Current Trends in Pharmacology and Clinical Trials
ISSN: 2642-0848

Academic Strive
Researcher's perception is our reality

Research Article *Volume 4 Issue 2*

Silymarin as an Adjunct to Oral Antidiabetic Agents: A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial

Sharifi S[1], Valizadeh N[2], Heidari M[3], Baradaran P[4] and Sharifi H[1,3]*

[1]Department of Pharmacology, Urmia University of Medical Sciences, Iran

[2]Maternal and Childhood Obesity Research Center, Urmia University of Medical Sciences, Iran

[3]Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, Iran

[4]Endocrinology and Diabetes Clinic, Urmia University of Medical Sciences, Iran

***Corresponding author:** Dr. Hamdollah Sharifi, Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran-Postal Code: 5715799313, Mail Box: 571571441; Tel: 0098-9143612123; Fax: 984433469935; Email: Sharifi.h@umsu.ac.ir

Received Date: July 27, 2021; **Published Date:** September 06, 2021

Abstract

Lack of highly effective drug-therapy with existing synthetic drugs and their adverse effects motivated further search into traditional medicine in order to find new natural entities to be used as anti-diabetic products. To investigate the hypothesis that the combination of silymarin in adjunct with oral anti-diabetic drugs is useful in improving glucose profile in type 2 diabetes mellitus patients in comparison with placebo. In this study, 50 patients suffering from type 2 diabetes mellitus were recruited and randomly divided into two groups. The intervention (n=25) and control (n=25) groups received either 280 mg silymarin in two divided doses or placebo respectively for 60 days. All subjects were treated with standard oral anti-diabetic agents during the intervention period. Serum levels of fasting blood sugar, 2hours post-prandial glucose and glycosylated hemoglobin A1c were measured before and after the intervention. Addition of silymarin with standard oral anti diabetic agents led to a significant decrease in the levels of fasting blood sugar, 2hours post-prandial glucose and glycosylated hemoglobin A1c in the intervention group. The glycosylated hemoglobin A1c increased in placebo group significantly. None of the patients in the silymarin group reported any adverse effects of silymarin. Administration of 280 mg silymarin in two divided doses over 60 days showed a superior efficacy than standard treatment alone in type 2 diabetes mellitus. It resulted in significant decreased serum levels of fasting blood sugar, 2hours post-prandial glucose, and glycosylated hemoglobin A1c.

Keywords: Type 2 Diabetes Mellitus; Silymarin; Herbal Medicine; FBS; Hba1c

Introduction

Type 2 diabetes mellitus (T2DM) is a worldwide disease that available drugs are not effective in long-term treatment [1]. In the pathophysiology of T2DM, several organs are involved such as liver, skeletal muscle, adipose tissue, etc. Insulin-mediated glucose disposal derangement in these organs eventually result in hyperglycemia, which is a hallmark for T2DM [2,3]. Hyperglycemia and free fatty academia cause reactive oxygen species (ROS) and oxidative stress which contributes to insulin resistance [4,5]. Reduction of oxidative stress indicators and hyperlipidemia can help to

better control of diabetes [6]. On the other hand, several trials have shown that control of hyperglycemic state does not necessarily improve oxidative stress [7]. This means that specific therapy directed toward oxidative stress is needed. The favorable effect of antioxidants in the treatment of oxidative metabolic impairment in diabetes has been reported in several experimental studies [8-10]. In this method, the natural compound silymarin has received increasing interest in recent decades. Silymarin has demonstrated protective effects against oxidative stress-induced damage in several experimental models and in human hepatic injury [11-13]. Recently some trials have reported the silymarin as an anti-diabetic agent [14-16].

The aims of this study were: a) to evaluate the efficacy of silymarin as adjuvant therapy to standard oral anti diabetic treatment in compared with placebo on glycemic control FBS, 2hpp and HbA1c in patients with type 2 diabetes mellitus, b) to evaluate the incidence of adverse events reported with silymarin or placebo.

Methods and Materials

Trial Design

The present study was designed as a double-blind randomized clinical trial, placebo-controlled which was conducted to compare the efficacy and safety of silymarin with placebo in patients with T2DM. The Medical Ethics Committee of Urmia University of Medical Sciences approved the protocol of the study (IR.UMSU.REC.1397.331) and a signed informed consent form was obtained from each participant. The trial was registered at the Iranian registry of clinical trials (www.irct.ir) under the registration number of IRCT20170814035697N5.

Patients

The participants were recruited from Endocrinology clinic of Imam Khomeini Hospital of Urmia University of Medical Sciences, Urmia, Iran from October to September 2019. The sample size was determined based on PD (Pocket depth) (156 ± 46 vs 133 ± 39, reduction rate in the beginning and end of study) as the main outcome obtained from the study by Huseini HF, et al. For α value equal to 0.05 (confidence level of 95%) and a power of 80%, the sample size was computed by using this formula: as 46 subjects per group. Considering the withdrawal rate of 10%, 50 T2DM patients were selected for each group.

➢ **Inclusion Criteria**

- Being 30 to 65 years old.
- History of Type 2 diabetes mellitus based on endocrinologist diagnosis > 1 year.
- Conscious informed consent to participate in the study.

➢ **Exclusion Criteria**

- Insulin therapy.
- Taking drugs that interfere with the level of plasma glucose.
- Any diseases affect levels of glycosylated hemoglobin such as anemia, hemodialysis, hemoglobinopathies, uremia, pregnancy and lactation.
- Hospitalized due to any complications of diabetes or undergoing surgery.
- Receiving immunosuppressive drugs, smoking, any dietary supplements including antioxidant supplements.

Randomization and Blinding

The patients were randomly allocated to two groups using a balanced randomization method. The patients and the investigators who carried out clinical and para clinical assessments were unaware of the treatment groups and type of medication. The drug and the placebo were administered to the patients in similar packages and the same dose (containers were equal in weight and similar in appearance).

Interventions

Patients were randomly divided into two groups: silymarin group (25 patients who received 140 mg silymarin tablets (Goldaru, Livergol, Isfahan, Iran) two times daily with their standard anti-diabetic treatment for 60 days) and placebo control group (25 patients who received identical placebo tablets two times daily with their standard anti-diabetic treatment for 60 days). At the beginning, all patients underwent thorough history taking and clinical examination. Blood samples were collected to measure the following parameters at the beginning and the end of treatment and used to evaluate the treatment outcomes, FBS, HbA1c, and 2hpp. A written informed consent was obtained from patients at the beginning of the study and about the confidentiality of the study was explained to the patients. Drug compliance was assessed and six patients were excluded from the study, due to nausea and gastroenteritis in placebo group (n=2), irregular drug use (n=2), and lack of good control and shift to insulin (n=2) and other patients were replaced.

Outcomes

The primary outcome was the effect of silymarin and placebo on the FBS, 2hpp and HbA1c which were assessed at baseline and at the end of second month of treatment. The secondary outcome was to evaluate the incidence of adverse events reported with silymarin or placebo. The baseline characteristics of the participants of age, sex and weight as well as FBS, 2hpp and HbA1c before and two month after treatment was obtained using a checklist.

Statistical Analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Mean and standard deviation was used to describe the quantitative variables. All p-values are two-sided. The statistical analysis of the recorded data at the beginning and after 2 months was performed using independent and paired Student's t-test employing SPSS statistical software for quantitative variables. P-values < 0.05 were considered significant.

Results

All 50 patients completed the study. The patients' demographic characteristics and the baseline findings of patients in the two groups (silymarin and placebo) regarding FBS, HbA1c and 2hpp are summarized in Table 1.

Group	Silymarin (n = 25)	Placebo (n = 25)	Total (n=50)
Age (year) (mean ± SD)	53.8 ± 7.3	54.3 ± 8.2	54.1 ± 7.7
Weight (kg) (mean ± SD)	72.9 ± 9.1	74.2 ± 8.1	73.6 ± 8.6
Sex (male/female)	13M/12F	13M/12F	26M/24F
	(mean ± SD)	**(mean ± SD)**	**P_ value**
FBS (mg/dl)	145.4 ± 32.4	148.1 ± 31.4	0.76
2HPP (mg/dl)	200.9 ± 57.7	201.9 ± 49.5	0.94
HbA1c (%)	7.0 ± 1.3	7.2 ± 1.4	0.68

Table 1: Demographic Characteristics and the Baseline Findings of Patients in the Two Groups.

Fbs

The average FBS level in the silymarin group at the beginning of the study was 145.4±32.4 mg/dl, which decreased significantly (p<0.001) to 132.5±28.1 mg/dl after 2 months of silymarin treatment. The average FBS level in the placebo group at the beginning of the study was 148.1±31.4 mg/dl, which decreased to 146.4±30.1 mg/dl after 2 months of placebo treatment that was insignificant (p<0.65) (Table 2).

Group	Silymarin (mean ± SD)			Placebo (mean ± SD)		
	Beginning	After	p value	Beginning	After	p value
FBS (mg/dl)	145.4 ± 32.4	132.5 ± 28.1	<0.001	148.1 ± 31.4	146.4± 30.1	0.65
2HPP (mg/dl)	200.9 ± 57.7	182.2 ± 50.8	0.001	201.9 ± 49.5	214.2 ± 57.9	0.08
HbA1c (%)	7.0 ± 1.3	6.4 ± 0.8	0.003	7.2 ± 1.4	7.4 ± 1.4	0.009

Table 2: The average level of studied parameters at the beginning and after 2 months in placebo and silymarin treated groups.

2hpp

The average 2hpp level in the silymarin group at the beginning of the study was 200.9±57.7 mg/dl, which decreased significantly (p<0.001) to 182.2±50.8 mg/dl after 2 months of silymarin treatment. The average 2hpp level in the placebo group at the beginning of the study was 201.9±49.5 mg/dl, which increased to 214.2±57.9 mg/dl after 2 months of placebo treatment that was insignificant (p<0.08) (Table 2).

Hba1c

The average HbA1c level in the silymarin group at the beginning of the study was 7.0±1.3%, which decreased significantly (p<0.003) to 6.4±0.8% after 2 months silymarin treatment. The average HbA1c level in the placebo group at the beginning of the study was 7.2±1.4%, which increased significantly (p<0.009) to 7.4±1.4% after 2 months of placebo treatment. Finally, no side effects of the treatment were reported during the study and there were no changes in therapy or surgical intervention in both groups (Table 2).

Discussion

Silymarin has several biological activities that supposed to be as a candidate for the treatment of diabetes including antioxidant, anti-inflammatory, inhibition of gluconeogenesis, increase insulin gene expression as well as beta-cell proliferation [17-19]. On the basis of these suggestions we studied the effects of silymarin on the glucose profile in type 2 diabetic patients who received oral anti-diabetic agents.

The first important finding of this study suggested that consuming 140 mg silymarin supplement twice daily for 60 days modulates glycemic markers. Silymarin significantly

decreased FBS (p<0.001), 2hpp (p<0.001) and HbA1c (p<0.003) compared to placebo controlled group. Our results in this trial were consistent with Hosseini, et al. results [2]. Of course, in their study, patients were given 600 mg daily silymarin, but we used 280 mg daily (140 mg twice times daily). The results of Hussein's study which were consistent with the present study also, used only 200 mg daily of silymarin for 2 months [3].

However, according to pharmacological studies, silymarin has been accepted as a safe herbal drug, that physiological doses of silymarin are not toxic [20]. Silymarin modulates glucose metabolism through various mechanisms, such as increased insulin secretion, glycolysis stimulation, and increased glucokinase activity, and so on [21]. Some of these effects are also seen with metformin and sulfonylureas [22]. It seems that the study of Yin, et al. [15], who compared the effect of silymarin with metformin, may support this fact too. Of course, in this study, silymarin was given as a supplement with oral anti-diabetic drugs, and in fact their synergistic effects were also considered and their effects compared with placebo. This is probably because there was a more significant reduction in FBS, 2hpp and HbA1c in the present study compared to the study of Yin, et al. [15]. (0.001 vs. 0.01). Based on diabetes mellitus pathophysiology, the newest and the best treatment options are needed to control the disease process and its complications. In this regard, this research is particularly important for finding alternative drugs [18]. The inefficiency of existing diabetes therapies has led to the use of hypoglycemic supplements in the US of 2-3.6 million diabetic patients, although their efficacy and safety was not confirmed [23]. In support of this result, one of the important findings of the present study showed that in the control group patients, despite receiving conventional anti-diabetic drugs, their 2hpp and HbA1c in the second month increased compared to the baseline. These findings are also in same long with the results of Hosseini, et al. In both studies, patients received standard oral anti-diabetic drugs. Other studies [1,7] have found similar findings, although, none of these studies emboss this finding.

Another important finding of this study was that none of the patients in the silymarin group reported any adverse effects of silymarin. In placebo group two patients complained of mild nausea and gastroenteritis without a need to medication therapy and were excluded.

Conclusion

Administration of 140 mg silymarin twice daily over 60 days showed a superior efficacy than standard treatment alone. It resulted in significant decrease in serum levels of FBS, 2hpp, and HbA1c. Moreover, silymarin was superior to standard treatment alone in improving glucose profile in type 2 diabetic patients undergoing oral anti-diabetic drugs.

Ethic Approval

The study was approved by the ethics committee of Urmia University of Medical Sciences (Code: IR.UMSU.REC.1397.331). The trial was registered at the Iranian registry of clinical trials (www.irct.ir) under the registration number of IRCT20170814035697N5.

Acknowledgment

The authors would like to express their gratitude and appreciation to Urmia Imam Khomeini Hospital's Endocrinology and Diabetes Clinic staff for their relentless cooperation.

References

1. Elgarf AT, Mahdy MM, Sabri NA (2015) Effect of Silymarin Supplementation on Glycemic Control, Lipid Profile and Insulin Resistance in Patients with Type 2 Diabetes Mellitus. International Journal of Advanced Research 3(12): 812-821.

2. Huseini HF, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, et al. (2006) The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. Phytother Res 20(12): 1036-1039.

3. Cornell S (2015) Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options. Ther Clin Risk Manag 11: 621-632.

4. Babaei H, Rahbanian R, Malchi F, Mohebbi G, Farzadinia P, et al. (2016) Comparing the effects of metformin with silymarin in biochemical parameters related to diabetes and pancreatic tissue in streptozotocin- induced diabetic rats. Entomology and Applied Science Letters 3(1): 21-25.

5. Bouderba S, Martin CS, Villanueva GR, Detaille D, Koceir EA (2014) Beneficial effects of silibinin against the progression of metabolic syndrome, increased oxidative stress, and liver steatosis in Psammomys obesus, a relevant animal model of human obesity and diabetes. J Diabetes 6(2): 184-192.

6. Koujan SE, Gargari BP, Mobasseri M, Valizadeh H, Jafarabadi MA (2015) Effects of Silybum marianum (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: a randomized, triple-blind, placebo-controlled clinical trial. Phytomedicine 22(2): 290-296.

7. Hussain SAR (2007) Silymarin as an adjunct to glibenclamide therapy improves long-term and postprandial glycemic control and body mass index in type 2 diabetes. J Med Food 10(3): 543-547.

8. Khazim K, Gorin Y, Cavaglieri RC, Abboud HE, Fanti P (2013) The antioxidant silybin prevents high glucose-induced oxidative stress and podocyte injury in vitro and in vivo. Am J Physiol Renal Physiol 305(5): F691-700.

9. Malihi F, Tabatabaei AH, Esmaily H, Khorasani R, Baeeri M, et al. (2009) Improvement of inflammatory and toxic stress biomarkers by silymarin in a murine model of type one diabetes mellitus. Central European Journal of Biology 4(3): 369-380.

10. Marrazzo G, Bosco P, Delia FL, Scapagnini G, Giacomo CD, et al. (2011) Neuroprotective effect of silibinin in diabetic mice. Neurosci Lett 504(3): 252-256.

11. Kheiripour N, Karimi J, Khodadadi I, Tavilani H, Goodarzi MT, et al. (2019) Hepatoprotective Effects of Silymarin on Liver Injury via Irisin Upregulation and Oxidative Stress Reduction in Rats with Type 2 Diabetes. Iran J Med Sci 44(2): 108-117.

12. Salamone F, Galvano F, Gammazza AM, Paternostro C, Tibullo D, et al. (2012) Silibinin improves hepatic and myocardial injury in mice with nonalcoholic steatohepatitis. Dig Liver Dis 44(4): 334-342.

13. Surai PF (2015) Silymarin as a natural antioxidant: An overview of the current evidence and perspectives. Antioxidants (Basel) 4(1): 204-247.

14. Fallahzadeh MK, Dormanesh B, Sagheb MM, Roozbeh J, Vessal G, et al. (2012) Effect of Addition of Silymarin to Renin-Angiotensin System Inhibitors on Proteinuria in Type 2 Diabetic Patients With Overt Nephropathy: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Kidney Dis 60(6): 896-903.

15. Yin J, Xing H, Ye J (2008) Efficacy of berberine in Patients with type 2 diabetes mellitus. Metabolism 57(5): 712-717.

16. Koujan SE, Gargari BP, Mobasseri M, Valizadeh H, Jafarabadi MA (2018) 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 15(44): 39-44.

17. Soto C, Raya L, Juarez J, Perez J, Gonzalez I (2014) Effect of Silymarin in Pdx-1 expression and the proliferation of pancreatic β-cells in a pancreatectomy model. Phytomedicine 21(3): 233-239.

18. Voroneanu L, Nistor I, Dumea R, Apetrii M, Covic A (2016) Silymarin in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Diabetes Res.

19. Kazazis CE, Evangelopoulos AA, Kollas A, Vallianou NG (2014) The Therapeutic Potential of Milk Thistle in Diabetes. Rev Diabet Stud 11(2): 167-174.

20. Wu JW, Lin LC, Tsai TH (2009) Drug-drug interactions of silymarin on the perspective of pharmacokinetics. J Ethnopharmacol 121(2): 185-193.

21. Fogacci F, Grassi D, Rizzo M, Cicero AFG (2019) Metabolic effect of berberine–silymarin association: A meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Phytother Res 33(4): 862-870.

22. Katzung BG (2018) Basic & Clinical Pharmacology, 14th (Edn.), McGraw-Hill Education publisher, pp: 1-1265.

23. Shojaii A, Goushegir A, Dabaghian F, Fard MA, Huseini HF (2011) Herbs and herbal preparations for glycemic control in diabetes mellitus (a systematic review). Journal of Medicinal Plants Research 5(16): 3846-3855.