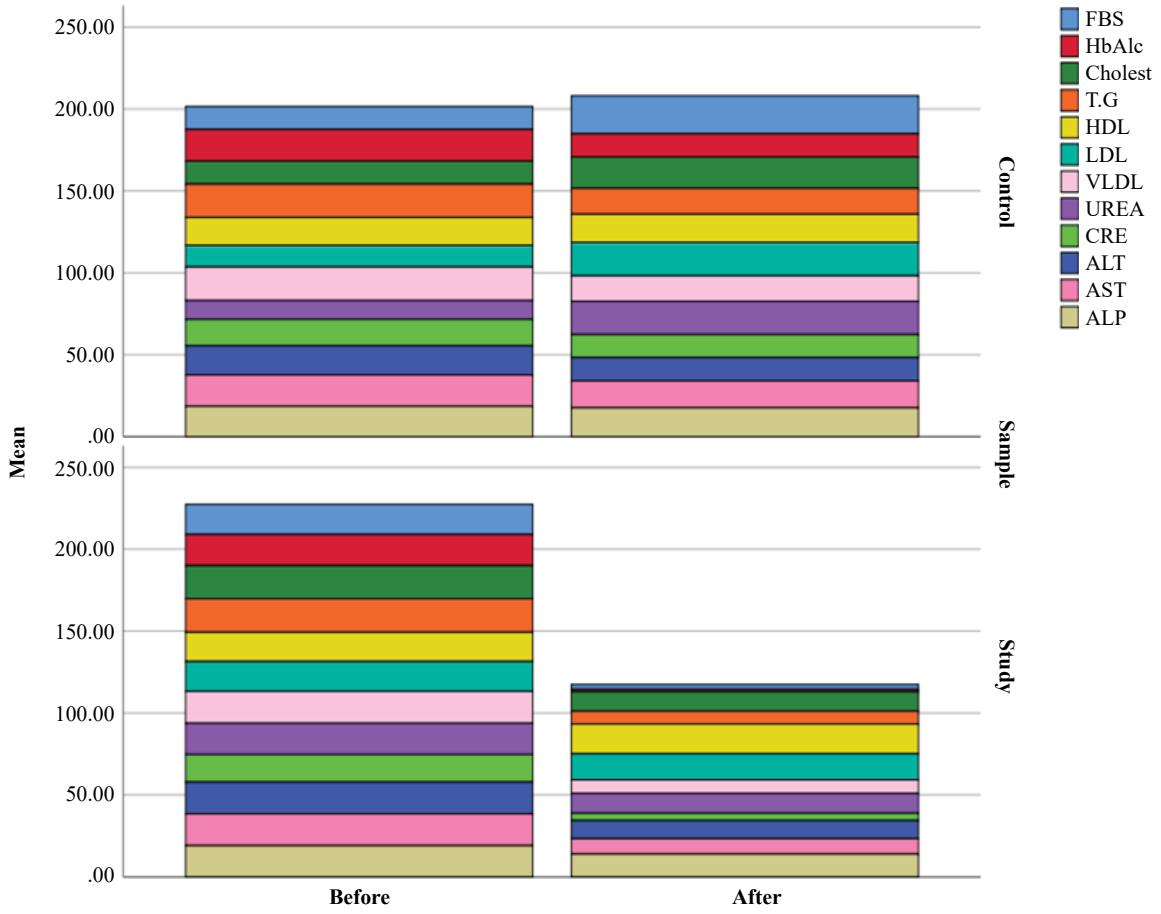

Figure 1: Summary of Results.

4. Discussion

Silymarin, a naturally occurring compound extracted from milk thistle seeds, is proposed as a promising option for the management of various disorders, including diabetes and its consequences through their capacity to influence several physiological pathways that affect glycemia and lipid metabolism, hepatorenal function, and other main organ systems, along with related biomarkers for hepatic and renal diseases [15]. This study's key findings indicated that the administration of 140 mg of silymarin twice a day for 60 days influences glycemic, lipid, as well as hepatorenal biomarkers. Silymarin markedly reduced fasting blood glucose (FBG) and haemoglobin A1c (HbA1c) when administered as adjunctive therapy compared to the control group who did not receive silymarin supplementation. The silymarin group exhibited a significant reduction in total cholesterol, triglycerides, and VLDL-C compared to the control group. When serum urea and creatinine levels were elevated in the control group, they experienced a surprising decline in the silymarin group. Hepatic enzyme levels diminished marginally in the control group, whereas a significant reduction was observed in the silymarin group.

Regarding glycemic and lipid control, our research results align with those of prior studies [16-18]. Consumption of 140 mg of SLM three times a day for 3 months exhibited more effectiveness than conventional treatment solely. The initial with the post-3 months measurements of FBG, HbA1c, FSI, TC, TG, LDL, VLDL, hs-CRP, and HOMA-IR exhibited a statistically important distinction between the two groups. The HDL-c level exhibited a statistically substantial distinction among the research groups [16].

Patients were administered 140 mg of SLM three times a day for 45 days. Results showed that Silymarin supplementation significantly lowered FBG, serum insulin, homeostatic model assessment for insulin resistance, serum triglyceride, and triglyceride to HDL cholesterol ratio compared to placebo. Compared to the placebo group, silymarin increased high-density lipoprotein cholesterol and quantitative insulin sensitivity check index. In the silymarin group, total cholesterol and low-density lipoprotein cholesterol

dramatically fell compared to baseline [17]. Following three months of Silymarin supplementation (200mg daily) as an adjunct to their oral antidiabetic regimen (glimepiride and metformin), the fasting blood glucose (FBG), random blood glucose (RBG), A1C, fasting insulin (FI), and HOMA-IR were reassessed and shown to have improved. Statistically significant differences were observed when compared to the control group that received glimepiride plus metformin alone [18].

The enhancement in glycemic parameters may be associated with the antioxidant effects of silymarin [19], and an elevation in the GSH/GSSG ratio of pancreatic beta cells [20]. Additionally, silymarin may inhibit the protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) signalling pathways associated with insulin resistance and hyperglycemia [21]. Silymarin is thought to activate peroxisome proliferator-activated receptor gamma (PPAR γ) in specific tissues, mainly in the liver, skeletal muscles, and adipose tissue. This process may enhance insulin sensitivity, peripheral glucose disposal, and lipid metabolism, thereby helping to manage disorders like metabolic syndrome or type 2 diabetes and reducing the likelihood of insulin resistance [22, 23]. So, silymarin exerts a hypoglycemic effect independent of insulin secretion [24]. Several research have examined the potential processes underlying the lipid-lowering properties of silymarin. The observed beneficial benefits may be associated with enhanced insulin sensitivity and a reduction in HOMA-IR in the silymarin group [18]. The hepatoprotective effects of silymarin are purportedly linked to alterations in lipids, cholesterol, and phospholipids affecting cell membrane permeability [23, 25]. Evidence indicates that silymarin can normalize serum lipid levels by limiting fatty acid synthesis [26], diminishing de novo cholesterol production, obstructing cholesterol absorption [27] and lowering cytochrome P450 CYP2E1 levels [28]. Furthermore, silymarin enhances fatty acid oxidation and lipoprotein metabolism by up-regulating the gene expression of peroxisome proliferator-activated receptor α (PPARα) [23]. Silymarin, also suppresses hepatic lipogenesis by down-regulating peroxisome proliferator-activated receptor gamma coactivator-1 beta (PGC-1β), sterol regulatory element-binding protein-1c (SREBP-1c), and liver X receptor beta (LXRβ) [29].

Various findings support the role of silymarin in preventing the expression of TGF-β1, fibronectin, collagen IV, and mesangial expansion in the renal tissues of diabetic rats. These agents helped to alleviate hepatic as well as renal disorders in a type 2 diabetes mellitus (T2DM) animal model [30]. A number of in vivo and in vitro studies have shed light on the renoprotective properties of silymarin in diabetic conditions [31]. Silymarin was found to have a retarding effect on alterations in creatinine (Cr), urea, and urinary protein in an STZ-diabetic rat model [32]. In another study employing an in vitro method, silymarin efficiently achieved results on normal rat kidney cells by demonstrating antioxidant and anti-inflammatory activities [33]. Their results from an in vivo study demonstrated that co-treatment of rats with silymarin showed a reduction in mean serum urea and creatinine levels of STZ-induced rats and improved structural alterations in the kidney, such as necrosis, glomerulosclerosis, renal podocyte effacement, and mesangial expansion via restoration of the ERK/JNK/NF-kB/MAPK signalling pathway in the rat model of T2DM [32, 33].

Many mechanisms display the struggle of silymarin's effect on liver enzymes [34]. Aspects concerning life indicate that silymarin is an antioxidant, which converts cell apoptosis, inhibits ischemia/reperfusion, and therefore prevents lipid peroxidation [35]. It acts as an anti-inflammatory by preventing the activation of neutrophils, modulating T lymphocytes, and altering cyclooxygenase signalling [36]. It promotes hepatocyte synthesis of proteins from the ribosomes and has nucleolar effects, thereby promoting hepatocyte regeneration [37]. Along with cellular processes, silymarin also interacts with enzymes in the Kupffer cells, and receptors and peroxisomal β-oxidation enzymes in the hepatocytes [38].

Potential variability in silymarin absorption differences in bioavailability among individuals may affect results [39]. We use standard silymarin products available in the market because silymarin's variable absorption and bioavailability highlight the need for optimized formulations and further research into genetic and physiological factors affecting its pharmacokinetics. Addressing these variables could improve clinical outcomes and consistency in therapeutic applications. Silymarin (particularly its main active constituent, silybin) has low aqueous solubility, leading to inconsistent gastrointestinal absorption [40]. Bioavailability in its natural form is typically low (<50%), but formulations with enhanced solubility (e.g., phytosomes, liposomes, or complexation with phospholipids) show improved absorption. First-pass metabolism: Silymarin undergoes extensive hepatic and intestinal metabolism via phase II enzymes (UGTs, SULTs), reducing systemic availability [39]. Variations in drug-metabolizing enzymes (e.g., UGT1A1, CYP450 isoforms) and transporters (e.g., P-glycoprotein, BCRP) may alter silymarin pharmacokinetics [40]. The microbiome may modify silymarin metabolism, affecting its conversion to active or inactive metabolites [39].

Limitations of the study; while silymarin supplementation shows promise in improving metabolic and hepatorenal parameters in T2DM, several limitations may affect the interpretation and generalizability of the findings, including the study had a small number of participants, the results may lack statistical power to detect subtle but clinically meaningful effects. The restricted demographic representation (e.g., age, ethnicity, comorbidities) could limit applicability to broader T2DM populations. Uncontrolled dietary habits,

concurrent antidiabetic drugs (e.g., metformin, insulin), and poor adherence could influence outcomes. Physical activity and other lifestyle factors were not monitored.

5. Conclusion

Supplementation with 140 mg of Silymarin twice daily for 60 days exhibited more effectiveness than standard therapy solely. This regimen resulted in a substantial reduction in fasting blood glucose (FBG), HbA1c, total cholesterol, triglycerides, VLDL-cholesterol (VLDL-C), and hepatorenal biomarkers. Further investigations are advised about the renal-protective properties of silymarin, since it may provide a feasible therapeutic alternative for numerous renal problems, especially in people who has diabetes.

■ References

1. **Suganya M, Maragatham S, Parimala L**. Efficacious Outcome of Peripheral Retinal Laser Photocoagulation to Severe Non-Proliferative Diabetic Retinopathy in Young-onset Type 1 Diabetic Mellitus: A Case Report. *Texila International Journal of Public Health* 2025. 13(1):640-4.
2. **Atiya LG, Yahya OM, Mohmmed SJ**. Synthesis, Evaluation of New Imidazolidin-4-one and Thiazolidine-4-one compound on Insulin in the Serum of Type 1 Diabetes Albino Rats. *Journal of Chemical Health Risks* 2024. 14(2):403-13.
3. **Ellahham S**. Artificial Intelligence: The Future for Diabetes Care. *Am J Med* 2020. 133(8):895-900.
4. **Jyotsna F, Mahfooz K, Patel T, Parshant F, Simran F, Harsha F, et al.** A Systematic Review and Meta-Analysis on the Efficacy and Safety of Finerenone Therapy in Patients with Cardiovascular and Chronic Kidney Diseases in Type 2 Diabetes Mellitus. *Cureus* 2023. 15(7):e41746.
5. **Zaveri F, Naser S**. Efficacy and Safety of Finerenone in Patients with Heart Failure, Chronic Kidney Disease, and Type 2 Diabetes: A Comprehensive Review of the FINE-HEART Pooled Analysis. *Texila International Journal of Public Health* 2025. 13(1):526-9.
6. **Nandabaram A, Nelson VK, Mayasa V**. Assessment of Possible Food-Drug Interactions of Pearl Millet Diet on Gliclazide in Diabetic Rats. *Texila International Journal of Public Health* 2025. 13(1):614-28.
7. **Pham TB, Nguyen TT, Truong HT, Trinh CH, Du HNT, Ngo TT, et al.** Effects of Diabetic Complications on Health-Related Quality of Life Impairment in Vietnamese Patients with Type 2 Diabetes. *J Diabetes Res* 2020. 2020:4360804.
8. **Saucedo R, Ortega-Camarillo C, Ferreira-Hermosillo A, Díaz-Velázquez MF, Meixueiro-Calderón C, Valencia-Ortega J**. Role of Oxidative Stress and Inflammation in Gestational Diabetes Mellitus. *Antioxidants (Basel)* 2023. 12(10):1812.
9. **Artasensi A, Pedretti A, Vistoli G, Fumagalli L**. Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. *Molecules* 2020. 25(8):1987.
10. **Jaffar HM, Al-Asmari F, Khan FA, Rahim MA, Zongo E**. Silymarin: Unveiling its pharmacological spectrum and therapeutic potential in liver diseases-A comprehensive narrative review. *Food Sci Nutr* 2024. 12(5):3097-111.
11. **Surai PF**. Silymarin as a Natural Antioxidant: An Overview of the Current Evidence and Perspectives. *Antioxidants (Basel)* 2015. 4(1):204-47.
12. **Bai Y, Wang L, TingYang, Wang L, Ge W**. Silymarin ameliorates peritoneal fibrosis by inhibiting the TGF-β/Smad signaling pathway. *Naunyn Schmiedebergs Arch Pharmacol* 2023. 396(10):2379-91.
13. **Delmas D**. Silymarin and Derivatives: From Biosynthesis to Health Benefits. *Molecules* 2020. 25(10):2415.
14. **Friedewald WT, Levy RI, Fredrickson DS**. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972. 18(6):499-502.
15. **Bahari H, Shahraki Jazinaki M, Rashidmayvan M, Taheri S, Amini MR, Malekahmadi M**. The effects of silymarin consumption on inflammation and oxidative stress in adults: a systematic review and meta-analysis. *Inflammopharmacology* 2024. 32(2):949-63.
16. **Elgarf AT, Mahdy MM, Sabri NA**. Effect of Silymarin Supplementation on Glycemic Control, Lipid Profile and Insulin Resistance in Patients with Type 2 Diabetes Mellitus. *Int J Adv Res (Indore)* 2015. 3(12):812-21.
17. **Ebrahimpour-Koujan S, Gargari BP, Mobasseri M, Valizadeh H, Asghari-Jafarabadi M**. Lower glycemic indices and lipid profile among type 2 diabetes mellitus patients who received novel dose of Silybum marianum (L.) Gaertn. (silymarin) extract supplement: A Triple-blinded randomized controlled clinical trial. *Phytomedicine* 2018. 44:39-44.
18. **Memon A, Siddiqui SS, Ata MA, Shaikh KR, Soomro UA, Shaikh S**. Silymarin improves glycemic control through reduction of insulin resistance in newly diagnosed patients of type 2 diabetes mellitus. *Professional Med J* 2022. 29(03):362-6.
19. **Soto C, Pérez J, García V, Uría E, Vadillo M, Raya L**. Effect of silymarin on kidneys of rats suffering from alloxan-induced diabetes mellitus. *Phytomedicine* 2010. 17(14):1090-4.
20. **MacDonald-Ramos K, Michán L, Martínez-Ibarra A, Cerbón M**. Silymarin is an ally against insulin resistance: A review. *Ann Hepatol* 2021. 23:100255.
21. **Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al.** IDF Diabetes Atlas: Global estimates for the

prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017. 128:40-50.

22. **Younis HY, Thanoon IA, Fadhil NN, Merkhan MM**. Effect of Zinc as an Add-On to Metformin Therapy on Glycemic control, Serum Insulin, and C-peptide Levels and Insulin Resistance in Type 2 Diabetes Mellitus Patient. *Research Journal of Pharmacy and Technology* 2022. 15(3):1184-8.
23. **Tailleux A, Wouters K, Staels B**. Roles of PPARs in NAFLD: potential therapeutic targets. *Biochim Biophys Acta* 2012. 1821(5):809-18.
24. **Miranda LMO, Agostini LDC, Lima WG, Camini FC, Costa DC**. Silymarin Attenuates Hepatic and Pancreatic Redox Imbalance Independent of Glycemic Regulation in the Alloxan-induced Diabetic Rat Model. *Biomed Environ Sci* 2020. 33(9):690-700.
25. **Dhiaa S, Thanoon IA, Fadhil NN**. Vitamin E Versus Propolis as an Add-on Therapy to Sitagliptin/Metformin on Oxidant/Antioxidant Status and Lipid Profile in Type 2 Diabetic Patients. *Vojen Zdrav Listy* 2023. 92(1):14-21.
26. **Vahabzadeh M, Amiri N, Karimi G**. Effects of silymarin on metabolic syndrome: a review. *J Sci Food Agric* 2018. 98(13):4816-23.
27. **Ferdowsi S, Shidfar F, Heidari I, Kashi M, Sohouli MH, Sarrafi Zadeh S**. Effect of silymarin on lipid profile and glycemic control in patients with type 2 diabetes mellitus. *Phytother Res* 2024. 38(9):4667-74.
28. **Mohammadi H, Hadi A, Arab A, Moradi S, Rouhani MH**. Effects of silymarin supplementation on blood lipids: A systematic review and meta-analysis of clinical trials. *Phytother Res* 2019. 33(4):871-80.
29. **Prakash P, Singh V, Jain M, Rana M, Khanna V, Barthwal MK, et al.** Silymarin ameliorates fructose induced insulin resistance syndrome by reducing de novo hepatic lipogenesis in the rat. *Eur J Pharmacol* 2014. 727:15-28.
30. **Golestaneh E, Hasanpour Dehkordi A, Yalameha B, Noorshargh P, Nasri P, Nasri H**. Comparative study of nephroprotective effects of resveratrol and silymarin in diabetic rats; an experimental histopathologic study. *J Nephropharmacol* 2024. 13(1):e10381.
31. **Mohammadi S, Ashtary-Larky D, Asbaghi O, Farrokhi V, Jadidi Y, Mofidi F, et al.** Effects of silymarin supplementation on liver and kidney functions: A systematic review and dose-response meta-analysis. *Phytother Res* 2024. 38(5):2572-93.
32. **Sakr NH, Elmetwally AA-m, Hamed E, Abubakr S**. Targeting autophagy explaining therapeutic potential of silymarin against streptozotocin-induced type 2 diabetic nephropathy in a rat model: A histological and immunohistochemical study. *Bulletin of Egyptian Society for Physiological Sciences* 2024. 44(3):185-95.
33. **Al-Kadi A, Ahmed A-S, El-Tahawy NFG, Khalifa MMA, El-Daly M**. Silymarin protects against sepsis-induced acute liver and kidney injury via anti-inflammatory and antioxidant mechanisms in the rat. *Journal of advanced Biomedical and Pharmaceutical Sciences* 2020. 3(4):190-7.
34. **El-Kot SM, Wanas W, Hafez AM, Mahmoud NA, Tolba AM, Younis AH, et al.** Effect of silymarin on the relative gene expressions of some inflammatory cytokines in the liver of CCl(4)-intoxicated male rats. *Sci Rep* 2023. 13(1):15245.
35. **Ghalandari K, Shabani M, Khajehlandi A, Mohammadi A**. Effect of aerobic training with silymarin consumption on glycemic indices and liver enzymes in men with type 2 diabetes. *Arch Physiol Biochem* 2023. 129(1):76-81.
36. **Mirnezami M, Jafarimanesh H, Rezagholizamenjany**
37. **M, Alimoradian A, Ranjbaran M**. The effect of silymarin on liver enzymes in patients taking isotretinoin: A randomized clinical trial. *Dermatol Ther* 2020. 33(2):e13236.
38. **Mohtashaminia F, Amini MR, Sheikhhossein F, Djafarian K, Shab-Bidar S**. Effects berberine-silymarin on liver enzymes: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN* 2022. 49:181-6.
39. **Kim SH, Oh DS, Oh JY, Son TG, Yuk DY, Jung YS**. Silymarin Prevents Restraint Stress-Induced Acute Liver Injury by Ameliorating Oxidative Stress and Reducing Inflammatory Response. *Molecules* 2016. 21(4):443.
40. **Theodosiou E, Purchartová K, Stamatis H, Kolisis F, Křen V**. Bioavailability of silymarin flavonolignans: drug formulations and biotransformation. *Phytochem Rev* 2014. 13(1):1-18.
41. **Dixit N, Baboota S, Kohli K, Ahmad S, Ali J**. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. *Indian J Pharmacol* 2007. 39(4):172-9.