

## Hypoglycemic and Antioxidant Effect of *Morus alba* L. Stem Bark Extracts in Streptozotocin-Induced Diabetes in Rats

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### Abstract

The present study aims to evaluate the antidiabetic effect of *Morus alba* L. stem bark extract in experimental model of diabetes. The animals were divided into six groups as: control group (I); pathogenic control group (II) injected intravenously (i.v.) with single dose of STZ (60 mg/kg); *M. alba* stem bark extract (group-III; 200 mg/kg), and group-IV (400 mg/kg); group-V animals treated with glibenclamide (5 mg/kg, p.o.) following STZ treatment; group-VI, animals treated with bark extract per se (400 mg/kg). The results of this study showed a significant increase in lipid peroxidation, blood glucose level, glycosylated hemoglobin level, and reduction in glutathione and insulin level after STZ administration. These parameters were significantly ( $p < 0.05$ ) reversed by extracts dose dependently. The biochemical findings were also supported by histopathological studies of pancreas where STZ produced histological changes in pancreas and treatment with *M. alba* stem bark extract restored these changes. Thus, we conclude that *M. alba* stem bark extracts produced significant antidiabetic and antioxidant effect which might be due to the presence of bioactive components such as phenolic and flavonoid content in the extract. The study warrant the need for further evaluated in certain other models of diabetes.

**Keywords:** *Morus alba*; Stem bark; Streptozotocin; Glibenclamide; Diabetes

### Introduction

Since antiquity the nature has been a source of medicinal agents. The importance of herbs in the management of human ailments cannot be overemphasized. It is clear, that the plant kingdom harbours an inexhaustible source of active ingredients [1,2]. The Indian traditional system of medicine is replete with the use of plants for the management of diabetic conditions. There are about 800 plants which have been reported to show antidiabetic potential [3]. The leaves and root bark preparations from *Morus alba* have been used in traditional phytomedicine.

Diabetes is a chronic metabolic disorder that continues to present a major worldwide health problem, characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycaemia and disturbances of carbohydrate, lipid, and protein metabolism. It is fast growing disease, gains the status of a potential epidemic in India with prevalence of more than 62 million diabetic individuals currently diagnosed with the diabetes [4]. Globally diabetes is considered as most common and largest endocrine disorder and it is the fifth leading cause of death in the world [5]. Wild et al. [6] reported the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.

It has been reported in both preclinical and clinical studies that oxidative stress plays an important role in the pathogenesis of both types of diabetes mellitus. There is disproportionate production of free radicals in diabetes due to oxidation of glucose, nonenzymatic glycation of proteins, followed by subsequent oxidative degradation of glycated proteins. Insulin resistance as result of increased lipid peroxidation is associated with abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzyme. The development of complications of diabetes is the consequence of high oxidative stress in both types of diabetes.

Streptozotocin (STZ), an antibiotic produced by *Streptomyces achromogenes*, clinically used for the treatment of certain cancers of the Islets of Langerhans because of its selective toxicity to the insulin-producing  $\beta$ -cells of pancreas. Therefore, it has been widely used in medical research for induction of type 1 diabetes in a variety of animals by affecting degeneration and necrosis of pancreatic  $\beta$ -cells [7]. Ample of accumulating evidence suggests that free radicals play a crucial role in the streptozotocin-induced diabetes. In addition it has been reported that streptozotocin produced oxidative stress and depletion of antioxidant systems in both blood and tissues particularly, liver [8]. Moreover, Kedziora et al. [9] found a reduction in antioxidant systems and elevation in lipid peroxidation in kidney of streptozotocin-induced diabetic rats.

Plants have always been a source of drugs for humans since time immemorial. Interestingly, a report of World Health Organization (WHO) estimated that up to 90% of the population in developing countries uses plants and its products as traditional medicine for primary health care [10]. Out of the 21,000 WHO listed plants which are used for medicinal purposes around the world about 2500 plant species are present in India [11]. A wide collection of plant-derived active principles representing numerous bioactive compounds have established their role for possible use in the treatment of diabetes [12].

The genus *Morus*, consists of over 150 species; among them, *M. alba* is predominant species [13], found in temperate to subtropical regions

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of the Northern hemisphere to the tropics of the Southern hemisphere. *M. alba* Linn commonly known as white mulberry belongs to family Moraceae is also known as Tut in India. It is cultivated throughout the world, wherever silkworms are raised. Several parts of *M. alba* has been reported for their medicinal importance particularly in ayurveda and in folklore. *M. alba* has gained the status of nature's functional tonic because of its unique nutritional profile containing proteins, phenolics, flavonoids and anthocyanins. Its bark, fruits, and leaves have been used also in both conventional and natural medicine. Mulberry plant extract has been reported in various experimental studies to exhibit potent antioxidant activity [14], antitumor activity [15], hypolipidemic effect [14], macrophage activating effect [16], and neuroprotective activity [17]. The bark of the large stem is brown, rough, fissures mostly vertical, considered as vermifuge and purgative. Furthermore, polyphenolic compounds especially the flavonoids and among the flavonoids quercetin 3-(6-malonylglucoside) is most significant for antioxidant potential of mulberry plant [18]. To our knowledge, there were no reports regarding the hypoglycemic effect of *M. alba* stem bark. Therefore, it is interesting to elucidate the antioxidant and antidiabetic effect of *M. alba* stem bark extracts in experimentally induced diabetes in animals.

## Materials and Methods

### Drugs and chemicals

Streptozotocin was purchased from Sigma Aldrich, USA. Glibenclamide was obtained as gift from Panacea Biotech, Baddi, and Himachal Pradesh, India. Serum insulin ELISA kits for rats were purchased from Genxbio, manufactured by Cusabio (China). Blood glucose level was measured using commercial diagnostic kits manufactured by SPAN diagnostics, Surat, India. Whereas glycosylated haemoglobin level in whole blood sample was measured by the methods recommended by Reckon diagnostics, Gujrat, India. All others reagents and chemicals used in this study were of analytical grade.

### Plant material

The stem bark of *Morus alba* L. was procured from Rawal HerMed consultants, New Delhi, India. The plant material was authenticated by Dr. H.B. Singh, Scientist F and Head, Raw Materials Herbarium and Museum, National Institute of Science Communication and Information Resources (NISCAIR), New Delhi. A voucher specimen (RIVTE-06/15) has been kept for further reference.

### Preparation of the stem bark extract

The air-dried powdered stem bark (2 kg) of *M. alba* were defatted with petroleum ether (60-80°C) in a soxhlet extractor and then with chloroform. The defatted material was further extracted exhaustively with 70% ethanol at ambient temperature. The ethanolic extract was concentrated in rotary evaporator at 35-40°C under reduced pressure. The concentrate is stored at 2-8°C until the completion of pharmacological studies. 100 mg of *M. alba* stem bark extract was suspended in 0.5 ml distilled water and administered orally to the rats through an intragastric tube at a dose of 200 mg/kg and 400 mg/kg body weight. The vehicle was used as a control throughout the study.

### Animals

Male wistar albino rats (150-200 g) were raised from animal facility of Ram-Eesh institute of vocational and technical Education, Greater NOIDA, and Uttar Pradesh, India. They were housed in polypropylene cages (6 animals per cage) under natural light-dark cycle. The animals were fed with standard pellet diet (Amrut rat and mice feed, Pune,

India) and allowed to drink water *ad libitum*. The animals were treated in the most humane and ethically acceptable manner with maximum care to ensure that the animals were treated. The study was undertaken with prior approval from the Institutional Animals Ethics Committee (CPCSEA/2/2015/403).

### Experimental protocol

Diabetes was induced in overnight fasted animals by STZ (60 mg/kg, I.V.) [19]. The STZ was dissolved in freshly prepared citrate buffer (0.1 mol/ml, pH 4.5). The blood glucose was measured after 3 days following the STZ administration to confirm the induction of diabetes. The rats were divided at random into six groups of 6 animals each. Group I animals served as normal control (received normal saline only). Group II as toxic control, treated with STZ (60 mg/kg, i.v.). The animals of group-III, IV were treated with graded doses (200 and 400 mg/kg respectively) of ethanolic extract of *M. alba* stem bark. Glibenclamide was administered at dose of 5 mg/kg to positive control animals (Group V). Animals of group VI were treated with MASBE (400 mg/kg) per se. The animals of group II-V were made diabetic by injection of a single dose of STZ (60 mg/kg; i.v.). STZ-treated rats were given 5% glucose in their drinking water for the first 24 h to counter any initial hypoglycemia. Urine glucose level was checked on day third of STZ administration by using enzymatic test strips. The drug treatment lasted for 21 days after the induction of diabetes. Blood sample was collected for biochemical estimation in serum and finally the animals were sacrificed under ether anesthesia for dissection of pancreas for biochemical measurements in tissue and histopathological studies on the last day of treatment.

### Biochemical estimations in blood

At the end of treatment (21 days), blood samples were collected from the tail vein of rats. Whole blood was used for estimation of blood glucose and glycosylated haemoglobin

(HbA1C) level by using the methods prescribed in the commercial kits. Serum was separated for estimation of serum insulin level by using the commercial rat specific serum insulin ELISA kit manufactured by Cusabio (China).

### Biochemical estimations in tissues

The rats were sacrificed and pancreas were immediately excised and washed in ice-cold normal saline and weighed. Subsequently, pancreatic tissue pieces of all the groups were weighed, homogenized (10% w/v) in chilled phosphate buffer (50 mM and 0.1 M, pH 7.4) and/or potassium chloride (1.17%), and centrifuged at 10,000 g for 20 min in high-speed cooling centrifuge (-4°C). The clear supernatants were used for assaying the levels of Thiobarbituric Acid Reactive Substance (TBARS) [20], Glutathione (GSH) [21], Superoxide Dismutase (SOD) [22], and proteins [23].

### Histopathological investigations

The pancreas were fixed with 10% formalin solution and embedded in paraffin. Sections of dehydrated pancreatic tissue, 3-5 m thickness, were prepared and stained with Hematoxylin and Eosin (H & E) for histological examination. The histological examination of the pancreatic sections was carried out by a pathologist in a blinded fashion.

### Statistical analysis

All the data expressed as mean  $\pm$  SEM were analysed by One-way Analysis of Variance (ANOVA) followed by Dunnett's t test for multiple comparison. The statistical analyses were performed using

Graphpad Prism 3.0 (San Diego, CA, USA). P values <0.05 were considered as statistically significant.

## Results

### Effect of *M. alba* stem bark extracts on blood glucose level in STZ-induced diabetic rats

Administration of STZ resulted in significant ( $p < 0.05$ ) increase in mean blood glucose level on day 0 and day 21 (group-II) as compared to normal control animals (group-I). Post treatment with *M. alba* stem bark extract in STZ treated rats significantly reduced the increased blood glucose level as compared to group-II. Although the extract produced dose dependent effect but the lowering of mean blood glucose was statistically insignificant with lower dose (200 mg/kg; p.o.) of *M. alba* stem bark extract. However, per se treatment with MASBE did not produce any significant effect on blood glucose level. Treatment with glibenclamide after induction of diabetes significantly ( $p < 0.05$ ) reduced the increased blood glucose level as compared to group-II (Table 1).

### Effect of *M. alba* stem bark extracts on HbA1C level in STZ-induced diabetic rats

As shown in Table 2, administration of STZ (60 mg/kg; i.v.) significantly ( $p < 0.05$ ) raised the level of glycosylated haemoglobin (HbA1C) in pathogenic control (group-II) as compared to normal control (group-I). Post-treatment with MASBE (200, 400 mg/kg; p.o.) reverses the HbA1C level as compared to pathogenic control group in dose dependent manner. The reduction of HbA1C level with MASBE (200 mg/kg) was statistically insignificant. However, glibenclamide significantly ( $p < 0.05$ ) reduced the HbA1C level whereas MASBE per se did not produce any significant change in HbA1C level as compared to control group.

### Effects of *M. alba* stem bark extracts on Serum insulin levels (ng/ml) in STZ-induced diabetic rats

STZ (60 mg/kg; i.v.) significantly ( $p < 0.05$ ) reduced the serum insulin level as compared to control group. MASBE (400 mg/kg) significantly increased the serum insulin level however, lower dose (MASBE; 200 mg/kg) also tends to increase the serum insulin level though statistically insignificant. Glibenclamide (5 mg/kg; p.o.) significantly ( $p < 0.05$ ) reversed the STZ induced reduction in serum insulin level as compared to pathogenic control group. However, MASBE per se (400 mg/kg) did not produce significant change in serum insulin level as compared to control group (Table 2).

### Effects of *M. alba* extracts on MDA, GSH, and SOD activity in pancreatic tissues in STZ-induced diabetic rats

STZ induced oxidative stress manifested by significant ( $p < 0.01$ ) increase in lipid peroxidation measured as TBARS and reduction in glutathione ( $p < 0.01$ ), superoxide dismutase (SOD) activity in pancreatic tissues (Table 3) as compared to control. MASBE (200 mg/kg and 400 mg/kg) post treatment following STZ induced diabetes produced significant antioxidant effect by reversing the increased TBARS and altered GSH, and SOD activity as compared to pathogenic control group. Moreover, Glibenclamide also produced significant antioxidant effect by restoring the oxidative stress parameters. However, *M. alba* (400 mg/kg) alone as per se did not produce any significant alteration in biochemical markers of oxidative stress (TBARS, GSH, and SOD) as compared to control group.

### Effect of methanolic *M. alba* extracts on histopathological studies of pancreas

Histopathological analysis of pancreas treated with STZ (Figure 1A) showed prominent inflammation with evidence of necrotic tissue as compared with the control (Figure 1A). Treatment with *M. alba*

Group n=6	Treatment	Glucose (mg/dl)	
		(Day 0)	(Day 21)
1	Normal saline (1 mg/kg, p.o)	62.95 ± 1.27	64.61 ± 1.49
2	STZ (40 mg/kg, i.v)	295.12 ± 14.27 <sup>**</sup>	306.95 ± 17.33 <sup>**</sup>
4	STZ+MASBE (200 mg/kg, p.o)	217.4 ± 8.92 <sup>**##</sup>	176.2 ± 3.77 <sup>**##</sup>
5	STZ+MASBE (400 mg/kg, p.o)	186.06 ± 8.65 <sup>**##</sup>	80.9 ± 1.88 <sup>##</sup>
3	STZ+Glibenclamide (5 mg/kg, p.o)	142.88 ± 12.17 <sup>**##</sup>	64.88 ± 2.59 <sup>##</sup>
6	MASBE <i>per se</i> (400 mg/kg, p.o)	68.8 ± 2.32 <sup>##</sup>	65.97 ± 2.06 <sup>##</sup>

All values are expressed as mean ± SEM.

STZ was administered intravenously while extract and glibenclamide was administered by oral route. Treatment duration=21 days (Post-treatment after STZ).

n: Number of animals; STZ: streptozotocin; MASBE: *Morus alba* stem bark extract (200 mg/kg, 400 mg/kg).

<sup>\*\*</sup>P<0.01 vs. Group I (Normal); <sup>##</sup>P<0.01 vs. Group II (Toxic control), significant by ANOVA followed by Dunnett's t-test.

Table 1: Effect of *Morus alba* stem bark extracts on blood glucose in STZ-induced diabetic rats.

Group n=6	Treatment	HbA1c (%)	
		(Day 0)	(Day 21)
1	Normal saline (1 mg/kg)	6.017 ± 0.087	0.1303 ± 0.007
2	STZ (40 mg/kg)	15.41 ± 0.294 <sup>**</sup>	0.073 ± 0.0083 <sup>##</sup>
4	STZ+MASBE (200 mg/kg)	11.15 ± 0.483 <sup>**##</sup>	0.085 ± 0.0055 <sup>**##</sup>
5	STZ+MASBE (400 mg/kg)	6.983 ± 0.296 <sup>##</sup>	0.1285 ± 0.0017 <sup>##</sup>
3	STZ+Glibenclamide (5 mg/kg)	6.517 ± 0.186 <sup>##</sup>	0.139 ± 0.0031 <sup>##</sup>
6	MASBE <i>per se</i> (400 mg/kg)	6.033 ± 0.223 <sup>##</sup>	0.146 ± 0.0037 <sup>##</sup>

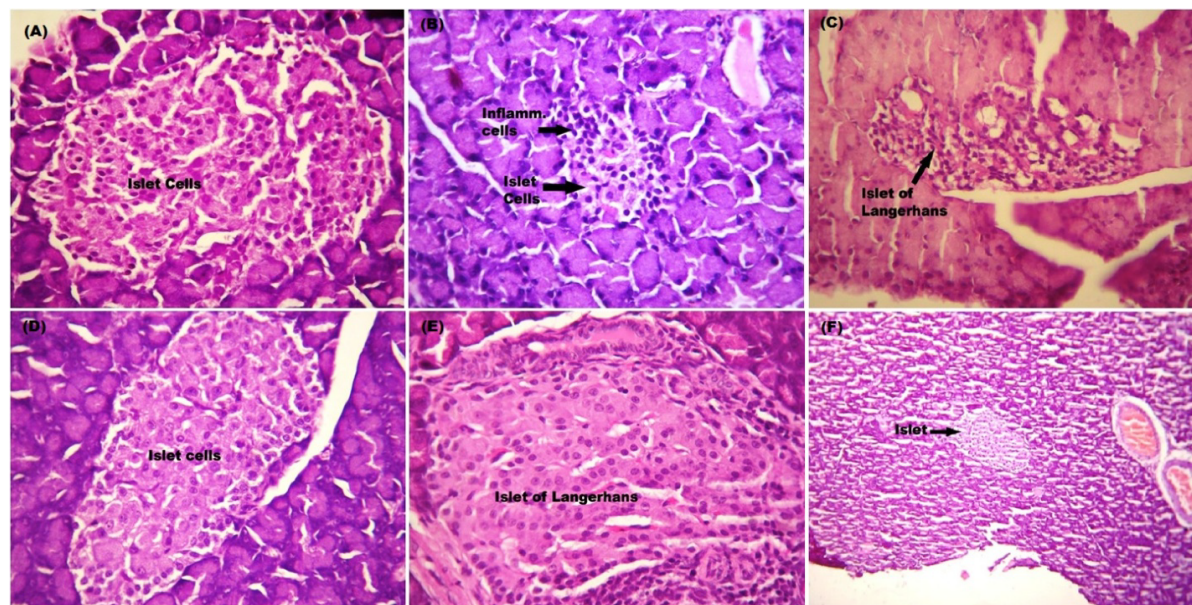
All values are expressed as mean ± SEM.

STZ was administered intravenously while extract and glibenclamide was administered by oral route. Treatment duration=21 days (Post-treatment after STZ).

n: Number of animals; STZ: streptozotocin; MASBE: *Morus alba* stem bark extract (200 mg/kg, 400 mg/kg).

<sup>\*\*</sup>P<0.01 vs. Group I (Normal); <sup>##</sup>P<0.01 vs. Group II (Toxic control), significant by ANOVA followed by Dunnett's t-test.

Table 2: Effect of *Morus alba* stem bark extracts on HbA1C and serum insulin in STZ-induced diabetic rats.



**Figure 1:** Effect of *Morus alba* stem bark extracts on STZ-induced diabetes in rats. Histology of Pancreas (1A-1F): STZ treatment (Figure 1B) showed evidence of inflammation and necrosis of  $\beta$ -cells as compared to normal control (Figure 1A). *Morus alba* L. stem bark extract at a dose of 200 mg/kg and 400 mg/kg (Figure 1C and 1D) showed reversal of these changes produced by STZ and manifests as increased number of  $\beta$ -cells. Glibenclamide (5 mg/kg) also restored these changes (Figure 1E). However, *M. alba per se* (Figure 1F) did not produce any histopathological alteration in pancreatic tissue (Magnification, 40X).

stem bark extract (200, 400 mg/kg, p.o.) restored these ultrastructural changes as compared to pathogenic control (Figure 1C and D) with abundance of  $\beta$  cells in the islets of Langerhans. Glibenclamide treatment for 21 days (Figure 1E) demonstrated marked improvement in the STZ-induced micro-architectural changes endocrine part of pancreatic tissues. However, *M. alba per se* (Figure 1F) alone-treatment did not show any structural changes in pancreatic  $\beta$  cells as compared to control group.

## Discussion

The objective of treatment in diabetic patient is to lower blood glucose to normal level [24]. In the present study, *M. alba* stem bark extract (MASBE) showed significant lowering of blood glucose level, an index of diabetic control. STZ-induced diabetes is one of the widely used animal models that mimic the human diabetes mellitus. The selective destruction of insulin-producing  $\beta$ -cells of the pancreas by STZ is mediated by induction of high levels of DNA strand breaks in these cells, causing activation of poly (ADP-ribose) polymerase (PARP), resulting in reduction of cellular NAD<sup>+</sup>, and cell death [25]. The metabolism of glucose, proteins and lipids is abnormal in diabetes due to insulin secretion defect, leading to various metabolic disorders [26,27] and complications [28,29]. In addition, STZ generates potential free radicals such as nitric oxide (NO) by intracellular metabolism of STZ and precipitate further  $\beta$ -cells DNA damage by strand break [30].

The concentration of blood glucose was significantly increased in diabetic as compared with STZ as compared to normal control. Administration of MASBE (200 mg/kg and 400 mg/kg) significantly reduced the raised blood glucose level in STZ induced diabetic rats and the lowering was almost comparable to glibenclamide (5 mg/kg, p.o.) (Table 1). Further, this antidiabetic activity of MASBE was associated with an increase in the serum insulin level revealed that MASBE may stimulate insulin secretion from regenerated  $\beta$  cells and remaining  $\beta$ -cells (Table 2). The blood glucose lowering effect of the extract could

be due to the presence of terpenoid compounds as reported by the previous study [31]. These findings were also supported by the previous experimental findings wherein they reported the blood glucose lowering effect of triterpenoids from *Psidium guajava* leaves [32].

Glycated haemoglobin (HbA1c) is a routinely used as a marker for long-term glycemic control. Persistent hyperglycemia in diabetes manifest as increased HbA1c level as a result of glycation of haemoglobin. Diabetic patient were reported with increased level of HbA1c upto 16% [33]. The raised HbA1c level well correlates with the complication such as diabetic retinopathy, nephropathy, and neuropathy. In addition, there is relative deficiency of insulin leads to decreased protein synthesis in all tissues consequently reduced synthesis of haemoglobin in diabetes [34]. Thus the findings of the present study showed that administration of MASBE (200, 400 mg/kg) significantly decreased the raised HbA1c level in STZ-induced diabetic rats. However *per se* treatment (MASBE alone) did not produce significant change in HbA1c level (Table 2). Our findings were in agreement with previous study reported the restoration of raised HbA1c level after treatment with *Tectona grandis* flower extract in STZ-induced diabetic rats [35].

Lipid peroxidation is a marker of cellular oxidative damage initiated by reactive oxygen species [36]. Ample of experimental and clinical evidence suggests that oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed disproportionately in diabetes by glucose oxidation, nonenzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins. Further, it was reported that diabetics are highly sensitive to oxidative stress [37]. It has been reported that STZ generates nitric oxide, a powerful free radical oxidant [38] which results in an increase in serum level of lipid peroxides due to oxidation of cells. There was significant elevation of MDA level, an index of lipid peroxidation (expressed as nmol TBARS/mg of protein) in STZ treated rats (Table 3) as compared to normal control. In this study, the oral

Group	Treatment	TBARS (nM/mg of proteins)	Glutathione (GSH) (µg/mg of protein)	Superoxide dismutase (SOD) (U/mg of protein)
	Normal saline (1 mg/kg)	0.527 ± 0.019	5.733 ± 0.203	4.998 ± 0.05
	STZ (40 mg/kg)	3.26 ± 0.118 <sup>∗∗</sup>	2.252 ± 0.147 <sup>∗∗∗</sup>	1.453 ± 0.119 <sup>∗∗</sup>
	STZ+MASBE (200 mg/kg)	2.18 ± 0.085 <sup>∗∗</sup>	3.953 ± 0.174 <sup>∗∗,##</sup>	3.36 ± 0.146 <sup>∗∗,##</sup>
	STZ+MASBE (400 mg/kg)	0.768 ± 0.061 <sup>##</sup>	5.48 ± 0.2 <sup>##</sup>	4.547 ± 0.144 <sup>##</sup>
	STZ+Glibenclamide (5 mg/kg)	0.722 ± 0.056 <sup>##</sup>	5.697 ± 0.126 <sup>##</sup>	4.618 ± 0.139 <sup>##</sup>
	MASBE (400 mg/kg)	0.615 ± 0.015 <sup>##</sup>	5.822 ± 0.169 <sup>##</sup>	4.955 ± 0.198 <sup>##</sup>

All values are expressed as mean ± SEM.

STZ was administered intravenously while extract and glibenclamide was administered by oral route. Treatment duration=21 days (Post-treatment after STZ).

n: Number of animals; STZ: streptozotocin; MASBE: *Morus alba* stem bark extract (200 mg/kg, 400 mg/kg).

**Table 3:** Effect of *Morus alba* stem bark extracts on MDA, GSH and SOD in STZ-induced diabetic rats.

administration of the extract of *M. alba* stem bark (MASBE; 200 mg/kg, 400 mg/kg) reverses the elevated level of lipid peroxides in STZ-diabetic rats compared with control. Thus the findings of present study suggest that *M. alba* extracts prevents STZ induced cellular damage mediated via inhibition of lipid peroxidation. This antioxidant effect of *M. alba* stem bark extract could be due to its high flavonoid [39] and terpenoid content [31], congruent with the previous study wherein they reported on this kind of compounds [40], as well as it preserves the capability of insulin secretion.

Further, several lines of evidence suggest the lower level antioxidant defence system in diabetes. These include reports of reduced plasma/serum total antioxidant status such as reduced Glutathione (GSH) and Superoxide Dismutase (SOD) activity in diabetics [41]. They mitigate oxidative stress by eliminating reactive oxygen free radicals such as Superoxide (O<sub>2</sub><sup>-</sup>) and Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>), and preventing the formation of highly reactive hydroxyl free radical (°OH). Streptozotocin (STZ) penetrates into the beta-cell and generates nitrogen monoxide (NO) that leads to its destruction by peroxynitrite resulting from NO and superoxide (O<sub>2</sub><sup>-</sup>) [42]. Furthermore, evidence suggests that hyperglycemia can lower both the activity of antioxidant enzymes including SOD [43] and glutathione synthesis [44]. Table 3 showed that the pancreatic GSH level and SOD activity were significantly reduced in STZ-treated diabetic animals as compared to control group, and they were significantly restored in *M. alba* treated diabetic animals compared to diabetic group. Therefore, these results suggest that *M. alba* stem bark extract have protective effects on antioxidant defenses and thereby improves glucose metabolism. Support to our findings comes from the mentioned earlier work by Katsube et al. [18] wherein the antioxidant activities of the 60% ethanol *M. alba* leaf extract and the activity of individual polyphenols was measured.

The histopathological study of pancreatic tissue further confirmed the destruction of pancreatic β-cell evidenced by reduced number as a result of necrosis by STZ in diabetic control group. The underlying mechanism of STZ-induced histopathological changes is mainly the splitting of streptozotocin into its glucose and methylnitrosourea moiety. Owing to its alkylating properties, the latter modifies biological macromolecules, fragments DNA and destroys the beta cells, causing a state of insulin-dependent diabetes. *M. alba* stem bark extract preserved all these changes in pancreatic tissue produced by STZ, there effects could be attributed to the presence of potent antioxidants such as flavonoid and terpenoid compounds (Figure 1).

## Conclusion

The results showed that *M. alba* stem bark extract markedly reduced hyperglycemia in STZ-induced diabetic rats by control oxidative stress and preserve the histopathological changes produced by STZ. However, the study warrants additional investigation to confirm the

effects in other animal models of diabetes and to identify the active constituents responsible for antidiabetic activity.

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