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# Protective Effects of Ginger and Silymarin on Alloxan-Induced Diabetic Rats

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## ABSTRACT

There is a close link between hyperglycemia, oxidative stress and diabetic complication. This study was carried out to clarify the effect of ginger and silymarin, as beneficial in the treatment of diabetes. Forty adult male albino rats were used in this study divided into four groups of ten rats each: group 1 represent normal control group, group 2 diabetic groups induced by alloxan, group 3 was diabetic and received daily ginger, group 4 was diabetic and received daily silymarin. Alloxan-induced diabetic rats, showed a significant increase of plasma glucose, triglyceride, total cholesterol, LDL–cholesterol, malondialdehyde, nitric oxide and uric acid while HDL–cholesterol and insulin levels are significantly decreased. Glutathione peroxidase, catalase and superoxide dismutase activities were significantly decreased in homogenates of liver and kidney, while malondialdehyde levels were increased in tissue homogenates of liver and kidney. Plasma levels of glucose, triglyceride, cholesterol, LDL–cholesterol and uric acid were decreased significantly after treatment with silymarin or ginger, while HDL–cholesterol and insulin were increased. Nitric oxide levels were decreased significantly in rats treated with silymarin only. In liver homogenates of rats treated with silymarin or ginger, malondialdehyde were decreased significantly, and catalase increased significantly, while superoxide dismutase activities and glutathione peroxidase were increased significantly in liver and kidney after silymarin or ginger treatment. The effects of both agents may be useful in delaying the complicated effects of diabetes due to imbalance between free radicals Moreover; silymarin may be more powerful free radical scavenger than ginger.

**Keywords**: Alloxan, Ginger, Silymarin, Antioxidants, Lipid profile, Diabetes

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## INTRODUCTION

Diabetes mellitus is a common metabolic disease characterized by increased circulating glucose concentrations associated with abnormalities in carbohydrate, fat and protein metabolism. Lipid abnormalities occur in diabetes, even in those who have reasonable glycaemic control[1].Oxidative stress plays an important role in the etiology of diabetes and diabetic complications[2]**.** Diabetic animal exhibit high-oxidative stress due to hyperglycemia, thereby deplete the activity of the antioxidative defense system and thus promote free radicals generation[3]**.** Oxidative stress can impair insulin action through a change in the physical state of the plasma membrane of target cells, an increase in intracellular calcium content and a reduction in nitric oxide availability[4]**.**

Ginger *(Zingiber officinale)* is well known all over the world especially for its use in disorders of the gastrointestinal tract such as constipation, dyspepsia, nausea and vomiting[5]. In addition, ginger is hypolipidemic**,** hypoglycemic, anti-atherosclerotic properties, antihypertensive**,** anti-renal injury and an antioxidant against free radicals[6,7].

Silymarin, a standardized extract obtained from seeds of *Silybum marianum*, is widely used in treatment of liver diseases of varying origin[8]. Silymarin functioned as a free radical scavenger, increasing reduced glutathione (GSH) available which functions as a detoxificant of intermediary oxygen reactive products of lipoperoxidation. Silymarin might function to inhibit enzymatic peroxidation in rats through the lipoxygenase pathway, avoiding leukotriene synthesis[9].

This work was conducted to elucidate probable changes in free radicals and antioxidants in either plasma or liver and kidney homogenates of diabetic rats induced by alloxan and to determine the mechanism of protective effect of ginger or silymarin on diabetes mellitus.

## MATERIALS AND METHODS

### Chemicals

Silymarin was obtained from CID Co. (Cairo, Egypt) and ginger from local market (Egypt). Nitric oxide and malondialdehyde assay kits were provided by Biodiagnostic Co. (Cairo, Egypt). Kits of glucose, cholesterol, triglycerides (TG), LDL–cholesterol (LDL-C), HDL–cholesterol (HDL-C) and uric acid were purchased from Spinreact, S.A. Ctra. Santa Coloma, Spain. All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO, USA).

### Preparation of ginger extract

Aqueous ginger extract was prepared as from locally available ginger roots. Ginger roots (100 g) were peeled on crushed ice and was cut into small pieces and homogenized in 150 ml cold, sterile 0.9% physiological saline solution and 50 ml ice cold water to make the volume 200 ml.

The homogenization was carried out in a blender for 12 minutes. The homogenized mixture was filtered three times through cheese-cloth. The filtrate was centrifuged at 2000 rpm for 10 min and the clear supernatant fraction was separated and volume made up to 200 ml with normal saline. The concentration of this ginger preparation was considered to have 100 mg/ml[6]. The extract was stored in sample tubes at -20°C until fed to rats.

**Induction of diabetes**

Forty male albino rats weighing 150-180 gm were used in this study were purchased from Helwan Breeding Farm, and left in our laboratory for 2 weeks before beginning the experiment for acclimatization. The ethical committee permission were gotten from Faculty of Medicine, Al-Azhar University, Cairo. The animals were kept under good ventilation and received a balanced diet and water ad libitum throughout the experimental period. They were kept at 22–24 °C with the 12 h light/dark cycle. Diabetes was induced in fasted rats (12 hrs) by a single dose intraperitoneal injection of 120 mg/kg of alloxan dissolved in 0.2 ml saline and it was used immediately after solubility[10]. Seven days later, rats were fasted overnight and administered glucose (3 gm/kg) by gastric intubation to counter hypoglycemic shock. After 2 hours of glucose administration, blood samples were taken from the tip of the tail for plasma glucose levels. The rats were considered as diabetics if the fasting blood glucose levels were higher than 250 mg / dL[11]**.** Rats in all groups were sacrificed after 4 weeks. Blood samples were collected via heart puncture into tubes containing EDTA. Liver and kidney were excised from control and experimental groups, immediately and homogenized in volume/tissue ratio of 100 mM phosphate buffer (pH 7.4), containing 22 mg% EDTA. The tissue homogenate was then stored at -20 $^{\circ}$C for determination of activities of MDA, CAT, GPx and SOD.

**Drug Administration**

The animals were randomly divided into four groups having 10 rats in each as follows:

- The first group received saline solution (i.p.) and it was kept as control.
- The second group was injected with a single dose of alloxan.
- The third group was diabetic and received daily with ginger (500 mg/kg, orally for 4 successive weeks).
- The fourth group was diabetic and received silymarin oral dose (200 mg/kg daily for 4 successive weeks), the vehicle used for silymarin was carbopol, 0.5% orally[12]**.**

The concentrations of the following substances were determined in the serum samples using the spectrophotometer: TG, total cholesterol, LDL–C, HDL-C, glucose and insulin. Uric acid was

determined by enzymatic colorimetric method**.**

**Detection of malondialdehyde and nitric oxide**

Plasma and tissue extracts lipid peroxidations were determined by quantifying malondialdehyde (MDA) concentrations[13]. The absorbance was measured photometrically at 532nm. Nitric oxide (NO) was determined in plasma as nitrite concentration after reduction of nitrate to nitrite. The reaction was performed at 22 °C for 20 min and the absorbance at 546 nm was measured using $NaNO_3$ solution as standard[14].

**Enzymatic antioxidants assays**

Superoxide dismutase (SOD) activity was determined in plasma and tissue homogenates according to its ability to inhibit the auto-oxidation of pyrogallol[15]. Catalase (CAT) activity was measured by monitoring decrease in absorbance of $H_2O_2$ at 240 nm[16]. Glutathione peroxidase (GPx) activity was determined by using cumene-hydroperoxide as the substrate and enzyme activity was monitored by recording oxidation of NADPH at 340 nm[17].

**Statistical analysis**

Statistical analysis was carried out using student ″ t ″ test. The results were expressed as mean ± S.D. (N=10). $P<0.05$ was accepted as the level of significance

## RESULTS AND DISCUSSION

Alloxan directly generates ROS and the hyperglycemia induced by this compound also produces reactive oxygen species (ROS) from the electron transport chain and glucose auto-oxidation[18]. Furthermore, protein kinase C (PKC) activated by superoxide anion induces cellular ROS which can damage pancreas, liver and kidney[19]. Free radicals produced by the reduction of alloxan to dialuric acid[20]. In the present experiment, there were significant increased in the plasma levels of blood glucose, TG, cholesterol and LDL-c while HDL-c and insulin levels are significant decreased in diabetic rats when compared with control rats. Alloxan treatment caused a significant increase in the MDA in plasma and liver while antioxidant enzymes activities of GPx and SOD showed significant decreases in plasma, liver and kidney in comparison with control rats. Hyperglycemia decreases the antioxidant capacity through glycation of the antioxidant enzyme activities of GPx and SOD. Basically, in diabetic rats increased MDA was associated with increase TG in the blood[21]**.** Increased glycation of collagen and plasma proteins in diabetes may stimulate the oxidation of lipids, which in turn may stimulate auto-oxidative reactions of sugars and continuing the cycle of oxidative stress[23].

Lipid peroxides were increased in liver, unchanged in kidney of diabetic rats. Unaltered MDA in kidney may be due to the increased resistance of kidney toward lipid peroxidation[22].

Plasma NO activity was elevated in diabetic rats as shown in Table-2. NO synthase is present in pancreatic β-cells and may be involved in the release of insulin under normal physiological conditions[23]. Induction of NO formation may play a role in β-cell death[23]. NO inhibits insulin secretion by attenuating the oxidation of glucose to $CO_2$, reducing cellular levels of ATP and, thereby, attenuating ATP-inhibited $K^+$ channel activity. The net effect is the inhibition of β-cell depolarization, entry of $Ca^{++}$, and $Ca^{++}$-dependent exocytosis. In addition to the inhibition of β-cell function, NO induces DNA damage in β-cells[24]

**Table 1: Levels of lipids profile, glucose & insulin in plasma of different groups**

| parameter | Control rats | Diabetic rats | Diabetics treated with Silymarin | Diabetics treated with ginger |
|---|---|---|---|---|
| Triglycerides(mg/dl) | 110.94± 3.08 | 170.75 ± 4.48 [a]* | 145.88±3.50 [b]* | 129.82±5.65 [b]* |
| Cholesterol (mg/dl) | 148.81 ± 5.05 | 183.44 ± 29.57 [a]* | 165.65±4.08 [b]* | 162.36±4.61 [b]* |
| HDL-C (mg/dl) | 43.43 ± 3.06 | 35.29 ± 1.42 [a]* | 43.04 ± 2.77 [b]* | 48.08±2.01 [b]* |
| LDL-C (mg/dl) | 83.74 ± 3.81 | 129.74 ± 3.30 [a]* | 96.80±7.11 [b]* | 88.04±2.67 [b]* |
| Glucose (mg/dl) | 90.64±4.50 | 387.51±7.91[a]* | 243.24±6.09 [b]* | 214.43 ± 15.10 [b]* |
| Insulin (Iu / ml) | 14.77 ± 0.97 | 8.74 ± 0.68 [a]* | 12.37±0.67 [b]* | 13.55±0.63 [b]* |

Values given are mean ± SD, (*) P < 0.05, (a) compared with the control group, (b) compared with the diabetic group.

**Table 2: Levels of Uric acid, NO, MDA, SOD, GPx in plasma of different groups**

| Parameter | Control rats | Diabetic rats | Diabetics treated with silymarin | Diabetics treated with ginger |
|---|---|---|---|---|
| Uric acid (mmol/l) | 4.20±0.55 | 11.87±0.92[a]* | 6.84±0.63 [b]* | 5.45±0.58 [b]* |
| NO (ng / ml) | 36.56±1.29 | 49.12±1.84[a]* | 43.50±1.27 [b]* | 48.4±1.17 [b] |
| MDA (nmol/ml) | 3.31±0.81 | 8.33±0.70[a]* | 3.02 ± 0.50 [b]* | 3.84±0.54 [b]* |
| SOD (ng/ml) | 115.3±2.00 | 71.7±2.91[a]* | 111.8±5.94 [b]* | 108.8±3.41 [b]* |
| GPx (u/ml) | 66.80 ± 1.81 | 46.8 ±1.8[a]* | 66.5± 1.90 [b]* | 62.3 ±1.83 [b]* |

Values given are mean ± SD, (*) P < 0.05, (a) compared with the control group, (b) compared with the diabetic group.

**Table 3: Levels of MDA, CAT, GPx and SOD in tissue homogenates of liver & kidney in different groups**

| Parameter | Control rats | Diabetic rats | Diabetics treated with silymarin | Diabetics treated with ginger |
|---|---|---|---|---|
| MDA (nmol/g proteins) | | | | |
| Liver | 36±2.54 | 83.1±2.22 [a]* | 60.8±2.30 [b]* | 65.6±1.43 [b]* |
| Kidney | 25.7±1.16 | 28.7±2.11 | 26.8±1.55 | 27.7±0.95 |
| CAT (μ/mg proteins) | | | | |
| Liver | 27.2±1.75 | 26.9±1.37 | 24.9±1.52 | 32.4±1.07 |

| | | | | |
|---|---|---|---|---|
| Kidney | 14.5±1.27 | 12.11±0.49 | 13.28±0.71 | 12.47±0.76 |
| GPx (µ/mg proteins)<br>Liver<br>Kidney | <br>23.8 ±1.55<br>16.3 ±1.25 | <br>14.7 ±1.16 [a]*<br>11.52±0.79 [a]* | <br>22.5 ±1.08 [b]*<br>10.03±0.52 [b]* | <br>19.2 ±1.69 [b]*<br>7.73 ±0.82 [b]* |
| SOD (ng/mg proteins)<br>Liver<br>Kidney | <br>7.6±1.07<br>5.9±0.88 | <br>5.86±0.72 [a]*<br>2.13±0.34 [a]* | <br>7.19±0.53 [b]*<br>5.24±0.64 [b]* | <br>6.29±0.50 [b]*<br>4.35±0.44 [b]* |

Values given are mean ± SD, (*) P < 0.05, (a) compared with the control group, (b) compared with the diabetic group.

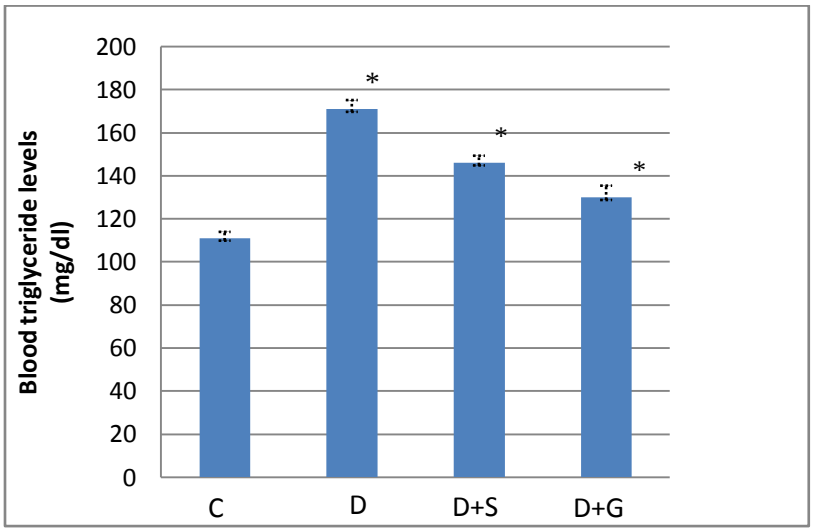


**Figure 1: Plasma triglyceride levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). * P<0.05.**

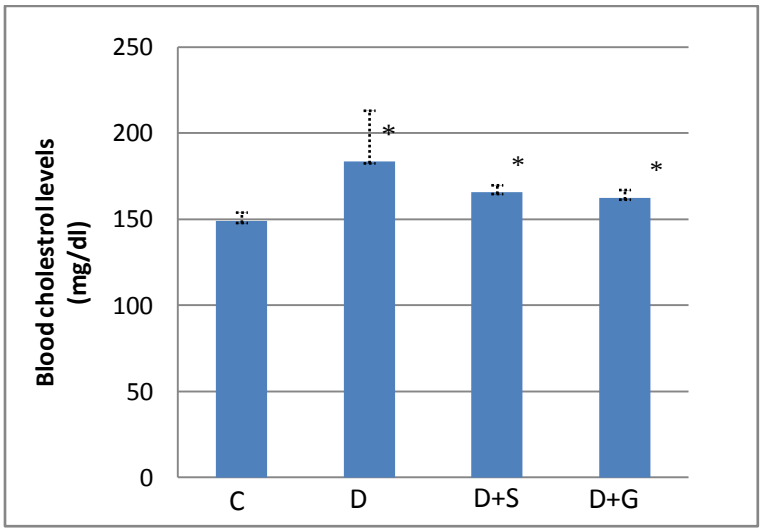


**Figure 2: Plasma cholesterol levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). * P<0.05**

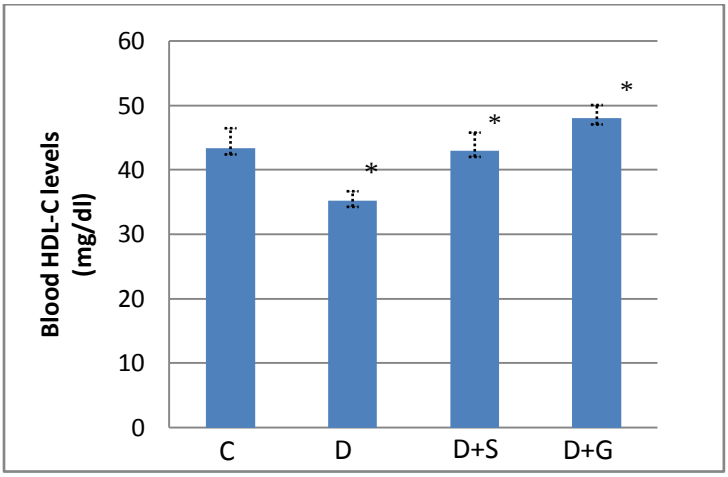


**Figure 3: Plasma HDL-C levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). * P<0.05.**

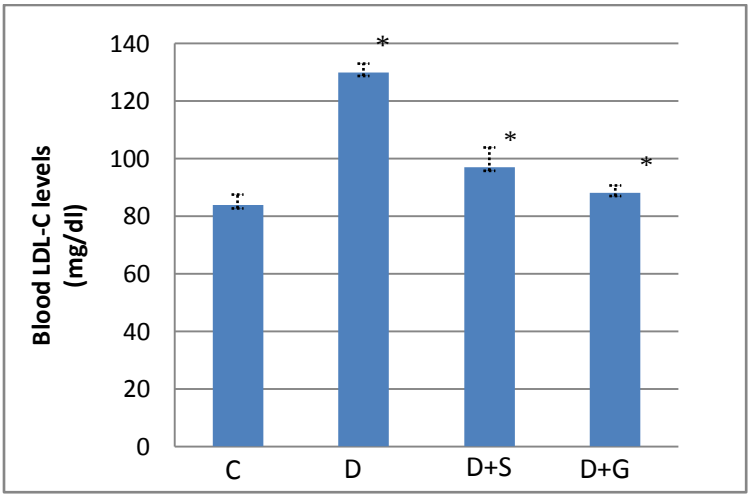


**Figure 4: Plasma LDL-C levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). * P<0.05.**

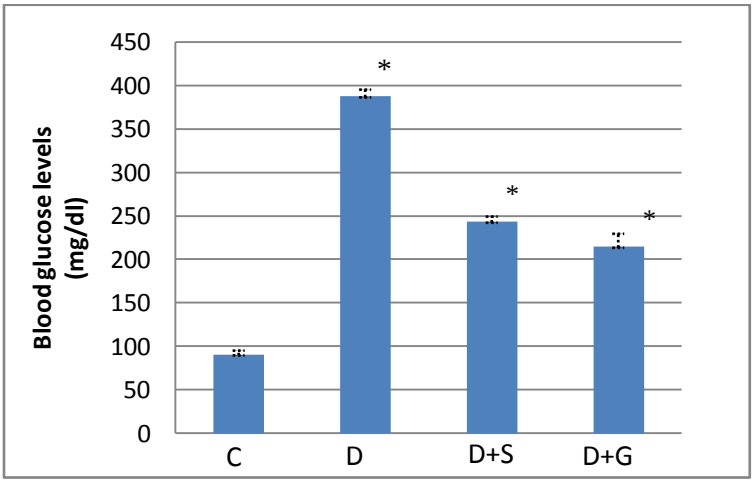


**Figure 5: Plasma glucose levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). * P<0.05.**

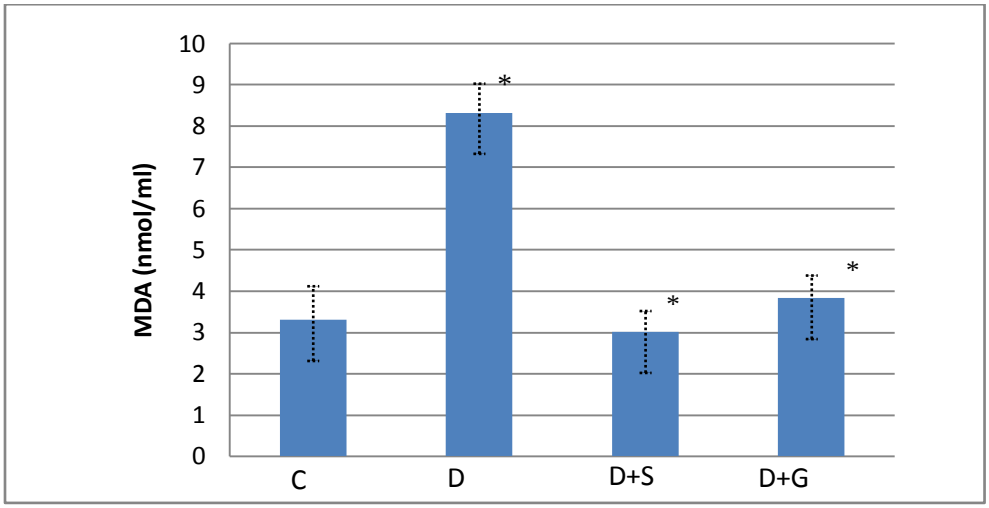


**Figure 6: Plasma MDA levels in control (C), diabetic (D) treated with silymarin (D+S) and diabetic treated with ginger (D+G). *P<0.05.**

Oral administration of ginger extract effectively lowers plasma glucose and increased the insulin level. However, it should be noted that all the previous values in ginger-treated diabetic rats did not reach normal levels at the dosage used in the present experiment as shown in Table-1. Ginger extract produced a significant increase in glucose-induced insulin release from the pancreas of alloxan-diabetic rats. This effect was more prominent in the presence of exogenous serotonin[25]. The serotonin receptor blocking activity of ginger and its component since serotonin has been reported to induce hyperglycemic and hypoinsulinamia[26]. It was found that ginger can act on 5-HT3 receptor ion channel complex by binding to a modulatory site distinct from the serotonin binding site[27]. Ginger extract enhanced glucose uptake in cultured L6 rat skeletal muscle cells and 3T3-L1 adipocytes[25,28].

Treatment of diabetic rats with ginger extract reduced serum TG, total cholesterol and LDL-c while HDL-c levels are increases and the hypocholesterolemic effects of ginger stem from the inhibition of cellular cholesterol synthesis. The attenuation of cholesterol synthesis results in augmenting the LDL receptor activity, leading to the elimination of LDL from plasma. It is well established that insulin resistance in peripheral tissues is tightly associated with elevated circulating lipids and tissue lipid accumulation. The mechanism studies showed that excessive free fatty acid and fatty acid oxidation inhibited glucose transport into peripheral tissues, the first rate-limiting step in glucose metabolism[29]. Ginger possessed prominent lipid lowering effects, and subsequently increased insulin sensitivity[28].

Treatment with ginger extract minimized intracellular oxidative stress and then may increase the activity of GPx in treated rats[30]. Then, a decrease in the MDA level was accompanied by

significant increases in the activities of GPx, CAT and SOD and thus causing inactivation of lipid peroxidation in ginger-treated diabetic rats. The antioxidant defense activity of ginger extract via the induction of Nrf2/ARE-mediated antioxidant enzyme HO-1 coupled with p38 MAPK pathway in cell line level[31]. Moreover, the normalization of lipid peroxides in the diabetic rats that was treated by ginger extract inhibited the thiobarbituric acid-reactive substances (TBARS) levels in liver and renal tissues[32].

There were significant decreased in the plasma levels of glucose, TG, cholesterol and LDH-c while HDL-c and insulin showed significant increases in diabetic rats treated with silymarin as shown in Table-1. This result suggested the effective treatment of silymarin against alloxan action. It has been shown that silymarin prevents the damage induced by oxidative agents in hepatic membranes, microsomes and mitochondria[33]. These observations of the effect of silymarin in the area of hepatocyte protection may contribute to explaining why this compound has a protective effect on lipid peroxidation with the recovery of the ß-cells function. This, in turn, may contribute to the regulation of plasma glucose. The effects of silymarin on plasma glucose and lipid peroxidation produced by alloxan may be related to the significant rise in plasma GPx. Silymarin induced an increase in pancreatic glutathione content which may induce the GSH/GSSG ratio[34].

Treatment with silymarin reduced plasma levels of MDA, NO and uric acid while elevating enzymatic and non-enzymatic antioxidant systems in blood and liver and kidney homogenates as shown in Table-1,2. Silymarin had a potent reducing effect on the production of MDA in rats exposed to oxidative stress with diethylnitrosamine[35]. The reduction of NO levels may be due to inhibition of NO synthase enzyme activity by silymarin[36]. Silymarin reduced the lipopolysaccharide (LPS)-induced nitrite, iNOS mRNA and protein levels in a dose-dependent manner[36]. Moreover, LPS could induce the activation of p38 mitogen-activated protein kinase (MAPK) and c-jun N-terminal kinase but not extracellular signal-regulated kinase. These indicated that the p38 MAPK signaling pathway was involved in the LPS-induced NO production. However, the activation of p38 MAPK was not inhibited by silymarin. Uric acid is considered as one of non-enzymatic antioxidant, but increased production of uric acid means increased free radical production due to activation of the xanthine oxidase enzyme system[37]. This may be due to metabolic disturbance in diabetes reflected in high activities of xanthine oxidase, lipid peroxidation and increased TG and cholesterol[38]. Moreover, protein glycation in diabetes may lead to muscle wasting and increased release of purine, the main source of uric acid as well as in activity of xanthine oxidase. The reduction in uric acid levels after silymarin treatment may

be due to reduction of MDA, TG and total cholesterol, while elevation of these substances may increase uric acid synthesis. Moreover, silymarin produced a dramatic decrease in free radicals production and increased the activities of SOD, CAT and GPx activities in plasma, liver and kidney tissues.

## CONCLUSION:

Ginger extract and silymarin have significant potential in the treatment of diabetes through decreasing blood glucose, blood lipids, free radicals and increasing antioxidative enzyme activities. The antioxidant effects of silymarin were better and caused dramatic elevation in the antioxidant activity and reduced oxidative stress. However, ginger is better than silymarin in lowering blood glucose levels and lipid profile. However further studies are still required to entirely cover the protective effect of ginger and silymarin on diabetes mellitus and in order to isolate the pharmacological compounds responsible for the effect of ginger and silymarin

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