EFFECTS OF NEW 1st, 2nd, 3rd TRIAZOLE PRODUCTS ON BIOCHEMICAL INDICATORS OF BLOOD PLASMA AND ACTIVITY OF LIVER ANTIOXIDANT IN DIABETES CAUSED BY ALLOXAN

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ABSTRACT:
This study established the effect of new derivatives of TF-25, TS-27, and ISO-31-triazoles on the activity of triglycerides, total cholesterol, the hormone insulin and the antioxidant enzyme

superoxide dismutase (SOD), catalase in rat liver homogenate in diabetes mellitus caused by alloxan, and also on the amount of MDA, the product of lipid peroxidation.
Studies were performed on male, white, breedless rats weighing 190–210 g. A solution of alloxan monohydrate (150 mg/kg) was used to create a diabetes model in rats. The experimental animals were divided into five groups. New TF-25 (40 mg/kg), TS-27 (15 mg/kg) and ISO-31 (25 mg/kg) derivatives of 1,2,3-triazoles were administered to alloxan diabetes mice for 10 days on a *"per os"* method. TF-25, TS-27, and ISO-31 triazole derivatives reversed body weight loss in rats in alloxan diabetes. New TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazole reduced the increase in plasma triglycerides and total cholesterol in diabetics. It was found that by increasing the amount of insulin, its secretion was restored. The new TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazole restored the activity of the enzymes SOD and catalase, which had decreased antioxidant activity in the liver homogenate of rats in alloxan diabetes. In diabetes mellitus, the LPO product in liver homogenate inhibited the intensity of MDA formation, the new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazole.
KEY WORDS: liver, plasma, triglycerides, total cholesterol, insulin, SOD, catalase, MDA, 1,2,3-triazole, TF-25, TS-27, ISO-31.

INTRODUCTION: Diabetes mellitus is a complex endocrine disease characterized by many metabolic diseases. Insulin-dependent (type 1) and non-insulin-dependent diabetes mellitus (type 2) are one of the most common diseases in modern society. The development of this disease in hyperglycemia is the most important risk factor for complications of disruption of the capillary vascular endothelial layer, leading to clinically severe tissue damage and diabetic retinopathy, nephropathy, and neuropathy[1]. Oxidative stress associated with hyperglycemia and impaired nitric oxide production plays a key role in the pathogenesis of diabetes and its complications. Insulin hormone is important in glucose homeostasis, in the utilization of glucose by skeletal muscle cells, and in the reduction of glucose production in the liver. In 2005, M. Brownlee presented a mechanism hypothesis proving the decisive role of oxidative stress in the development of diabetes[2]. According to him, mitochondrial dysfunction is the main mechanism of activation of tissue and cell damage in diabetes mellitus, an excessive increase in the generation of superoxide radicals[3].

The insulin-dependent mechanism of glucose utilization consists of a sequence of insulin signal cascade reactions. According to him, the insulin hormone interacts with its corresponding receptors (insulin receptor substrate - 1 IRS1). Insulin receptors consist of subunits α and β. Insulin converts inactive IRS1 to active IRS1 under existing conditions. IRS1, on the other hand, changes from the inactive state to the active state of phosphatidylinositol-3 kinase (PI3K). In the plasma membrane of the skeletal muscle cell, glucose enters the cell via GLUT-4 and biochemical processes initiate a signal cascade pathway[4].

Today, the response of cells to the effects of biological substances in various pathological conditions is widely studied[5]. Currently, there is an increase in demand for such drugs in medicine. The growing demand for highly biologically active, low-toxic, nonsteroidal heterocyclic compounds in the world is not in vain. Because the demand for medicinal substances cannot be met by biologically active substances derived from plant raw materials [6,7,8,9,10]. 1,2,3-Triazole derivatives are low-toxic heterocyclic compounds whose chemistry and biological activity are currently being intensively studied [11,12,13,14,15].

OBJECTIVES: To determine the effect of new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles on the activity of triglycerides in blood plasma, total cholesterol, insulin hormone and antioxidant enzymes in liver homogenate in rats with diabetes caused by alloxan.

RESEARCH METHODS AND MATERIALS: Studies were performed on male, white, breedless rats weighing 190–210 g. Alloxan monohydrate solution was used to create an experimental diabetes model in experimental animals. In experimental animals, alloxan was injected once daily at a dose of 150 mg/kg of alloxan monohydrate solution into the subcutaneous area of the abdomen after a day of starvation to induce diabetes[16]. The experimental animals were divided into five groups:

I - Control: Healthy (n = 5)
II - Alloxan diabetes 150 mg/kg (n = 5);
III –Alloxan diabetes + TF-25 40 mg/kg (n = 6);
IV - Alloxan diabetes + TS-27 15 mg/kg (n = 6);
V - Alloxan diabetes + ISO-31 25 mg/kg (n = 6);

Group II, III, IV, and V animals were injected with 150 mg/kg alloxan monohydrate dissolved in saline once daily. Twelve days after injection of alloxan monohydrate in rats, when blood glucose levels exceeded 11 mmol/l, fresh derivatives of 1,2,3-triazoles were administered once daily for 10 days on a per os basis to group III animals through TF-25, to group IV animals through TS-27 and to group V through ISO-31. The animals in the group were sent. Blood glucose was determined by the method of "glucose oxidase" ("Glucose - enzymatic-colorimetric test", Cypress diagnostic, Belgium).

For the preparation of liver tissue homogenate, experimental groups isolated animal liver. A Potter homogenizer homogenized at 120 mM KCI and 30 mM phosphate buffer (pH 7.4) at 0-4 ºC. The nucleus and cell were centrifuged at 600 g for 10 min to remove fractions. The resulting supernatant was used to determine the activity of antioxidant enzymes as liver tissue homogenate. The protein concentration in liver homogenate was determined by the Lowry method [17].

The amount of MDA, SOD and catalase activity in liver homogenate was determined. The amount of MDA in the liver homogenate of experimental animals determined by the method of these researchers[7]. The principle of this method was determined by the method based on the interaction of thiobarbiturate acid with MDA formed from the peroxidation of unsaturated fatty acids containing 2-3 diene bonds.

Superoxide dismutase activity (SOD) was determined based on the Chumakov method [18]. Enzyme activity was expressed in units of Ed / mg protein.

Catalase activity was determined using a method based on the formation of a yellow compound of hydrogen peroxide with molybdenum salts [19].

In the experimental group of rats, peripheral blood was taken in sterile solutions to determine the amount of triglycerides, total cholesterol, and insulin in the blood plasma and kept at room temperature for 2 h. The blood in the solutions was then centrifuged at 4°C for 15 min at 1500 rpm. Plasma triglycerides and cholesterol levels were determined using an enzymatic colorimetric method using a set of reagents Novoxol Vector-Best (Russia). Plasma insulin levels were determined using Insulin ELISA kit reagents (Mercodia AB, Sweden).

Statistical processing of the obtained results and drawing of images were carried out using the program OriginPro 7.5. In this case, the values of $R<0.05$ and $R<0.01$ represented statistical reliability.

OBTAINED RESULTS AND THEIR ANALYSIS: In the alloxan-induced diabetes mellitus model, changes in not only cell-level but also morphological markers were observed in experimental animals. One such morphological feature is the change in body weight of rats in the context of diabetes mellitus. The results showed that in the initial period of the experiment, the control group rats had an average body weight of 195±2.5 g, and on average 21 days of the experiment, 249±3.4 g (Table 1). It was found that the increase in body weight of animals fed on protein-rich rations in healthy animals vivarium was 27.7±1.1 g. The body weight of animals in the Alloxan diabetes model group was found to be decreased by 18.2±0.8 g, averaging 166±2.8 g at the end of the experiment, compared with an average of 203±2.1 g at the beginning of the experiment (Table 1).

Table 1

Effects of 1,2,3- triazoles on new TF-25, TS-27, and ISO-31 derivatives in rat body mass in alloxan diabetes

Experiment groups	Initial body weight (g)	Final body weight (g)	Changes in body weight (g)
I group. Control (healthy)	195±2,5	249±3,4	27,7±1,1
Group II. Alloxan diabetes	203±2,1	166±2,8	-18,2±0,8
Group III. Alloxan diabetes + TF-25	196±1,7	220±3,1	12,2±0,5
IV group. Alloxan diabetes + TS-27	196±2,2	235±2,0	19,9±1,1
V group. Alloxan diabetes + ISO-31	198±2,0	230±1,8	16,1±0,9

In the model of alloxan diabetes, the decrease in body weight of rats is accompanied by a violation of metabolism in the body. The decrease in body mass of rats in the diabetes model has also been reported in many literatures [20,21]. When rats with alloxan diabetes mellitus III, IV and V were treated with new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles for 10 days, their body weight increased to 12.2±0.5, 19.9±1.1 and 16.1 g, respectively (Table 1). Thus, the new derivatives of 1,2,3-triazoles TF-25, TS-27 and ISO-31 in the model of alloxan diabetes did not lead to a decrease in body mass by correcting metabolic disorders in animals. In the diabetes model, changes in body weight are accompanied by changes in their blood glucose levels, triglycerides, total cholesterol, and insulin levels [22].

In our next experiment, the effect of the new TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazoles on triglycerides, total cholesterol, and insulin levels in the blood plasma of rats in the alloxan diabetes model was determined. The results showed that the level of triglyceride in the blood of rats in group II alloxan diabetes mellitus was 176.4±6.3 mg / dl, which was higher than the control (Table 2). The main constituents of hepatocyte lipids are triglycerides, the synthesis of which requires subcutaneous fatty acids and glycerophosphates. The main sources of glycerophosphate in hepatocytes are glycerol and glucose, which are formed during lipid hydrolysis and are converted to phosphatidic acid during glycolysis. This causes triglyceride synthesis reactions. Thus, the synthesis of triglycerides in hepatocytes depends on the content of glucose, fatty acids, and acetyl coenzyme A [23.] An increase in triglycerides alloxan in the blood

plasma in diabetes mellitus indicates a violation of glucose utilization, increased production of fatty acids.

When rats with alloxan diabetes mellitus group III were treated orally with TF-25 triazole for 10 days, their plasma glycerin levels were equal to 120.7±5.4 mg/dl and much less than group II rats. When we treated experimental rats with alloxan diabetes group IV and V with TS-27 and ISO-31 triazole derivatives for 10 days, their plasma glycerin levels were 74.4±5.3 and 104.8±6.1 mg / dl, respectively, and decreased relative to the second group (Table 2).

Table 2

Effect of new TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazoles on blood plasma triglycerides, total cholesterol, and insulin in healthy and alloxan diabetic rats

Experiment groups	**Triglyceride (mg / dl)**	**Total Cholesterol (mg / dl)**	**Insulin content (mkEd / ml)**
Group I: Control (healthy)	52,5±3,6	57,3±4,5	14,7±1,2
Group II: Alloxan diabetes	176,4±6,3**	96,6±6,1**	5,3±0,4**
Group III: Alloxan diabetes + TF-25	120,7±5,4**	72,5±3,8*	8,2±0,6*
Group IV: Alloxan diabetes + TS-27	74,4±5,3*	64,1±4,2*	11,8±1,0*
Group V: Alloxan diabetes + ISO-31	104,8±6,1**	70,3±5,2*	9,9±0,8*

Note: *P<0,05; **P<0,01; n=6

Hence, new derivatives of triazoles reduced triglyceride levels in alloxan diabetes rats. In this regard, there is information in the literature on the effective reduction of triglycerides of biologically active compounds in streptozotocin diabetes[24], and the results we obtained are consistent with such literature.

In our next experiment, changes in total plasma cholesterol levels in alloxan diabetes mellitus and the effect of 1,2,3-triazoles on the new derivatives TF-25, TS-27 and ISO-31 were studied. The results showed that the total cholesterol in the plasma of alloxan diabetes mellitus group II rats was 96.6±6.1 mg / dl, which was higher than the control. Rats of group III with alloxan diabetes were pharmacotherapied for 10 days in 'preoral' way with a new yield of TF-25 triazole product, group IV animals with a TS-27 yield, and diabetes rats from group V with the ISO-31 triazole product. The total cholesterol in the plasma of pharmacotherapeutic group III (72.5±3.8), group IV (64.1±4.2) and group V (70.3±5.2) diabetic rats was higher than that of alloxan diabetic group II decreased (Table 2).

Decreased concentrations of phospholipids, hypercholesterolemia, increased lipoproteins, create conditions for the development of angiopathy-atherosclerosis in diabetes. Lipocaine deficiency plays an important role in the development of atherosclerosis in diabetes. As a result of its deficiency, the synthesis of phosphorlipids in the liver will reduce. This in turn leads to the deposition of cholesterol in the blood vessel wall and the development of atherosclerosis. An increase in total cholesterol in diabetes conditions may be associated with a decrease in the hydrolysis of phospholipids [25]. Increased plasma concentrations of total cholesterol as a result of diabetes were reliably reduced by new derivatives of 1,2,3-triazoles TF-25, TS-27 and ISO-31.

Alloxan contains extracts that reduce the total cholesterol in the plasma of diabetic rats[26], but the effect of the new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles we studied is that these active substances can greatly affect total plasma cholesterol even at low concentrations.

Insulin stimulates anabolic processes at all stages of metabolism, enhances the synthesis of glycogen, fats and proteins, and inhibits the effects of glucagon, catecholamines, glucorticoids, and somatotropic hormones. Insulin enhances cell membrane hyperpolarization (excluding hepatocytes), glucose utilization and increased permeability, activation of Na-K-ATPase, cellular entry of K^+ ions, and absorption of amino acids. In the setting of diabetes, glucose deficiency in the cells begins as a result of a decrease in insulin secretion from the β-cells of the pancreas. This is manifested by inhibition of liver enzyme activity, protein enzyme synthesis and mitogenesis activity, including organs[27].

We conducted another experiment to determine changes in plasma insulin levels in rat blood in alloxan diabetes and the effect of the new TF-25, TS-27, and ISO-31 derivatives of triazoles on them. The results showed that the amount of insulin in the blood plasma of animals with alloxan diabetes was 5.3±0.4 mkEd / ml, which is 2.7 times lower than the control (Table 2). A decrease in plasma insulin levels in diabetes is indicative of a decrease in insulin secretion of pancreatic β-cells under the influence of this alloxan. In order to restore insulin secretion, rats with alloxan diabetes mellitus groups III, IV and V were treated with pharmacotherapy by injecting new derivatives of 1,2,3-triazoles for 10 days. Plasma insulin content in group III animals treated with TF-25 was 8.2 ± 0.6 mkEd/ml, in group IV treated with TS-27 was 11.8±1.0 mkEd/ml, and in pharmacotherapy with ISO-31 V the amount of insulin in the blood plasma of the group of rats was 9.9±0.8 mkEd/ml. It was found that insulin was increased in the ratio 1.5:2.2 and 1.8 times, respectively, in animals with group II alloxan diabetes. This suggests that β-cell dysfunction in alloxan diabetes-induced rats was corrected under the influence of new derivatives TF-25, TS-27, and ISO-31, and that their function was restored relative to the pathological condition.

In experimental diabetes, metabolites begin to form as a result of increased free radical generation in the heart, pancreas, and liver mitochondria. The toxic effect of metabolites is associated with the acceleration of the process of lipoperoxidation, which leads to disruption of the structural and functional unit of the cell membrane [28]. In order to explain this mechanism, we determined the amount of MDA, the end product of the LPO process, in liver tissue. In our experiment, an increase in the amount of MDA in the liver homogenate of animals with group II alloxan diabetes was observed relative to the concentration of MDA in the liver homogenate of control rats (Fig. 1).

In particular, the increase in the amount of MDA in the liver homogenate of animals with group II diabetes was 3.9 times higher than the control values and amounted to 4.3±0.25 nmol / mg of protein. New TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazoles were administered orally to rats with alloxan diabetes for 10 days. Blood glucose was monitored and experiments were performed to determine the amount of MDA in the liver homogenate of rats close to control. In the experimental group of pharmacotherapy with new derivatives of triazoles TF-25, TS-27 and ISO-31, it was found that the amount of MDA in the liver homogenate of rats decreased compared to group II (Fig. 1).

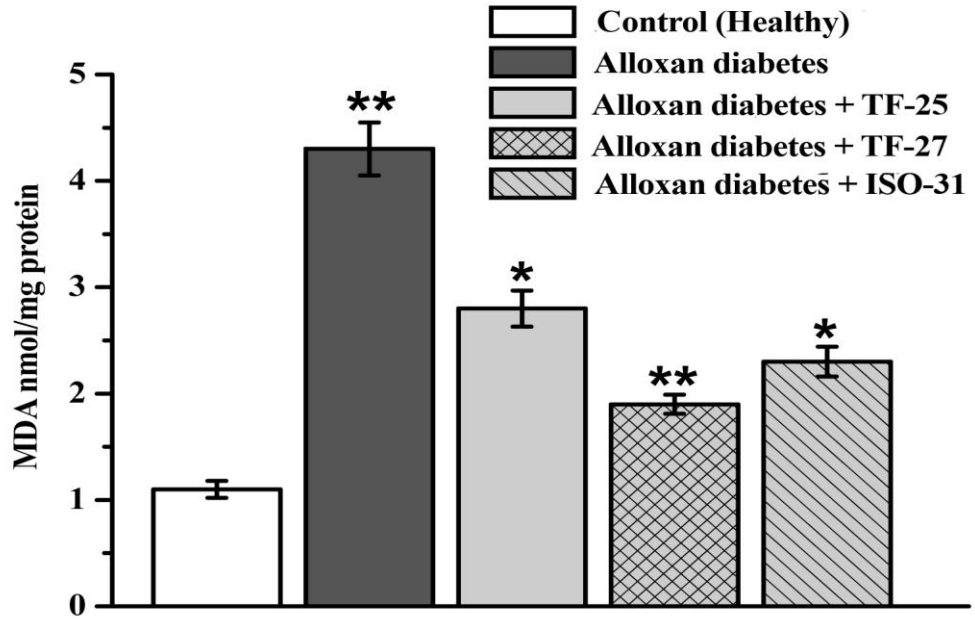

Figure 1. Influence of new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles on the amount of MDA in liver homogenate in alloxan diabetes. *R<0.05; **R<0.01; n = 6.

The amount of MDA in liver homogenate of rats in group III sent to TF-25 was 2.8±0.17 nmol / mg of protein, in group IV sent to TS-27 was 1.9±0.09 nmol / mg of protein, and in group V sent to ISO-31 was 2.3.±0.14 nmol / mg of protein was found to reduce the amount of MDA by 1.53, 2.26, and 1.72 times, respectively, compared to group II values (Fig. 1). The literature shows that an increase in the amount of MDA in the liver under the influence of activation of the process of lipid peroxidation in the conditions of experimental diabetes was detected[29]. Our experience also confirms the above points.

In our subsequent experiments, changes in the activity of the antioxidant enzyme SOD in liver homogenate were detected as a result of pharmacotrophy of alloxan diabetic rats with new derivatives TF-25, TS-27 and ISO-31 of 1,2,3-triazoles (Fig. 2). The results showed that the SOD content in the liver homogenate of rats with alloxan diabetes mellitus group II was 6.9±0.5 Ed/mg protein, a decrease of 45.3% compared to the control (12.6±0.7 Ed/mg protein). Pharmacotherapy with new derivatives of triazoles TF-25, TS-27 and ISO-31 III (8.7±0.7 Ed / mg protein), IV (11.2±0.8 Ed/mg protein) and V (9.6±0.8 Ed/mg protein) Experimental groups found that the amount of SOD in the liver homogenate of rats increased by 14.3%, 34.2%, and 21.5%, respectively, compared with group II indicators (Fig. 2). This means that in the case of diabetes, the activity of the enzyme SOD in the liver decreases and an antioxidant imbalance occurs. New derivatives of triazoles TF-25, TS-27 and ISO-31 reliably increase the activity of the enzyme SOD, which is reduced in the liver in alloxan diabetes (Fig.2).

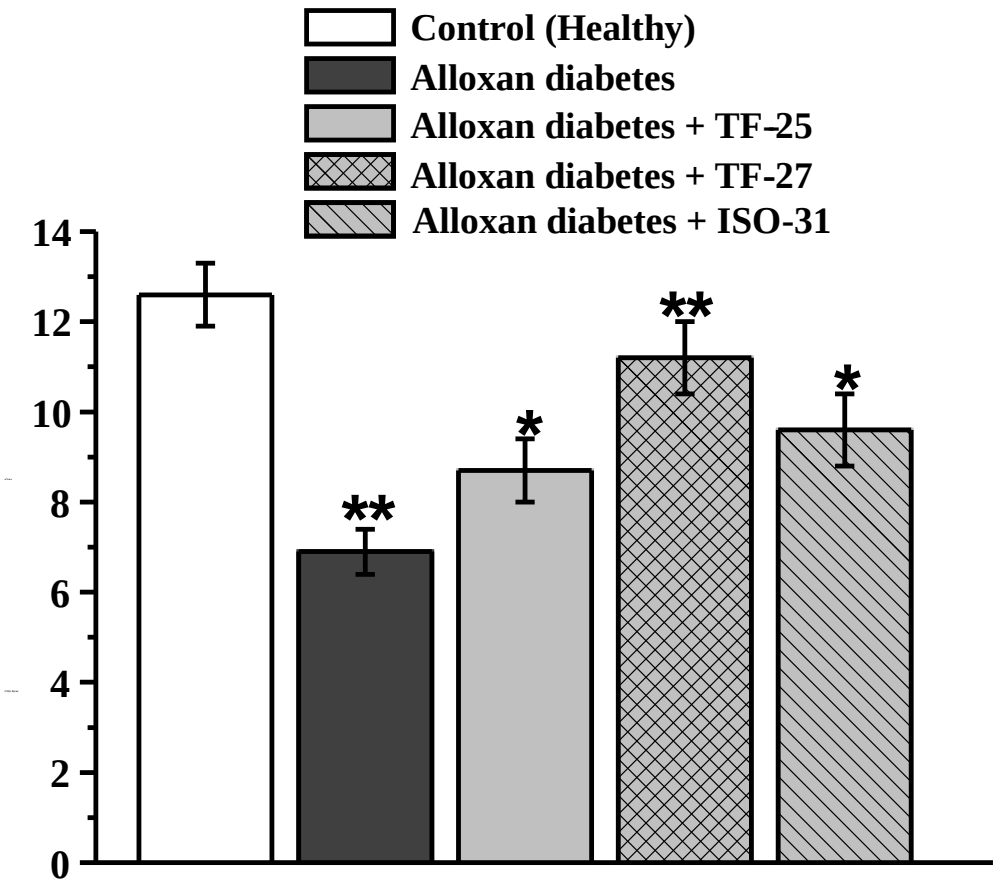

Figure 2. Influence of new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles on the amount of SOD in liver homogenate in alloxan diabetes. *R<0.05; **R<0.01; n = 6.

The development of an imbalance in the antioxidant system activity of liver cells in the context of alloxan diabetes has been proven in our experience. In our next experiment, changes in the activity of another antioxidant enzyme catalase in liver homogenate in a diabetes mellitus model and their effect on new derivatives of 1,2,3-triazoles were detected (Fig. 3). In particular, catalase activity in liver tissue was found to be 43.2±3.6 mkM/min/mg protein in group II rats in allosan-induced diabetes mellitus, a 43% decrease compared to controls. Treated alloxan diabetes mellitus III (56.9±4.1 mkM/min/mg protein), IV (69.7±5.1 mkM/min/mg protein) and V (63.1±4.4 mkM/min / mg protein)) in group rats, enzyme activity decreased by 18.1%, 35.3% and 26.3%, respectively, compared to group II, which was close to the control values (Fig. 3).

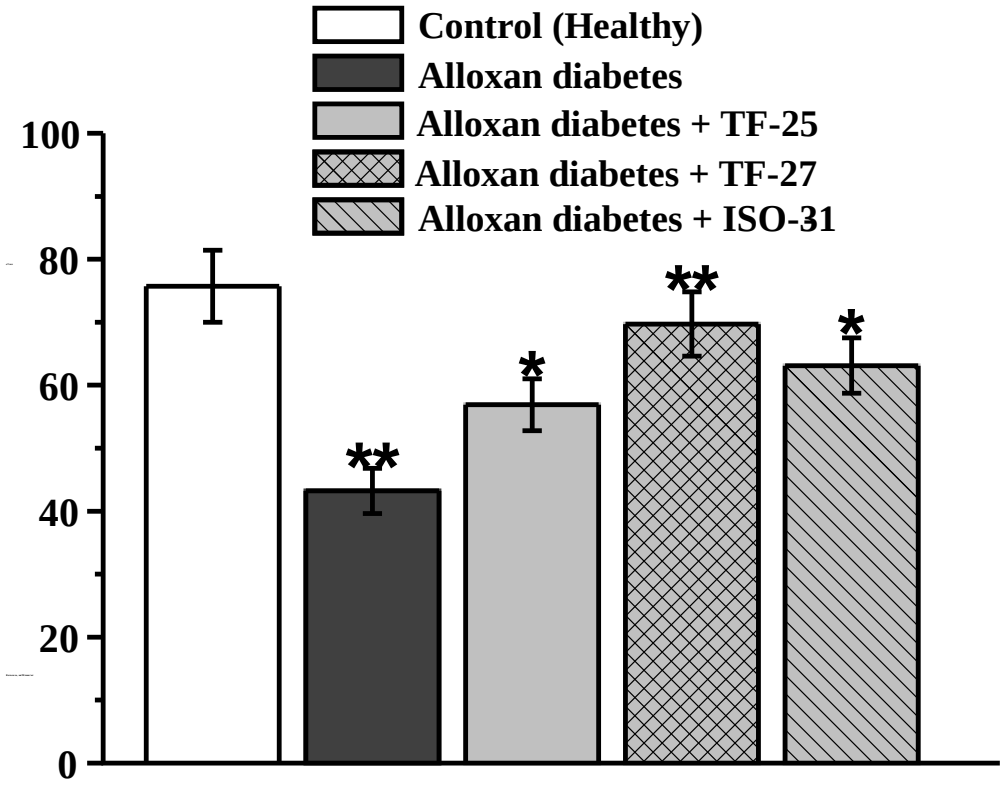

Figure 3. Influence of new TF-25, TS-27 and ISO-31 derivatives of 1,2,3-triazoles on catalase activity in liver homogenate in alloxan diabetes. *R<0.05; **R<0.01; n = 6.

Catalase is an enzyme that acts as an antioxidant and plays an important role in the protective system against LPO products. Numerous studies have found a significant decrease in catalase activity in experimental diabetes [29,30]. Changes in the activity of antioxidant system enzymes in diabetes are the result of excessive production of LPO products and active forms of oxygen. It is a potent inhibitor of superoxide radical catalase in particular. Thus, in the context of alloxan diabetes, rats were able to restore plasma triglycerides, total cholesterol, and insulin concentrations by new derivatives of triazoles, TF-25, TS-27, and ISO-31. New derivatives of triazoles such as TF-25, TS-27, and ISO-31 can reliably reverse the changes in the amount of SOD and catalase and LPO MDA in diabetes conditions, which control the antioxidant system. From that point, the activity of the TS-27 triazole derivative from these active substances was slightly higher than that of the TF-25 and ISO-31 derivatives.

CONCLUSION: TF-25, TS-27, and ISO-31 triazole derivatives reversed body weight loss in rats in alloxan diabetes. New TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazole reduced the increase in plasma triglycerides and total cholesterol in diabetics. It was found that by increasing the amount of insulin, its secretion is restored. The new TF-25, TS-27, and ISO-31 derivatives of 1,2,3-triazole restored the activity of the enzymes SOD and catalase, which had decreased antioxidant activity in the liver homogenate of rats in alloxan diabetes. New TF-25 TS-27 and ISO-31 derivatives of 1,2,3-triazole inhibited the intensity of MDA formation of LPO product in liver homogenate in diabetes mellitus.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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