

# Comparative Regulatory Effects of Morus Alba Leaf Extracts on Hepatic Enzymes in Streptozotocin-Induced Diabetic and Non-Diabetic Rats

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## Abstract

**Aim and objectives:** Diabetes is a metabolic disorder with hyperglycemia due to defects in insulin secretion and function. Several studies investigated the both effects of traditional herbal medicine in diabetes treatment. Therefore, the aim of the present study was to investigate the effects of Morus Alba leaf Extracts (MAE) on hepatic enzyme activity in normal and streptozotocin-induced diabetic rats.

**Methods:** Forty healthy adult male Wistar rats weighing  $250 \pm 10$  gr were taken for this experiment. Rats were divided into 4 groups (10 rats in each group). Animals treated by a gavage tube for a period of two months as follow: group I: non diabetic control rats which only received distilled water; group II: non-diabetic rats that received (MAE) 1.0 g/kg per day; group III: diabetic control rats treated with distilled water and group IV: Diabetic rats which received MAE 1.0 g/kg per day. At the end of the 8th week, blood samples were collected and serum levels of enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and total bilirubin were measured in all study groups using commercial assay kits. The activity of two antioxidant enzymes including glutathione peroxidase (GPX) and glutathione reductase (GR) were also measured.

**Results:** Findings of present study demonstrated that MAE significantly decreased serum levels of liver enzymes ALT, AST and ALP in diabetic rats in compare to the diabetic control groups while it increased GPX and GR activity ( $P < 0.05$ ). These results also indicated that MAE did not significantly affect LDH activity in diabetic rats treated with MAE in compared to the diabetic control groups.

**Conclusions:** According to the present findings it could possibility be suggested that the anti-hyperglycemic effect of MAE is mediated at least partially by increasing liver GPX and GR activity as well as decrease serum levels of liver enzymes ALT, AST and ALP. These results are the other definite evidence supporting MA as traditional medicine for diabetic patients.

**Keywords:** Morus Alba (Mulberry) leaf; Type 1 diabetes; Liver enzymes

## Introduction

According to the WHO reports, the diabetes mellitus (DM) will be the single largest non-communicable disease worldwide by the year 2025 with the largest diabetic population in India [1]. DM is a common disease in the world, with an increase in blood glucose, lipid and carbohydrate metabolism is impaired. An estimated 17 million people with diabetes in the world (2.4%) in 2000 to 366 million (4.4%) reached in 2030 [2]. Evidences suggest that oxidative stress and free radical production play important roles in diabetes and its pathogenesis [3]. The role of free radicals in tissue damage in streptozotocin-induced diabetic rats has also been demonstrated [4]. Liver is effectively maintain normal blood glucose levels and hyperglycemia leading to an imbalance in the reduction of oxidation reactions in the hepatocytes [5]. Thus it appears that the diabetic liver injury is induced by a several factors and cannot be controlled only with inhibiting hyperglycemia [6]. In other words, although in the early stages of diabetes, hyperglycemia-induced liver injury, occurs but its progression is linked to the maintenance of hyperglycemia [7]. Thus, controlling of blood glucose alone is not sufficient to delay or prevent diabetes complications. Living cells are protecting (by their multiple mechanisms against damage) from free radicals. Antioxidant enzymes Superoxide Dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase play a pivotal role in this regard. One important strategy of the areas of research in diabetes treatment is reducing the amount of free radicals [8]. In this regard, the effects of antioxidants

in preventing or reducing damage from free radicals in diabetes have been investigated [9]. Therefore, a promising drug for the treatment of diabetes should ideally have both hypoglycemic and antioxidant properties. Synthetic drugs in lowering blood glucose, not only are unable to control tissue damages in this disease but they also can cause many side effects [6]. Thus, pharmaceutical science saves looking for ways to be able to develop medication with minimal side effects. At present, consumption of herbal and natural medicines are more popular than synthetic drugs and this is an issue that is very important. Plants that we know as herbal plant compounds are numerous. These compounds together create a balanced situation and in this situation, none of the possessor compounds would have detrimental effects. Because they modify other properties and some compounds have the

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same task to counteract the effects of other compounds [10]. *Morus Alba* (MA) is a tropical and subtropical plant that grows in many parts of Asia. The importance of medicinal plants in the treatment of diseases such as gout backs to the ancient Chinese. Additionally MA is used for high blood pressure, diabetes and bacterial infections and different parts of the plant, especially the leaves and roots are used as herbal medicines [11]. Today, more attention attracted to the leaves of this plant, in some East Asian countries, a tea-like beverage is produced and is commercially available at markets [12]. Leaves of MA contain different compounds including salt, proteins, fibers, fats, carbohydrates, vitamin C,  $\beta$ -Carotene, iron, zinc, calcium and tannic acid. In addition, compounds such as dihydroxycoumarin, prenylflavone, cudraflavone B, Cresverato and oxyreseratrol are found to have anti-inflammatory and anti-oxidants properties that serve as free radical scavenger [13]. It has been established that plants reduce glucose, lipids, strengthening the body's antioxidant defense system and almost improve diabetes complications [14]. The MA leaf contains active compounds that can inhibit  $\alpha$ -galactosidases such as 1-deoxynojirimycin [15], and this may aid suppression of postprandial by reducing the rate of digestion and absorption of carbohydrates from intestines [2].

## Materials and Methods

### Preparation of MA leaf extract

Leaves of MA were collected from the local farms in south-eastern part of Iran (Rafsanjan, Iran) in the month of April. Following authentication by botany department of Vali-Asr University, dried MA leaves were extracted with 50% ethanol. The mixture was filtered, evaporated in vacuum evaporator (percolation method) and then lyophilized in order to obtain the dry extract [16]. Using this procedure, the yield was 22% of the starting dry weight of the leaves. The obtained MA leaf extract was kept in air-tight container at  $-80^{\circ}\text{C}$  for further use.

### Animals

All of animal procedures were approved by the Rafsanjan University of Medical Sciences ethical committee board. Male albino Wistar rats weighting ( $250 \pm 10$  g) were obtained from the experimental animal unit, faculty of medicine, Rafsanjan University of Medical Science, Rafsanjan- Iran. They were housed in an air-conditioned room ( $25^{\circ}\text{C}$ ), 12 hour dark/light cycle which had free access to standard diet and tap water.

### Induction of diabetes

Diabetes was induced by injection of a single Intra-peritoneal dose of 50 mg/kg STZ dissolved in 0.1 M citrate buffer (pH 4.5). Seven days after STZ (Sigma-USA) injection, blood was collected from the animal's tail vein and fasting level of blood glucose was measured. Animals were considered as diabetic, if had a fasting blood glucose level over 300 mg/dL and then were recruited in further assessments.

### Experimental design

Forty healthy adult male Wistar rats (eight weeks old) were used in this experiment. Rats were divided into 4 groups (10 rats in each groups). Animals treated by a gavage tube for a period of 56 days as follow: group I: non diabetic control rats which only received distilled water; group II: non-diabetic rats that received (MAE) 1.0 g/kg per day; group III: diabetic control rats treated with distilled water and group IV: Diabetic rats which received MAE 1.0 g/kg per day. At the end of the 8<sup>th</sup> week, all of rats were anesthetized and humanely killed. Blood samples were collected and the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)

and lactate dehydrogenase (LDH) were measured in all study groups by activity assay kit (Sigma-Aldrich) with BT-3000 auto analyzer (England). Livers were immediately excised, washed with ice cold normal saline and kept frozen at  $-70^{\circ}\text{C}$  until use. Liver tissue (1g) were homogenized using Ultra-Turrax homogenizer in 10 ml of normal saline and centrifuged at 8000 xg for 15 min at  $4^{\circ}\text{C}$ . The resulting supernatants were used for the determination of GPX and GR.

### Assay of glutathione peroxidase (GPX) and glutathione reductase activity (GR)

These were determined according to Jakoby[17].

### Statistical analysis

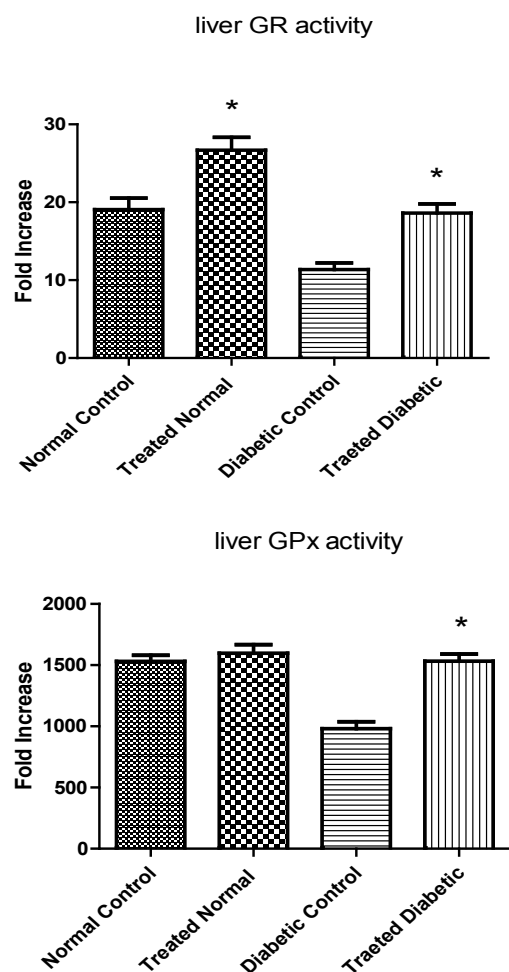
Data are reported as Mean  $\pm$  SEM (standard error of the mean). The difference between groups was evaluated using one-way analysis of variance (One Way ANOVA) and student t-test using SPSS version 18 statistical software. P values of less than 0.05 were considered significant.

## Results

In the present study we examined the impacts of MAE on enzymes activity such as GR and GPX and also serum levels of AST,ALT,ALP and LD enzymes and BT and BD in diabetic male rats following a period of 56 days orally treatment. As shown in Figure 1, the MAE significantly enhanced GR and GPX activities in diabetic treatment group compare to control ( $p < 0.05$ ). Our data analysis showed that the treatment of animals with MAE enhanced glutathione reductase (GR) activity in either normal or treated diabetic treatment group in compare to control ( $p < 0.05$ , Figure 1) . Our results also demonstrated that AST and ALT levels were significantly decreased where diabetic rats were treated with MAE ( $p < 0.05$ ), (Figure 2). Treatment of animals with MAE also significantly decreased the ALP level in diabetic MA treated rats in compare to diabetic control group ( $P < 0.05$ ) but MAE did not significantly decreased LD level in treatment group that in compared to control (Figure 3). Findings of the current study also indicated that BT (bilirubin total) and BD (bilirubin direct) serum level in treatment group in compare to control group (Figure 4). Also when animals fed with MA leaf extract the FBS level was also significantly decreased in compare to control ( $p < 0.05$ ), (Figure 5).

## Discussion

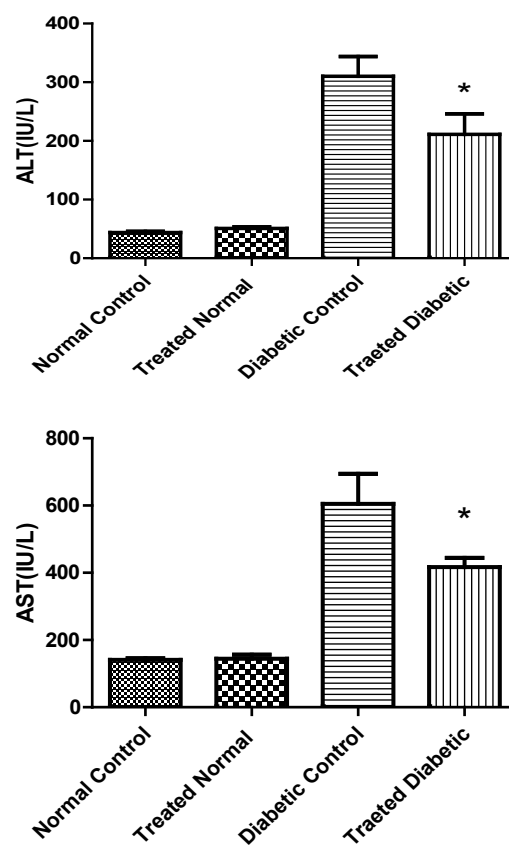
Mechanisms involve in elevation of oxidative stress in diabetes are mostly auto oxidative glycosylation, nonenzymatic glycation, metabolic stress resulting from changes in energy metabolism, changes in the level of inflammatory mediators and the status of antioxidant defense systems [18]. Several serum enzymes such as ALT and AST are defined as biomarkers of hepatocellular injuries. ALP is also a favorite indicator for hepatobiliary disease. ALP is mostly accumulated within the biliary canaliculi and belonging to a group of phosphatases found in at least all of body tissues. ALT, AST, gamma-glutamyl transferase (GGT), ALP and LD enzymes are released into the circulation from the cytosol and subcellular organelles of hepatocytes, once liver is injured or damaged [19]. The relationship between glycaemic metabolic control and intracellular concentration of reduced glutathione (GSH) and related enzymes GSH-peroxidase (GSH-Px), GSH-reductase (GSH-Red), GSH-transferase (GSH-Tr), glucose-6-P-dehydrogenase (G6PDH), and thioltransferase (TT) in insulin-dependent diabetes mellitus (IDDM) patients is controversial [20]. Glutathione (GSH) is an important intracellular factor that prevents the accumulation of hydroperoxides and plays a role in formation of arachidonic acid



**Figure 1:** The effects of MA on activity of liver GPx and GR enzymes, values are Means  $\pm$  SEM. Of 12 rats in each group, MA: MORUS ALBA LEAVES EXTRACT, GPx: glutathione peroxidase, GR: glutathione reductase. \* = significant difference with control subjects.

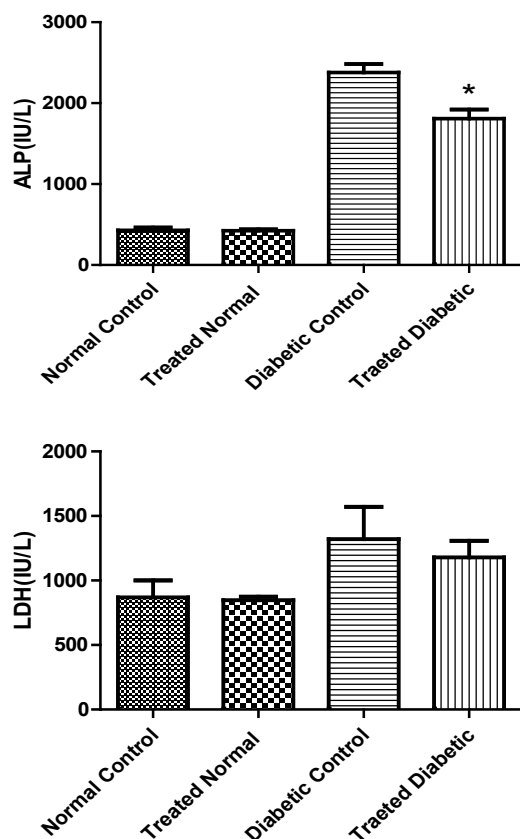
metabolites [21]. GSH biosynthesis and degradation as well as its inter-conversion from the oxidized to the reduced form is complex. Glutathione reductase (GSH-Red) catalyses the conversion of oxidized to reduced GSH, utilizing NADPH [22] which derives from the hexose monophosphate shunt and this process is altered in diabetic individuals [23]. Our results revealed that treating the diabetic rats with MAE could significantly enhance glutathione reductase (GR) and glutathione peroxidase (GPx) activities in diabetic treatment group compared to control. Our results also revealed that diabetic rats fed with MA leaf extract had significantly decreased AST, ALT and ALP levels in diabetic treatment group compared to control. But MA leaf extract did not significantly decrease LD level in treatment group compared to control. More examinations in the field of anti-hyperglycemic properties of medicinal plants or herbal components are deserved WHO (world health organization) as the number of diabetic patients is also continuously growing. The MA extract components, especially flavonoids (i.e. quercetin, rutin, and isoquercitrin), are among free radical scavengers family and indicating the possibility of antioxidant activity [24]. Antioxidant balance is altered by reducing the activity of catalase, superoxide dismutase and glutathione peroxidase and total antioxidant levels that may lead to insufficiency of antioxidant defense

against damages induced by ROS. Although, glutathione peroxidase enzyme is relatively stable, but it has been reported that is disabled at severe oxidative stress conditions [25]. Ugochukwo and colleagues showed that glutathione peroxidase activity and total antioxidant levels in diabetic rats increases [26]. The results obtained by Andallu, Sekeroglu and colleagues showed that levels of total antioxidant and glutathione peroxidase activity in diabetic mice reduced, the results of the present study also showed that reduced factors in diabetic rats [27]. Decrease in glutathione peroxidase activity may be due to glycation antioxidant enzymes by glucose [28]. Recently Grazler and colleagues shown that glutathione peroxidase by Peroxynitrite inactivated that is an oxidant potential [29]. Components of total antioxidant such as vitamin E and glutathione, cause removal of free radicals from the body. Thus, reduce glutathione peroxidase activity in diabetic rats which was observed in this study may reduce the total antioxidant response and thus increase the production levels of  $H_2O_2$  and  $O_2^-$  via nonenzymatic glycation and auto-oxidation glucose [30]. In this study, mulberry leaf extract increased the level of enzyme activity. Studies conducted by Soo-Yeul and colleagues with flavonoid substances, indicated increased activity of glutathione peroxidase, glutathione reductase and total antioxidant levels in diabetic rats that have received these compounds [31]. Because MAE containing abundant isoflavones, it is possible role of extract in increasing glutathione peroxidase activity and plasma antioxidant levels related to neutralize free radicals, especially hydroxyl radicals. It is also probable that the extract directly activates the enzyme glutathione peroxidase or increase expression it. The antioxidant compounds



\* = significant difference with control subjects

**Figure 2:** The effects of MA on serum levels of AST and ALT enzymes, values are Means  $\pm$  SEM. Of 12 rats in each group, MA: MORUS ALBA LEAVES EXTRACT.

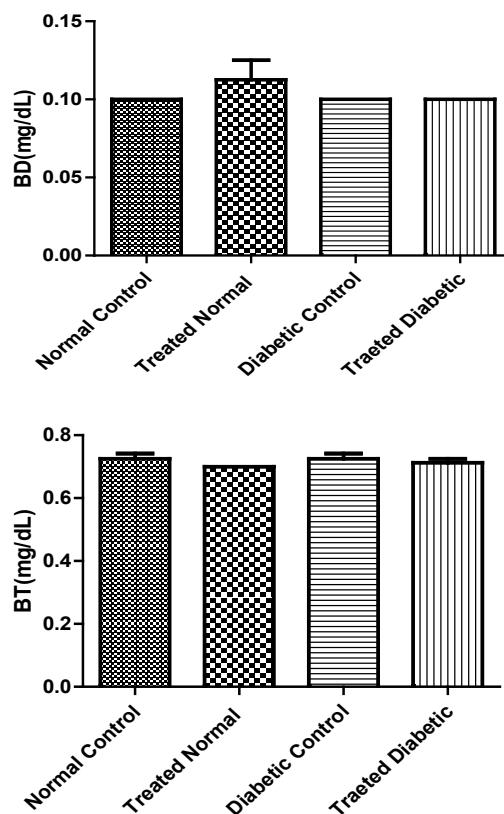


\*= significant difference with control subjects

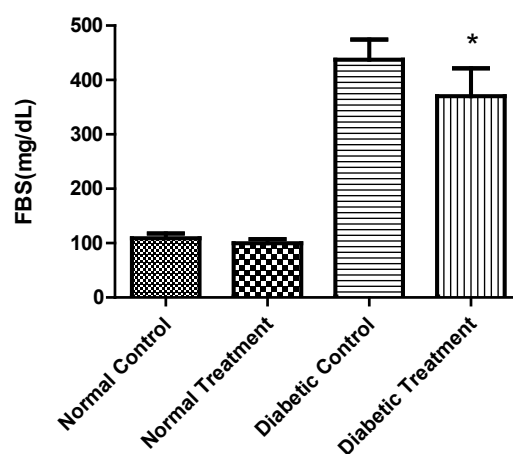
**Figure 3:** The effects of MA on serum levels of ALP and LDH enzymes, values are Means  $\pm$  SEM. Of 12 rats in each group, MA: MORUS ALBA LEAVES EXTRACT.

in MA enter to the circulation via passing through small intestine, where they do perform their biological functions as antioxidant [32]. The quercetin, metabolites are produced by microbial flora of the gut and retain systemic antioxidant activity [33]. Anthocyanin is another antioxidant reagent abundantly found in wild MA fruit and is absorbed from gastrointestinal tract, which even at the trace amount, giving antioxidant activity in plasma [34]. Growing evidences are in favor of the fact that structural damage to organs and tissues, or complications of DM, could be due to oxidative stress. Oxidative stresses may also play critical part in the development of STZ-induced diabetes in one side, and mitochondrion are proposed as a target organelle or STZ-induced toxicity processes on the other side [35]. Natural polyphenols are abundant biomaterials with plant origin and thousands of polyphenols have been discovered in natural products to date. The two main types of polyphenols are flavonoids and phenolic acids [36]. Polyphenols present in food and beverage, demonstrated to have potentially health benefits due to their antioxidant activities. These polyphenols are believed to acting protect cell constituents against oxidative stress as well as controlling tissue damage by directly on reactive oxygen species or by stimulating endogenous antioxidant defense systems [37]. Consequently, they may decrease the risk of various metabolic disorders, which are closely associated with oxidative stress damage. In fact, other investigators proposed that some types of polyphenol are capable of limiting the development of DM [38], cardiovascular disease [39], and cancer [40]. It has been suggested that polyphenols may modulate hyperglycemia through various mechanisms. First, they

reduce glucose absorption from intestinal mucosa and proximal renal tubule by inhibiting  $\alpha$ -glucosidase and/or sodium-glucose symporter in the peripheral tissues [41]. Second, polyphenols decrease hepatic gluconeogenesis [42], and induce adrenergic stimulation of muscle glucose uptake [43] and pancreatic B cell insulin release [44].



**Figure 4:** The effects of MA on serum levels of BT (bilirubin total) and BD (bilirubin direct) enzymes, values are Means  $\pm$  SEM of 12 rats in each group, MA: MORUS ALBA LEAVES EXTRACT.



\*= significant difference with control subjects

**Figure 5:** The effects of MA on FBS levels, values are Means  $\pm$  SEM of 12 rats in each group, MA: MORUS ALBA LEAVES EXTRACT, FBS: Fasting Blood Sugar.

## Concluding Remarks

Overlay the present study, MA leaf extract was found to decrease AST, ALT, ALP and LD levels in STZ induced diabetic rats, increase and modulate the activating of glutathione reductase (GR) and glutathione peroxidase (GPx), the enzymes involved in the processes of stress oxidative. However, this work is insufficient to precisely address the exact role of MA leaf extract on DM, more well designed studies and required to evaluate mechanisms of MA action of active constituent. Our study in a way may probably confirm the antihyperglycemic and strong antioxidative effects of the MA leaf extract in diabetic rats. These results also support the role of antioxidant therapy in diabetic complications.

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