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Change of Antioxidant System in Diabetic Model Rat Liver Cells and Its Correction with Complex Compounds

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ABSTRACT

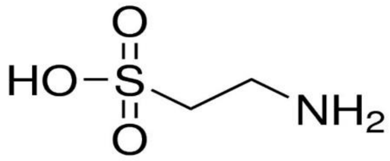
Diabetes is the most common disease associated with metabolic disorders. Diabetes mellitus is characterized by dysfunction of pancreatic beta cells. Taurine is a β-amino acid widely distributed in mammalian tissues and is not involved in protein synthesis. This study aimed to study the effect of a complex combination of taurine and a Schiff base derivative on the antioxidant system in the liver of model rats with diabetes. 12 male white rats were divided into 4 groups: Control, diabetic model (DM), diabetic treated with Metformin (DM+Metformin), and diabetic treated with Taurine and Schiff base (DM+Tau/Schiff base). Rats were injected subcutaneously for 3 days at a dose of 140 mg/kg of alloxan to induce diabetes. It was observed that blood glucose levels and daily water intake increased over two weeks, and body weight decreased. The 3rd and 4th groups with diabetes were treated with Metformin and a complex combination for 10 days. Treatment with taurine reduced the decrease in liver catalase and protein content and lowered the increased levels of gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in the blood. In addition, it was found to reduce the level of malondialdehyde (MDA), a secondary metabolite of lipids in the liver and blood. These results indicate that taurine and the Schiff base complex effectively alleviate diabetes by reducing oxidative stress and blood glucose levels.

Keywords: *Diabetes, Metformin, taurine, Schiff base, alloxan, antioxidant, lipid peroxidation, liver, alanine aminotransferase, aspartate aminotransferase, malondialdehyde.*

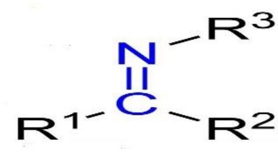
1. INTRODUCTION

More than half a billion people worldwide live with diabetes, affecting men, women, and children of all ages in every country, and this number is expected to more than double to 1.3 billion in the next 30 years. The current global prevalence is 6.1%, making diabetes one of the top 10 causes of death and disability. It is projected to rise to 16.8% by 2050. This means an increase from 529 million to 1.3 billion. Approximately 3.5 million people worldwide die each year due to diabetes. Almost all of the 16 risk factors studied were found to be associated with type 2 diabetes (T2D) [1]. Type 1 diabetes (T1D) accounts for 5% to 10% of all diabetes (depending on the region of the world). It occurs suddenly due to acute illness and destroys insulin-producing β-cells in the pancreas through autoimmune mechanisms, ultimately causing complete insulin deficiency [2, 3]. Type 2 diabetes is associated with pancreatic β-cell damage and decreased insulin production [4, 5]. Disorders of carbohydrate, lipid, and protein metabolism play a key role in the complications of diabetes. Diabetes is a metabolic disorder typically characterized by increased free radical levels and decreased antioxidant concentration or activity [6]. Oxidative stress is an imbalance between the systemic expression of reactive oxygen species and the biological system's ability to rapidly neutralize reactive mediators or repair damage. Hyperglycemia exacerbates oxidative stress via multiple pathways. The primary mechanism is intracellular reactive oxygen species (ROS) produced by the proton electromechanical gradient produced by the mitochondrial electron transport chain and induced by hyperglycemia, which leads to increased superoxide production [7, 8]. Taurine is a conditionally essential amino acid that constitutes approximately 0.1% of human body weight. It is not involved in protein synthesis, is never incorporated into muscle proteins, and thus exists in the body primarily as a free molecule or in simple peptides [9, 10]. Although taurine is unable to directly scavenge classical ROS such as superoxide anion, hydroxyl radical, and hydrogen peroxide, many studies show that it is an effective inhibitor of ROS generation [11].

Hyperglycemia and hyperinsulinemia decrease taurine transporter activity, depriving the affected cell of a potentially important endogenous substance. Serum taurine depletion is associated with many oxidative stress pathologies, and taurine supplementation has been shown to improve these pathologies and their complications. Various physiological functions and roles are modulated by taurine, including antioxidant, osmoregulation, membrane stabilization, bile acid conjugation, neuromodulation, detoxification, and regulation of calcium homeostasis. Clinically, prophylactic and therapeutic taurine supplementation is beneficial in a wide range of oxidative stress-induced pathologies and clinical conditions, including hepatotoxicity and liver disease, alcoholism, Alzheimer's disease, developmental delay, retinal degeneration, and diabetes [12,13].



Chemical structure of taurine



Schiff base

A Schiff base is a compound with the general structure R²C=NR, classified as a subclass of amines. Imines, which are compounds containing a carbon-nitrogen double bond, can be either secondary aldehydes or secondary ketimines, depending on their structure. Schiff bases are widely used in organic chemistry. They are used as dyes, pigments, catalysts, intermediates in synthesizing organic compounds, and polymer stabilizers. Schiff bases exhibit a broad range of biological activities, including antibacterial, antifungal, antimalarial, anti-inflammatory, antiproliferative, antiviral, and antipyretic properties [14, 15]. Taurine, a sulfur-containing amino acid derivative, is abundant in mammalian bodies and plays an important role in maintaining cellular homeostasis by regulating osmotic pressure, stabilizing proteins, exerting antioxidant and anti-inflammatory effects, and regulating calcium ions. Taurine is also involved in basic life activities such as fetal development, maintaining organ function, and cellular metabolism. Numerous studies using animal models and cultured cells have demonstrated that taurine supplementation can mitigate the progression of various diseases [23]. Our study aims to enhance taurine's efficiency by utilizing its carrier properties.

2. MATERIALS AND METHODS

2.1 Animals

The use of laboratory animals was carried out under the International Organization for Medical Sciences Council's code of ethics for animal experiments, and the norms were confirmed by the glucose oxidase method. Experiments were carried out on male rats weighing 210-290 g, kept in standard vivarium conditions [16].

2.2 Experimental groups

Male white rats were divided into the following 4 groups (n=3): Group 1: healthy (control), Group 2: diabetic model (DM), Group 3: diabetes treated with Metformin (150 mg/kg) (DM+Metformin) and Group 4: diabetes treated with Taurine and Schiff's base complex (50 mg/kg) (DM+Tau/Schiff's base). Animals were monitored for 2 weeks, and groups 3 and 4 were treated for 10 days.

2.3 Creating a diabetes model

In groups 2, 3, and 4, alloxan was used to create a diabetes model. It was injected subcutaneously at a dose of 140 mg/kg for 3 days. After 3 days, their blood glucose levels were measured. The rats' blood glucose levels were elevated [17].

2.4 Measurement of blood glucose

A Satellite glucometer was used to measure blood glucose. Blood samples were collected from the rats' tail tips. A test strip was inserted into the glucometer, and a drop of blood was applied to the designated area. The device displayed the blood glucose concentration within five seconds. Measurements were taken before the experiment and after two weeks [18].

2.5 Quantification of MDA

The level of malondialdehyde (a secondary product) was measured to assess the degree of lipid peroxidation. 1 ml of tissue homogenate was carefully taken, mixed with 2 ml of TCA-TBA-HCl solution, and heated in a water bath for 15 minutes. After cooling, the precipitate was separated by centrifugation, and the remaining part was measured in a spectrophotometer at a wavelength of 535 nm [19].

2.6 Determination of protein content

The amount of protein in the liver homogenate was measured by the Lowry method, in which Cu^{2+} ions form a complex with peptide bonds in an alkaline medium and become a Cu^{2+} complex. Monovalent copper ions react with Folin's reagent (a mixture of phosphomolybdic acid and phenol) to produce an unstable compound that develops a molybdenum blue color, with maximum absorption at 750 nm. The increase in absorbance at 750 nm is proportional to the protein concentration [20].

2.7 Determination of catalase activity

The color intensity is measured in a spectrophotometer at a wavelength of 410 nm against a sample containing 2 ml of H_2O.

Reagents	**Control**	**Experience**	**Reminder**
H_2O_2	2 ml	2 ml	-
Serum or liver homogenate	-	0.1 ml	10 minutes 37 ^{0}C
H_2O	0.1	-	
$(NH_4)_6Mo_7O_{24}$	1 ml	1 ml	-

Catalase activity in blood serum and tissues is determined by the number of catalase and is found by the following formula [21].

$$(\mu kat/l)\ E = (A_{control} - A_{experiment}) * V * t * 22.2$$

2.8 Measurement of glutamyl transferase

2 different reagents are needed to measure GGT. 1-Reagent Tris Buffer 100 mmol/L, NaCl 5 mmol/L, glycylglycine 125 mmol/L, 2-Reagent Tris Buffer 100 mmol/L, L-gutamyl-3-carboxy-4-nitroaniline. Simple is stable for 7 days at 2-8 C.

1-Reagent 100 ml, 2 reagents 50 ml, sample amount 25 ml, central wavelength 405-420 nm, temperature 37 C, passage 1 cm, test time 60-120 sec, absorbance line 0 -2A [22].

3. RESULTS OBTAINED AND THEIR ANALYSIS

The amount of glucose in the blood.

Our experiments showed that blood glucose levels varied in diabetic model animals. The blood glucose concentration in healthy animals was 5.6 mmol/L. However, in alloxan-induced diabetic rats, blood glucose levels increased significantly, reaching 15.5 mmol/L. 150 per body weight of sick animals for 7 days. After that, mg/kg Metformin and 20 mg/kg taurine and Schiff base complex were administered. Diabetic animals were treated with 150 mg/kg Metformin and 50 mg/kg taurine, along with a Schiff base complex for seven consecutive days. At the end of the experiment, blood glucose levels were measured again. Glucose levels decreased by 7.2 mmol/ml in metformin-treated animals compared to model animals. In animals treated with the complex compound, blood glucose levels were 6.7 mmol/L lower than in untreated diabetic animals [*Figure 1*].

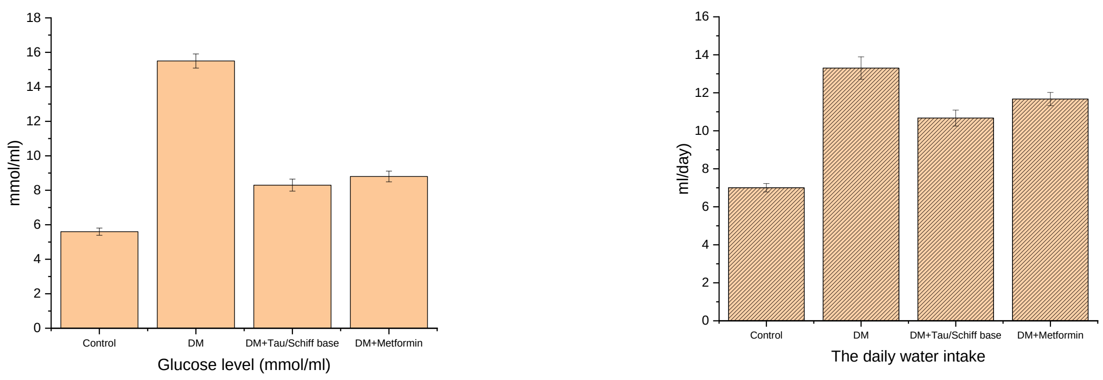


Figure 1 Changes in the amount of glucose in the blood plasma and the daily water intake of alloxan diabetes model animals and the effect of the complex compound on it (M±m, n=3)

Metformin is a well-known antidiabetic drug that increases insulin sensitivity, reduces gluconeogenesis by the liver, and improves cellular glucose uptake. This result suggests that Metformin helped reduce glucose levels. Treatment with Tau/Schiff base also helped to reduce glucose, but to a slightly greater extent than Metformin. This suggests that Tau/Schiff base may have specific mechanisms of action on glucose regulation but may not be as potent as Metformin. In the diabetic model, glucose levels were significantly higher than in the control group. Although Metformin and Tau/Schiff base effectively lowered glucose, Metformin was relatively more effective. Tau/Schiff base may have the potential to be used as an alternative agent in the management of diabetes, but further studies are needed to determine its mechanism of action and efficacy.

4. CHANGE IN THE AMOUNT OF MDA

Liver MDA levels and blood plasma oxidative stress markers were higher in diabetic animals compared to healthy ones, but after 10 days of treatment, they decreased under the effect of metformin, taurine and Schiff bases. In addition, our results suggest that the tested complex has a stronger effect than metformin.

In diabetic rats, the increase in the level of malondialdehyde (MDA) in liver homogenate and blood plasma is associated with oxidative stress and lipid peroxidation processes. This can be explained by the following principles: Hyperglycemia and oxidative stress in diabetes. Blood glucose levels increase, which leads to the formation of excess superoxide radicals (O_2^-) in the mitochondrial electron transport chain. NADPH deficiency occurs, weakening the antioxidant defense system. Increased aldose reductase activity results in sorbitol accumulation, which increases cellular osmotic stress. Free radicals oxidize polyunsaturated fatty acids (PUFAs) in the membrane, and as a result, lipid peroxidation initiates. In this process, MDA is formed as a byproduct of lipid peroxides. The liver is a metabolically active organ, and due to oxidative stress in it, MDA levels in liver homogenate increase. At the same time, MDA also enters the blood plasma and worsens the general systemic oxidative state. The activity of enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) decreases. As a result of a decrease in the GSH/GSSG ratio, the neutralization of free radicals slows down. This leads to an increase in MDA levels. In diabetes, an increase in MDA levels in the liver and blood plasma indicates increased lipid peroxidation and increased oxidative stress. This damages the membrane structures of cells and leads to the development of diabetic complications. Antioxidant therapy (e.g., vitamins E, C, flavonoids) may be effective in alleviating the diabetic condition.

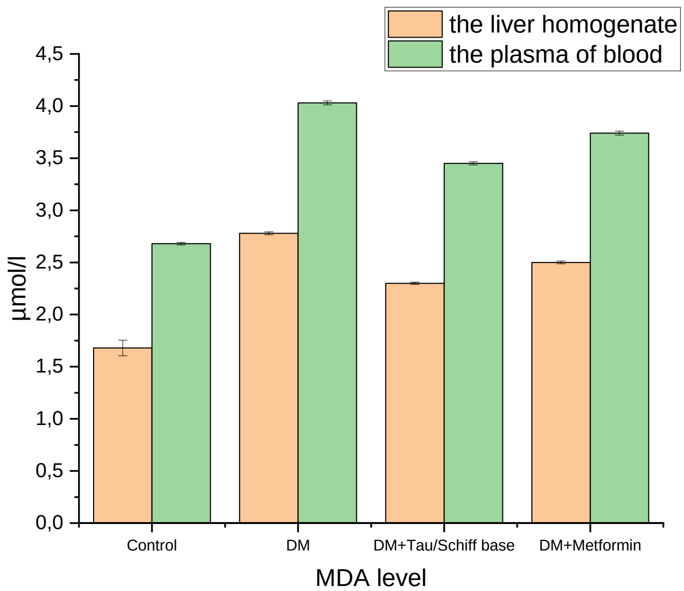


Figure 2 Changes in the amount of MDA in the liver homogenate and plasma of blood of alloxan diabetes model animals and the effect of the complex compound on it (M±m, n=3)

This figure clearly shows that MDA levels increased in diabetic rats. The results are analyzed as follows: The diabetes model (DM) led to increased MDA levels. Compared to the control group, MDA levels in the diabetic group increased significantly in liver homogenate (1.68 → 2.78 µmol/l) and blood (2.68 → 4.03 µmol/l). This indicates increased lipid peroxidation and oxidative stress. Metformin treatment slightly reduced MDA levels: Liver homogenate: 2.78 → 2.5 µmol/l, Blood plasma: 4.03 → 3.74 µmol/l. Metformin can reduce mitochondrial oxidative stress and reduce lipid peroxidation. Treatment with

Tau/Schiff base (DM+Tau/Schiff base). This group had the greatest decrease in MDA: In liver homogenate: 2.78 → 2.3 µmol/l and in blood plasma: 4.03 → 3.45 µmol/l [*Figure 2*]. This means that the Tau/Schiff base more effectively reduced lipid peroxidation and suppressed oxidative stress. In diabetes, an increase in MDA indicates heightened lipid peroxidation. Both Metformin and Tau/Schiff base exhibited antioxidant effects, but Tau/Schiff base led to a greater reduction in MDA. This suggests that the Tau/Schiff base may be more effective against diabetic oxidative stress.

5. CHANGES IN THE AMOUNT OF PROTEIN

Changes in protein content in liver homogenate of diabetic rats are based on the following factors. In diabetes, due to insulin deficiency, gluconeogenesis is activated, which means the body synthesizes glucose by breaking down amino acids in the liver and other tissues. As a result, protein catabolism in liver cells increases and the total protein content may decrease. Insulin is one of the main hormones that stimulate protein synthesis, which activates the ribosomal translation process. Due to a decrease in insulin levels in diabetes, protein synthesis slows down and the total protein content in liver homogenate decreases. In diabetes, reactive oxygen species (ROS) increase in liver cells, increasing oxidative stress. This can lead to oxidation and degradation of protein molecules. In addition, diabetes activates inflammatory mediators (IL-6, TNF-α), which accelerate the breakdown of proteins. One of the main proteins produced by the liver is albumin, and its synthesis may decrease in diabetes.

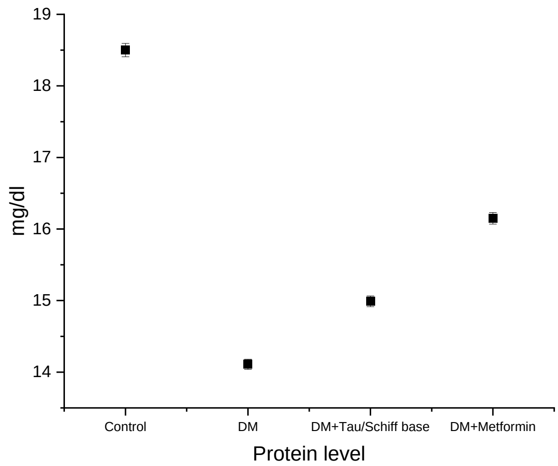


Figure 3 Changes in the amount of protein in the liver homogenate of alloxan diabetes model animals and the effect of the complex compound on it (M±m, n=3)

On the other hand, the body may increase the production of globulins in response to inflammation, which can have varying effects on total protein levels. Long-term diabetes can lead to fatty liver (hepatic steatosis) and liver failure. This further impairs protein synthesis and reduces protein levels in liver homogenates. It was noted that the total protein content in the liver of healthy animals was18.5 mg/dl, while in diabetic model rats, it was 14.11 mg/dl. At the end of the experiments, the livers of the animals were isolated, and their total protein content was determined. The total protein level was found to be 16.15 mg/dL in metformin-treated animals. When taurine and Schiff base derivatives were administered to the alloxan model, the total protein content in the liver was measured at 14.99 mg/dL [Figure 31].

6. CHANGES IN THE AMOUNT OF CATALASE

We can see that the amount of catalase decreased in the diabetic group and increased in the metformin group after 10 days of treatment. In the effect of our complex drug, the amount of catalase was found to be much higher than in the group treated with metformin.

Table 1 Changes in the amount of catalase in the liver homogenate and blood of alloxan diabetes model animals and the effect of the complex compound (M±m, n=3)

Experimental groups	Catalase µKat/mg protein (In liver homogenate)	Catalase µKat/mg protein (In blood)

Control	50.40 ± 1.43	37.92 ± 0.74
DM	39.57 ± 0.35*	22.9 ± 1.11
DM+Tau/Schiff base	44.77 ± 1.08	28.11 ± 0.84
DM+Metformin	47.13 ± 0.73*	30.13 ± 0.95*

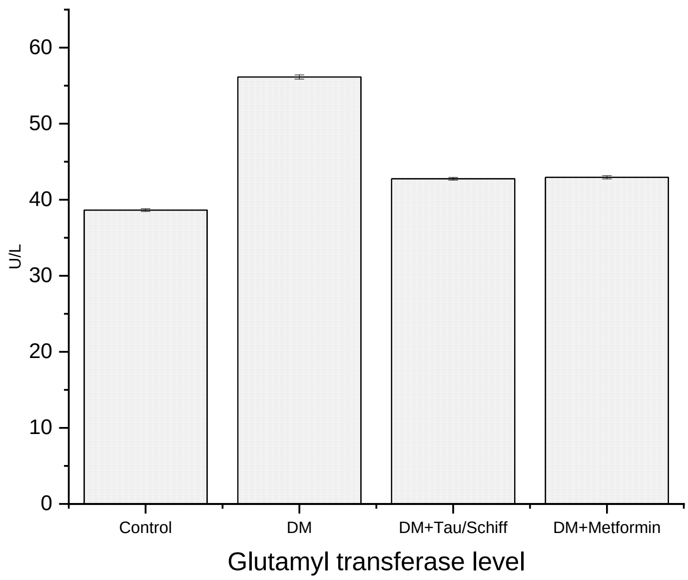
These results were aimed at evaluating the activity of the catalase enzyme in an experiment on a diabetes model (DM). Catalase is an antioxidant enzyme that protects cells from oxidative stress. These results can be interpreted as follows: In the control group, the liver homogenate was 50.40 ± 1.43 µKat/mg and in blood plasma 37.92 ± 0.74 µKat/mg, which indicates the activity of the catalase enzyme under normal physiological conditions. In the diabetes model (DM), the liver homogenate was 39.57 ± 0.35 µKat/mg and in blood plasma 22.9 ± 1.11 µKat/mg. Under diabetic conditions, catalase activity was significantly reduced. This indicates an increase in oxidative stress and a weakening of the antioxidant system in diabetes. When DM + Tau/Schiff base was administered, the liver homogenate was 44.77 ± 1.08 µKat/mg and in blood plasma 28.11 ± 0.84 µKat/mg. Tau/Schiff base increased catalase activity compared to the DM group, i.e., it partially restored antioxidant defense, though not to the control group. In the DM + Metformin group, it was 47.13 ± 0.73 µKat/mg in liver homogenate and 30.13 ± 0.95 µKat/mg in blood plasma [*Table1*]. Metformin significantly increased catalase activity and enhanced antioxidant defense. It was slightly more effective than Tau/Schiff base. Diabetes significantly reduced the antioxidant enzyme catalase, which indicates increased oxidative stress. Tau/Schiff base improved catalase activity, suggesting that it may be useful in restoring antioxidant defense in diabetes. Metformin restored catalase activity more effectively and improved antioxidant defense. These results indicate that Tau/Schiff base can be studied as an alternative drug to restore antioxidant defense in diabetes. Metformin was slightly more effective in increasing antioxidant enzyme activity, which confirms its ability to reduce oxidative stress in diabetes.

7. DETERMINING THE AMOUNT OF GGT

It was noted that the amount of GGT in the liver homogenate of diabetic model rats increased up to 17.5 Ed/l compared to healthy rats. Metformin and the complex compound were then administered to diabetic animals for 10 days. At the end of the experiments, the amount of GGT in the liver homogenate of the animals was checked. The amount of GGT decreased by 42.95 Ed/l in Metformin-treated animals and by 42.76 Ed/l in those administered a complex of taurine and Schiff's bases [*Figure 4*].

Figure 4 Glutamyl transferase (GGT) in the plasma of blood of alloxan diabetes model animals and the effect of the complex compound on it (M±m, n=3)

Amount of Glutamyl transferase in the blood (Ed/l)



GGT levels are elevated in diabetes, indicating liver dysfunction. Metformin and Tau/Schiff base have been shown to reduce GGT levels, suggesting that they have hepatoprotective properties. The effects of both drugs are similar, but further studies are needed to better understand the mechanism of Tau/Schiff base.

8. DISCUSSION

Streptozotocin and alloxan are commonly used to induce experimental diabetes models. In this study, we used alloxan throughout the experiment. Due to its structural similarity to glucose, alloxan enters cells via the GLUT4 transporter and generates reactive oxygen species (ROS), leading to pancreatic beta-cell destruction and diabetes. The use of alloxan in diabetes model induction has been widely documented in other studies. Taurine treatment for one week reduced blood glucose levels in rats, indicating its anti-diabetic properties. Previous studies have found that taurine protects pancreatic beta cells and modulate insulin sensitivity and insulin secretion. As a result, blood glucose levels decreased due to increased insulin secretion.

This study showed that plasma glucose levels were increased in alloxan-diabetic rats compared to control rats. In addition, protein levels decreased in plasma and liver homogenate. Given the important role of taurine in the body, including its antioxidant and osmoregulation effects, and the effect of the complex formed with Schiff bases, these parameters were restored to normal. The addition of Schiff base/taurine to diabetic rats increased pancreatic function and restored insulin secretion. These findings suggest that taurine plays a role in protecting cells from oxidative damage and suppressing functional impairment in diabetic rats. Similar decreases in tissue taurine levels have been previously reported in diabetic animals and humans. Indeed, plasma and platelet taurine levels were significantly lower in diabetic patients than in healthy subjects. Liver taurine levels also decreased in alloxan-induced diabetic rats. Previous studies have shown that taurine treatment attenuates the high-fat diet-induced decrease in enzymes and molecules involved in hepatic antioxidant defense. Based on these data, it is possible that the decreased hepatic taurine levels in alloxan diabetic rats may be at least partly due to impaired hepatic glucose metabolism and antioxidant defenses. This study and previously published results suggest that compounds and food components with antioxidant and anti-inflammatory properties may be effective in preventing the development of diabetes and diabetic complications. Some natural compounds, such as flavonoids, exert antidiabetic effects through their antioxidant and anti-inflammatory mechanisms. Thus, the Schiff base/taurine complex is expected to be effective in preventing diabetes and other diseases caused by impaired glucose metabolism [23].

As a result of diabetes, various organs, such as the liver, heart, and kidneys, are affected, leading to related diseases. Diabetes initially causes various changes in liver function. For example, decreased protein biosynthesis and reduced activity of antioxidant enzymes. The primary cause of this is the ROS production. During our experiment, protein biosynthesis decreased in diabetic rats. In addition, catalase enzyme activity also decreased. Taurine treatment restored protein biosynthesis, and enzyme activity significantly increased compared to diseased animals. Some experiments have shown that taurine's antioxidant properties depend on the Nrf 2 pathway. The Nrf 2 pathway protects against oxidative stress in early diabetes and increases the synthesis of antioxidant enzymes, resulting in increased enzyme activity. Taurine affects this Nrf 2 pathway and increases the activity of antioxidant enzymes. In addition, Nrf 2 pathway activation increases GSH-pX synthesis and reduces lipid peroxidation in the inflamed liver. This reduces the amount of MDA, which is the main indicator of lipid peroxidation [24]. Since GGT is located on the outer surface of most cells and mediates the uptake of glutathione, an important component of the intracellular antioxidant defense, its levels also reduced. Based on these findings, it can be concluded that the antioxidant properties of taurine are more effective in its complex with Schiff's bases. This complex may serve as a basis for developing antidiabetic drugs in the future.

This study showed that plasma glucose levels increased in alloxan-diabetic rats compared to control rats. In addition, protein levels decreased in plasma and liver homogenate [25]. Given the important role of taurine in the body, including its antioxidant and osmoregulation effects, these parameters were restored to normal by the complex formed with Schiff bases. The addition of Schiff base/taurine to diabetic mice increased pancreatic function and restored insulin secretion. These findings suggest that taurine plays a role in protecting cells from oxidative damage and suppressing functional impairment in diabetic rats. Additionally, the role of Schiff bases in the transport of taurine and its delivery to tissues is important. Similar decreases in tissue taurine levels have been previously reported in diabetic animals and humans. Liver taurine levels also decreased in alloxan-induced diabetic rats. We have previously shown that taurine treatment has both antioxidant and antidiabetic effects on enzymes and molecules involved in hepatic antioxidant defense. Based on these data, it is possible that the reduction in hepatic taurine levels in alloxan diabetic rats may be at least partly due to impaired hepatic glucose metabolism and antioxidant defenses. This study and previously published results suggest that compounds and food components with antioxidant and anti-inflammatory properties may be effective in preventing the development of diabetes and diabetic complications. Some natural compounds, such as flavonoids, exert antidiabetic effects through their antioxidant and anti-inflammatory mechanisms. Thus, the Schiff base/taurine complex is expected to be effective in preventing diabetes and other diseases resulting from impaired glucose metabolism.

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