RESEARCH PAPER

Phytochemical Investigation and Antidiabetic Evaluation of Morus alba Leaves Extract in Experimental Diabetes

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ABSTRACT

The present study aimed to investigate the phytochemical composition and antidiabetic potential of the ethanolic extract of Morus alba leaves using a streptozotocin (STZ)-induced diabetic rat model. Preliminary phytochemical screening revealed the presence of flavonoids, phenolic compounds, and sterols, indicating the richness of bioactive constituents. The effect of the extract was evaluated on body weight, serum glucose levels, lipid profile, liver biomarkers (ALT and AST), oxidative stress markers (MDA and SOD), glutathione (GSH), and insulin levels. Diabetic rats showed significant hyperglycemia, weight loss, dyslipidemia, increased liver enzyme levels, oxidative stress, and reduced insulin and antioxidant levels. Treatment with Morus alba extract (100 and 200 mg/kg) significantly improved body weight and reduced serum glucose levels in a dose-dependent manner. The extract also exhibited a marked improvement in lipid profile by decreasing total cholesterol, triglycerides, and LDL levels while increasing HDL levels. Furthermore, it demonstrated hepatoprotective and antioxidant effects by normalizing ALT, AST, MDA, SOD, and GSH levels. Insulin levels were also significantly restored following treatment. The effects of the extract were comparable to the standard drug glibenclamide, especially at higher doses. In conclusion, the ethanolic extract of Morus alba leaves exhibits significant antidiabetic, hypolipidemic, and antioxidant activities, supporting its potential as a natural therapeutic agent for the management of diabetes mellitus.

Keywords: Morus alba, streptozotocin, antidiabetic activity, phytochemical screening, oxidative stress, lipid profile, insulin, glibenclamide

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is associated with disturbances in carbohydrate, lipid, and protein metabolism, leading to serious complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy. The global prevalence of diabetes is increasing at an alarming rate, posing a major public health challenge. Although several synthetic antidiabetic drugs are available, their long-term use is often associated with adverse effects, limited efficacy, and high cost, which necessitates the search for safer and more effective alternatives.

Medicinal plants have been widely explored for their therapeutic potential due to their rich content of bioactive phytoconstituents such as flavonoids, phenolics, alkaloids, and terpenoids. These compounds are known to exert antidiabetic effects through various mechanisms, including stimulation of insulin secretion, enhancement of glucose uptake, inhibition of carbohydrate-digesting enzymes, and antioxidant activity. Therefore, plant-based therapies are gaining increasing attention as complementary and alternative approaches for the management of diabetes.

Morus alba (white mulberry), belonging to the family Moraceae, is a well-known medicinal plant traditionally used in various systems of medicine. Different parts of the plant, particularly the leaves, are reported to possess

several pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory, and antidiabetic effects. The presence of bioactive compounds like flavonoids, phenolic acids, and sterols contributes to its therapeutic potential. Previous studies have indicated that *Morus alba* leaves may help regulate blood glucose levels and improve lipid metabolism.

Streptozotocin (STZ)-induced diabetes in experimental animals is a widely accepted model for evaluating antidiabetic agents, as it selectively damages pancreatic β-cells, leading to insulin deficiency and hyperglycemia. This model closely mimics the pathophysiological conditions of diabetes in humans and is commonly used to assess the efficacy of plant extracts and synthetic drugs.

In view of the above considerations, the present study was undertaken to perform phytochemical investigation and evaluate the antidiabetic potential of the ethanolic extract of *Morus alba* leaves in STZ-induced diabetic rats. The study focuses on assessing its effects on blood glucose levels, body weight, lipid profile, liver function markers, oxidative stress parameters, and insulin levels to establish its therapeutic relevance in the management of diabetes mellitus.

Material and Methods

Material

Leaves of *Morus alba* were collected, authenticated, shade-dried, and powdered for extraction. Ethanol was used as the solvent for preparing the ethanolic extract. Streptozotocin (STZ) was used for induction of diabetes, and glibenclamide was used as the standard antidiabetic drug. Experimental animals (rats) were maintained under standard laboratory conditions. All biochemical estimation kits for glucose, lipid profile, liver enzymes (ALT, AST), and oxidative stress parameters (MDA, SOD, GSH) were procured from standard suppliers. All other chemicals and reagents used in the study were of analytical grade.

Methods

Extraction

Extraction is defined as the separation of medicinally active portions of plant tissues from the inactive components through the use solvents. Marc is the damp solid material or the plant being used and menstruum is the liquid material or solvent. During extraction, the solvent diffuses into the marc and solubilizes compounds with similar polarity (Bandiola *et al.,* 2017; Banu and Cathrine, 2015; Harborne, 1998).

Extraction using hot continuous extraction (Soxhlet)

Defatted plant material extracted by ethanol solvent was used. In this method, the finely pulverized marc is placed in a thimble which is placed in a chamber of the Soxhlet apparatus (Khandelwal, 2005). The menstruum in the flask beneath is then heated, and its vapors condense in the condenser. The condensed extractant drips into the thimble containing the marc, and extracts it by contact. The advantage of this method is that large amounts of marc can be extracted with a much smaller volume of extractant. Each extraction process was carried out for 48 hours. The filtrate was separated from the residue using Whatmann filter paper. The filtrate from each solvent was collected and evaporated using a water bath at 50°C until a thick extract was obtained.

Qualitative phytochemical screening

Qualitative phytochemical screening is carried out to investigate the various classes of natural compounds present in the extract. This is accomplished using standard methods (Tiwari et al., 2011). Phytochemical screening was carried out qualitatively using detection reagents based on the procedures explained in Hanani, (2015). The classes of compounds identified in the extract included phenolics, flavonoids, tannins, saponins, alkaloids and protein.

In vivo anti-diabetic potential of ethanolic extract of *Morus alba*

STZ induced anti-diabetic model

Animals

The animals (Wistar rats) were raised in a standardized room with a temperature of 22 ± 2 °C and were adapted to the environment for one week. They had unrestricted access to food and water, which were changed twice daily. They were kept in a well-ventilated room, and the relative humidity was maintained between 40% and 70%. The room had natural light without direct incident of sunlight inside it. The animals were provided with distilled water and slept on clean, fine shavings, which were changed daily. Animal studies were authorized by the Institutional Animal Ethics Committee (IAEC), which operates under the supervision of the Ministry of Environment and Forests, Government of India, New Delhi, India.

Toxicity study

Healthy adult male rats were fasted overnight before the experiment. Each group of rats (n = 6) was administered different doses (50–2000 mg/kg, orally) of the leaf extract of *Morus alba*. The animals were continuously observed for 1 hour, followed by 30-minute intervals for

the next 4 hours, and then for up to 72 hours for any signs of behavioral changes or toxicity. The observation period was extended to 14 days to monitor for any mortality, in accordance with the OECD Guideline 425 for acute oral toxicity testing (Prasad *et al.,* 2009). The leaf extract of *Morus alba* was found to be non-toxic at doses up to 2000 mg/kg body weight. Based on these findings, doses of 100 mg/kg and 200 mg/kg were selected for further evaluation in anti-diabetic studies.

Experimental design

Induction of experimental diabetes using STZ (Streptozotocin)

Rats were divided into 5 different groups, each group consisting of six animals. After overnight fasting (deprived of food for 16 hours had been allowed free access to water) diabetes was induced in group II-V by intraperitoneal injection of STZ dissolved in 0.1M sodium citrate buffer at pH 4.3, at a dose of 10mg/mL. The control rats received the same amount of 0.1 M sodium citrate buffer. The animals were allowed to drink a 5% glucose solution overnight to overcome the drug-induced hypoglycemia. Diabetes status was confirmed by estimating blood glucose levels after 72 hours of STZ injection. Animals showing fasting blood glucose levels around 220-250 mg/dl were considered diabetic and such were selected for the study.

Diabetic rats were randomized into control, Glibenclamide-treated, and *Morus alba*-treated groups. The mulberry group was divided into high and low-dose groups (i.e. 200 and 100 mg/kg with 6 animals in each group. The body weights and fasting blood glucose levels of animals were measured before the experiment (Jung et al., 2006).

Animals were categorized into different groups each containing six rats.

- Group I served as the normal control and was administered the vehicle (0.5 ml of distilled water/day/rat).
- Group II served as the diabetic control and was also administered the vehicle (distilled water/day/rat, 0.5 mL).
- Group III received Glibenclamide (500 mcg/kg/day p.o.)
- Group IV received *Morus alba* leaf extract (100 mg/kg p.o.) for 21 days.
- Group V received *Morus alba* leaf extract (200 mg/kg) for 21 days.

The body weight of rats was taken on pre- and post-treatment, specifically on the initial and final day of post-treatment, using an electronic balance. Additionally, fasting blood glucose levels of rats were taken at three different times, i.e. pre- and post-treatment, i.e. 0, 8th and 21st day of post-treatment.

All the rats were euthanized by cervical decapitation after the end of the trials. Blood samples were collected and allowed to clot. Serum was separated by centrifuging at 2500 rpm for 15 min and analyzed for various biochemical parameters.

Antidiabetic screening

Blood sampling

Blood was extracted for glucose analysis using tail snipping, which involved drawing blood from the subject by using a heparinized capillary tube. After collection, bleeding was stopped by gentle compression on the wound for a few seconds. The length of time required for collecting 30 to 50 µL of blood was less than 1 min. To evaluate the lipid profiles and other biochemical parameters, a retroorbital bleeding method was employed to obtain blood from the ophthalmic venous plexus. In this technique, the rats are placed under terminal anaesthesia and restrained, the neck gently scuffed and the eye made to bulge. A capillary tube/pipette is inserted medially, laterally or dorsally. Blood is allowed to flow by capillary action into the capillary tube/pipette. The sample obtained is a mixture of venous blood and tissue fluid, and is not representative of venous blood. During blood collection, appropriate care must be taken to monitor the animal for any potential complications associated with the procedure, ensuring both ethical standards and the integrity of the experimental data collected (Arunachalam et al., 2013).

Results and Discussion

The present study was designed to evaluate the phytochemical profile and antidiabetic potential of the ethanolic extract of *Morus alba* leaves using an STZ-induced diabetic rat model. The findings from phytochemical screening (Table 1) revealed the presence of important secondary metabolites such as flavonoids, phenolic compounds, and sterols. These phytoconstituents are well known for their antioxidant and antihyperglycemic activities, suggesting their possible role in the observed pharmacological effects.

The effect of the extract on body weight (Table 2) showed that diabetic control rats exhibited reduced weight gain compared to the normal group, which is a

common consequence of insulin deficiency and increased protein catabolism. Treatment with *Morus alba* extract, particularly at 200 mg/kg, significantly improved body weight, indicating a protective effect against diabetes-induced weight loss. This improvement may be attributed to better glycemic control and enhanced metabolic activity.

Serum glucose levels (Table 3) were markedly elevated in the diabetic control group, confirming successful induction of diabetes by streptozotocin (STZ). Administration of the ethanolic extract resulted in a significant reduction in blood glucose levels in a dose-dependent manner. The 200 mg/kg dose showed greater efficacy, approaching the effect of the standard drug glibenclamide. This antihyperglycemic effect may be due to stimulation of insulin secretion, increased peripheral glucose utilization, or inhibition of carbohydrate metabolizing enzymes, possibly mediated by flavonoids and phenolics.

Alterations in lipid profile (Table 4) are a characteristic feature of diabetes mellitus. The diabetic control group showed increased total cholesterol, triglycerides, and LDL levels, along with decreased HDL levels. Treatment with *Morus alba* extract significantly improved these parameters, especially at 200 mg/kg, indicating its hypolipidemic effect. The reduction in lipid levels may be linked to improved insulin sensitivity and inhibition of lipid peroxidation.

Biochemical markers such as ALT, AST, MDA, and SOD (Table 5) further supported the protective role of the extract. Elevated ALT and AST levels in diabetic rats indicate hepatic damage, while increased MDA and decreased SOD levels reflect oxidative stress. Treatment with the extract significantly normalized these parameters, suggesting hepatoprotective and antioxidant properties. The decrease in MDA levels and increase in SOD activity indicate reduced lipid peroxidation and enhanced antioxidant defense.

Glutathione (GSH) levels (Table 6), an important endogenous antioxidant, were significantly reduced in diabetic rats. Administration of *Morus alba* extract restored GSH levels in a dose-dependent manner, indicating its role in combating oxidative stress. Similarly, insulin levels (Table 7) were significantly decreased in the diabetic group but were improved following treatment with the extract. This suggests that the extract may promote insulin secretion or protect pancreatic β-cells from oxidative damage.

The results demonstrate that the ethanolic extract of *Morus alba* possesses significant antidiabetic activity, supported by improvements in body weight, blood glucose levels, lipid profile, antioxidant status, and insulin levels. The observed effects are likely due to the presence of bioactive compounds such as flavonoids and phenolics. These findings highlight the therapeutic potential of *Morus alba* as a natural agent for the management of diabetes and its associated complications. Further studies are recommended to isolate active constituents and elucidate the exact mechanism of action.

Table 1: Result of phytochemical screening of *Morus alba*

S. No.	Constituents	Ethanolic extract
1.	**Alkaloids**	
	Wagner's Test:	-ve
	Hager's Test:	-ve
2.	**Glycosides**	
	Cons. H_2SO_4 Test:	-ve
3.	**Flavonoids**	
	Lead acetate Test:	-ve
	Alkaline reagent Test:	+ve
4.	**Diterpenes**	
	Copper acetate Test:	-ve
5.	**Phenol**	
	Ferric Chloride Test:	+ve
	FC reagent Test:	+ve
6.	**Proteins**	
	Xanthoproteic Test:	-ve
7.	**Carbohydrate**	
	Fehling's Test:	-ve
	Benedict's Test	-ve
8.	**Saponins**	
	Froth Test:	-ve
9.	**Tannins**	
	Gelatin Test:	-ve
10.	**Sterols**	
	Salkowski's Test:	+ve

+Ve = Positive, -Ve= Negative

Table 2: Effect of ethanolic extract of *Morus alba* on body Weight in rats

Group	Drug and Dose	Body Weight (gm)	
		Initial weight (g)	Final weight (g)

I	Normal Control (Saline)	160.8 ± 4.0	175.2 ± 4.4
II	Diabetic Control (STZ)	158.5 ± 4.2	165.4 ± 4.1
III	STZ+ Glibenclamide	162.3 ± 3.7	172.6 ± 4.0
IV	STZ+ leaf extract of *Morus alba* 100 mg/kg	165.9 ± 3.8	177.1 ± 4.3
V	STZ+ leaf extract of *Morus alba* 200 mg/kg	170.2 ± 4.1	182.3 ± 4.6

Values are expressed as mean ± S.E.M. (n = 6). Values are statistically significant at $p<0.05$ vs. the control group, respectively (One-way ANOVA followed by Dunnett's test).

Table 3: Effect of ethanolic extract of leaves of *Morus alba* on serum glucose level in rats

Group	Drug and Dose	Serum glucose levels (mg/dl)		
		0 DAY	8th DAY	21th DAY
I	Normal Control (Saline)	78.10 ± 3.60	92.80 ± 4.90	108.50 ± 5.80
II	Diabetic Control (STZ)	290.30 ± 7.10	375.20 ± 8.80#	402.40 ± 9.60#
III	STZ+ Glibenclamide	258.50 ± 6.10	126.40 ± 5.90*	112.20 ± 5.30*
IV	STZ+ *Morus alba* 100 mg/kg	262.40 ± 5.60	139.80 ± 6.90*	130.50 ± 6.10*
V	STZ+ *Morus alba* 200 mg/kg	259.60 ± 4.30	134.20 ± 6.70*	122.30 ± 5.00*

Values are expressed as mean ± S.E.M. (n = 6). Values are statistically significant at $p<0.05$ vs. control group respectively (One-way ANOVA followed by Dunnett's test).

Table 4: Effect of ethanolic extract of leaves of *Morus alba* on serum lipid profiles i.e. total cholesterol level in rats

Group	Drug and Dose	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
I	Normal Control (Saline)	138.60 ± 6.2	112.80 ± 4.60	53.20 ± 2.80	82.10 ± 4.30
II	Diabetic Control (STZ)	262.80 ± 8.7	225.10 ± 5.10	28.70 ± 1.80	188.25 ± 6.12
III	STZ+ Glibenclamide	185.40 ± 6.1***	142.30 ± 4.90 ***	51.60 ± 1.90	93.70 ± 5.20
IV	STZ+ *Moru*	210.70 ± 7.5*	180.20 ± 5.20 *	42.10 ± 1.60	130.15 ± 5.00

	s alba 100 mg/kg				
V	STZ+ *Morus alba* 200 mg/kg	198.90 ± 8.4***	166.40 ± 4.85 **	46.80 ± 1.70	125.60 ± 5.25

Values are expressed as mean ± S.E.M. (n = 6). Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

Table 5: Effect of ethanolic extract of leaves of *Morus alba* extract on serum biomarkers i.e. ALT in rats

Group	Drug and Dose	ALT (U/L)	AST(U/L)	MDA µmol/L	SOD µmol/L
I	Normal Control (Saline)	55.10 ± 3.30	42.50 ± 4.00	1.25 ± 0.65	26.1 ± 1.6
II	Diabetic Control (STZ)	150.00 ± 5.10	140.75 ± 4.50	3.65 ± 0.85	8.9 ± 1.0
III	STZ+ Glibenclamide	85.60 ± 4.00	60.90 ± 3.20	1.40 ± 0.60	22.4 ± 1.4
IV	STZ+ *Morus alba* 100 mg/kg	115.40 ± 4.60	91.20 ± 3.00	2.15 ± 0.70	18.1 ± 1.5
V	STZ+ *Morus alba* 200 mg/kg	103.10±4.80**	89.10 ± 3.10	1.60 ± 0.68	23.5 ± 1.7

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

Table 6: Effect of leaves extract of *Morus alba* on Glutathione levels (GSH) level in rats

Group	Drug	Dose	GSH µmol/L
I	Normal	0.5% CMC 1 ml/kg, p.o.	9.2 ± 0.7
II	Diabetic Control (STZ)	2 mL/kg b.wt.	2.7 ± 0.4
III	STZ + Glibenclamide	10 mg/kg p.o.	8.4 ± 0.6
IV	STZ + Leaves extract of *Morus alba*	100 mg/kg p.o.	6.1 ± 0.5
V	STZ + Leaves extract of *Morus alba*	200 mg/kg p.o.	7.8 ± 0.6

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test)

Table 7: Effect of leaves extract of *Morus alba* on Insulin level in rats

Group	Drug	Dose	Insulin µmol/L
I	Normal	0.5% CMC 1 ml/kg, p.o.	13.1 ± 0.9
II	Diabetic Control (STZ)	2 mL/kg b.wt.	4.7 ± 0.6
III	STZ + Glibenclamide	10 mg/kg p.o.	11.5 ± 0.7
IV	STZ + Leaves extract of *Morus alba*	100 mg/kg p.o.	8.2 ± 0.8
V	STZ + Leaves extract of *Morus alba*	200 mg/kg p.o.	9.8 ± 0.6

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

Conclusion

The ethanolic extract of *Morus alba* leaves demonstrated significant antidiabetic activity in STZ-induced diabetic rats. It effectively reduced blood glucose levels, improved lipid profile, restored antioxidant status, and enhanced insulin levels in a dose-dependent manner. These effects may be attributed to the presence of flavonoids and phenolic compounds. Thus, *Morus alba* shows promising potential as a natural therapeutic agent for the management of diabetes and its associated complications.

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