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Research Article

Ameliorative Effect of a Vanadium-thiosemicarbazone Complex on Oxidative Stress in Stomach Tissue of Experimental Diabetic Rats

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ABSTRACT

Recently, we have shown that oral administrations of an oxidovanadium (IV) complex, VOL, with tetradentate thiosemicarbazone ligand normalizes hyperglycemia of streptozotocin-induced diabetic rats (STZ-rats). For the development of vanadium compounds that exhibit insulin-like behavior, it is essential to know some of the pharmacokinetic properties of these complexes. The goal of the current research is to examine the healing effect of new sythesed VOL complex on the oxidative stress parameters of diabetic stomac tissue. Rats used in the experiments were divided as control, VOL+control, diabetic and diabetic+VOL. The rats were sacrificed after 12 days of the experimental period. The levels of glutathione, lipid peroxidation, non-enzymatic glycosylation, advanced oxidized protein products levels and the activities of some enzymes were measured in stomach tissue of all the experimental animals. Although VOL treatment to diabetic rats increased the stomach glutathione levels; lipid peroxidation, non-enzymatic glycosylation and advanced oxidized protein products levels were decreased. Also, the activities of catalase, superoxide dismutase, glutathione-S-transferase, glutathione peroxidase, glutathione reductase and carbonic anhydrase were increased in VOL treated diabetic group. Whereas, lactate dehydrogenase and xanthine oxidase activities were decreased. According to the obtained outcomes, it can be said that VOL treatment has a healing effect on the stomach tissue of diabetic rats. This effect provided by VOL is most likely due to the insulin-like and antioxidant activity of the complex. In conclusion, we can say that VOL may be a suitable candidate for diabetes treatment

1. Introduction

In recent years, increasing urbanization and deteriorating lifestyle has led to an increasing level of diabetes mellitus (DM), which is estimated to reach 700 million worldwide by 2045 [1]. The main underlying causes are the disruptions in carbohydrate, lipid and protein metabolisms due to insufficient insulin levels or its action on target tissues such as eyes, skin, kidneys, heart, nerve and stomach [2-6]. In addition to disorders in insulin metabolism, recent reports show that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can also induce hyperglycemia and diabetic ketoacidosis as a result of coronavirus disease 2019 (COVID-19) complications even in nondiabetic patients [7].

Although the diffusiveness of diabetic gastroenteropathy has not been fully disclosed, there is shown that the 10-year cumulative

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incidence of diabetic gastroparesis is 5.2% for patients with type 1 DM, and 1% for type 2 DM patients [8]. The most common gastrointestinal dysfunctions in diabetic patients are nausea, vomiting, diarrhea, heartburn, constipation, and motor dysfunction in various segments of the system [9].

Hyperglycemia can alter oxidant/antioxidant balance in the biological system, which is an important factor causing oxidative stress [10]. High free radical production and accumulation, which occurs through metabolic reactions and immune cell responses as well as processes such as cell interactions and signaling, cell growth, aging, synaptic plasticity, autoimmune reactions, autophagy and apoptosis, can trigger devastating biological effects. [11].

Streptozotocin (STZ) is a diabetes-inducing agent that acts directly on the islet beta cells of the pancreas, causing an elevation of reactive oxygen species (ROS) levels and weakening of the defense system that neutralizes them [12]. The degeneration of insulin-producing beta cells in the pancreas leads to the pathogenesis of diabetic [13].

There are various oral antihyperglycemics currently available for the treatment of diabetes. From them, sulfonylureas and biguanides have been in use since the 1950s. The sulfonylurea family (glyburide, glimepiride and glipizide) bestows their antidiabetic action via a mechanism that involves stimulating insulin secretion [14-16], while biguanides (metformin) act by increasing insulin activity [17]. Contrary to these traditional agents whose glucose-lowering effects were serendipitously discovered, a new generation of oral antidiabetics such as dipeptidyl peptidase-4 inhibitors have been developed [18]. However, different prospective studies are rapidly underway to find the most effective orally active insulin replacements or insulin mimicking agents.

Vanadium is an ultra-trace element that acts as a cofactor for some intra cellular enzymatic reactions in the biological system. It is also closely related to glucose homeostasis, lipid metabolism, antioxidant functions and regulation of immunity in humans and animals [19]. Initial findings suggested that vanadium had replaced insulin in living organisms. However, it was later reported to enhance insulin secretion by regenerating pancreatic beta cells [20, 21]. Furthermore, vanadium and some of its complexes have curative effects on hyperlipidemia and hypertension. They are also potential agents to cure malignant tumors, heart and neuronal disorders, influenza and viral infections like human immunodeficiency virus (HIV) and SARS-CoV-2 [19, 22].

Although diabetic gastroenteropathy is often associated with other manifestations of DM, its prevalence is not well documented. The current research is aimed at determining the effects of thiosemicarbazone-based oxidovanadium (IV) complex (VOL) on biochemical changes in stomach tissue of diabetic rats as a candidate for alternative therapies.

2. Materials and Methods

2.1. Synthesis

2,4-dihydroxybenzaldehyde-S-methyl-thiosemicarbazone was used as starting material to obtain 2,4-dihydroxybenzylidene-N (4)-2-hydroxybenzylidene-S-methyl-thiosemicarbazidato-oxidovanadium (IV) (VOL). The compound was prepared according to previously reported methods [21, 23, 24]. 2,4-dihydroxybenzaldehyde (1 mmol) was added to the solution of S-methyl-thiosemicarbazide (1 mmol) in ethanol (50 ml), and refluxed for 4 hours. The cream-colored precipitate formed was filtered, and recrystallized with ethanol (m.p.:180-181 ^{o}C, yield: 92%).

Further reactions were proceeded when $VOSO_4.5H_2O$ (1 mmol) was dissolved in a balloon flask by adding ethanol (50 ml). The solution of the starting material (1 mmol), 2-hydroxybenzaldehyde (1 mmol) were added to balloon containing the metal solution and then stirred for 5 hours [21, 25]. The brownish-powder product formed was filtered, and its structural confirmation was evaluated by elemental analysis, UV and IR spectra (Fig 1). The characterization data are: Yield 68%, m.p. > 380-381^{o}C. μ_{eff}: 1.64 BM. Anal. Calc. for $C_{16}H_{13}N_3O_4SV$ (394.3 g mol^{-1}): Found (calc.): C,

48.77 (48.74); H, 3.30 (3.30); N, 10.69 (10.66); S, 8.12 (8.09). UV-Vis (λ nm in DMSO): 246, 316, 352, 418, 800, 958. IR (ATR, cm^{-1}): ν(OH) 3411, ν(C=N) 1605, 1595, 1578, ν(C−O) 1146-1123, ν(V=O) 985, ν(V-O) 477-434.

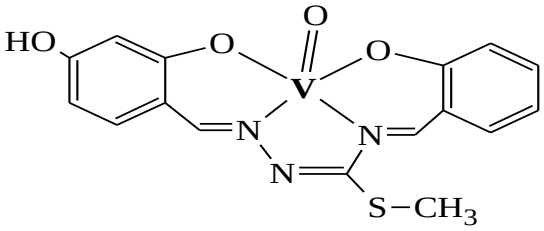

Figure 1. The oxidovanadium (IV) complex, VOL

2.2. Animal groupings

Male Swiss albino rats (between 3.0-3.5 months old and 200 ± 50 g weight) were provided from Animal Care and Use Institute's Committee of Istanbul University. Before starting the study, all rats were housed in the same conditions. Animals, fed with standard pellets, were allowed to access water *ad libitum.* The experimental protocols were reviewed and approved by the Animal Care and Use Institute's Committee of Istanbul University. Animals were randomly selected into four experimental groups as follows: two control groups divided as (Group 1; n=5) control group-intact and (Group 2; n=5) treated control-which received VOL (0.2 mM/kg/day); two diabetic groups separated as (Group 3; n=6) diabetic control-injectied with streptozotocin (STZ) (65 mg/kg body weight) and (Group 4; n=5) VOL treated diabetic group (received the same doses of STZ and VOL). VOL was given to the rats by gavage technique (upon dissolution in 3% gum arabic solution) for 12 days after the rats became diabetic [26]. On day 12, last day of the experiment, the animals were sacrificed under anesthesia and stomach tissue samples were collected.

2.3. Diabetic model induction

After overnight fasting but allowed free access to water, diabetes was induced via a single intraperitoneal injection (i.p.) of STZ (dissolved in cold citrate buffer (0.1 M, pH 4.5) to the rats (65 mg/kg) [27]. Diabetes was confirmed from tail blood samples after 24 hours of injection. A blood glucose level above 250 mg/dL was considered a standard for successful diabetic model induction. On the 0, 1, 6 and 12 days, blood glucose and weight of all animals were examined. This section was detailed in the study based on synthesis characterization and antidiabetic properties of the VOL complex [21].

2.4. Sample collection

After intervention for 12 days, the rats in each group were sacrificed and stomach specimens were carefully collected. Stomach tissues were homogenized in a cold saline solution (0.9 %), and centrifuged at 15000×g, +4°C for 10 minutes. The clear supernatant of each sample was aliquoted into several vials and stored at −76°C for biochemical analysis for later use.

2.5. Analysis of oxidative stress markers and antioxidant enzyme activities

The reduced glutathione (GSH), lipid peroxidation (LPO), advanced oxidized protein products (AOPP), non-enzymatic glycosylation (NEG), and total protein levels of the stomach homogenates were determined according to the methods of Beutler [28] - using Ellman's reagent, Ledwozyw et al. [29], Witko-Sarsat et al. [30], thiobarbituric acid method [31] and Lowry et al. 32], respectively. Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST) activities were assessed as described by Aebi [33], Mylorie et al. [34], Paglia & Valentine [35] and modified by Wendel [36], Beutler [37] and Habig & Jakoby [38], respectively. The activities of carbonic anhydrase (CA), lactate dehydrogenase (LDH) and xanthine oxidase (XO) were estimated according to Verpoorte et al. [39], Wroblewski [40] and Corte & Stirpe [41], respectively.

2.6. Statistical analysis

Biochemical findings were evaluated using GraphPad Prism Software, version 6.01 (San Diego, USA). Data were expressed as mean ± standard deviation (SD) using one-way analysis of variance (One-way ANOVA), followed by

Tukey's multiple comparison post hoc test. $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Synthesis and structural confirmation

Complex VOL was obtained from the template reaction of the starting material and aldehyde in the presence of oxovanadium (II) ion. Formation of the complex was monitored through IR spectrum, by tracking bands attributed to the 2-OH and NH_2 groups on the starting material. The disappearance of these bands and the emergence of bands related to the V=O and VO vibrations were evidence of VOL formation [21].

In IR spectrum of the starting material, the imine groups were observed at 1608 and 1585 cm−1, while the hydroxyl group was monitored at 3495 cm−1. In the infrared spectrum of VOL, bands attributed to C=N1 and N4=C were monitored at 1605, 1595, and 1578 cm−1 respectively. Additionally, while the stretching and bending bands at 3445, 3337 and 1624 cm−1 of amine group of the starting material disappeared, new bands formed at 985, 477-434 cm−1 assigned to V=O and VO groups were observed. The UV-Vis spectrum of VOL showed the charge transfer bands at the 246, 316 and 352 nm assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, d-d bands at 418, 800 and 958 nm [21].

The structure and purity of the products were checked by elemental and TLC analyses. Before the biological tests, the stability of VOL was investigated in gum arabic solution by monitoring UV-Vis spectrum. The absorptions and λmax values remained unchanged for 20 days.

3.2. Biochemical result

The findings regarding body weight and fasting blood glucose levels of the animals used in the present study has been previously reported [21]. The loss in body weight as well as increased blood glucose levels that arise due to STZ administration were diminished by VOL treatment.

Fig. 2 represents the levels of GSH and LPO parameters in the control and other experimental groups. An evident decrease in GSH ($p<0.05$) and significantly increased LPO ($p<0.05$) was observed in the diabetic group. In contrast, the administration of VOL to the diabetic animals markedly increased ($p<0.05$) GSH level, whereas the level of LPO significantly decreased ($p<0.0001$) as compared to non-treated diabetic rats (Fig. 2).

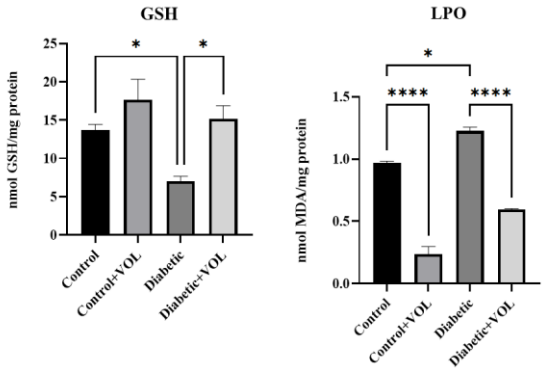

Figure 2. Effects of VOL on gastric tissue GSH and LPO levels in control and experimental animals

*p < 0.05; ****p < 0.0001; VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4)hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); GSH: reduced glutathione; LPO: lipid peroxidation

The levels of AOPP and NEG are presented in Fig. 3 Elevated AOPP and NEG levels were observed in the STZ-treated group when compared to the control group ($p<0.05$; $p<0.05$). The 12 days treatment of the diabetic animals with VOL resulted in a significant decline in the levels of both AOPP and NEG when compared to the solely STZ administered rats ($p<0.05$; $p<0.05$).

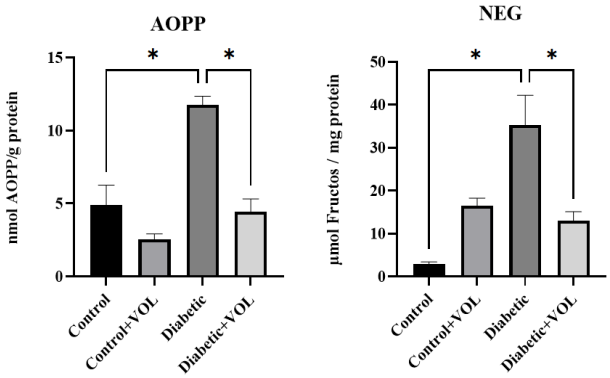

Figure 3. Effects of VOL on gastric tissue AOPP and NEG levels in control and experimental animals

*p < 0.05; VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4)hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); AOPP: advanced oxidized protein products; NEG: non enzymatic glycolisation

An apparent reduction in the activities, CAT and SOD (though not statistically significant) of diabetic rats in comparison to control was observed (Fig. 4). Moreover, the activities of these enzymes significantly increased upon treatment of the diabetic rats with VOL as compared to non-treated diabetic animals (p<0.01; p<0.0001).

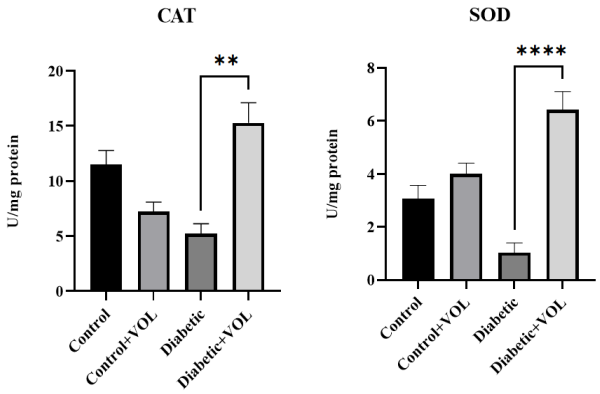

Figure 4. Effects of VOL on gastric tissue CAT and SOD activities in control and experimental animals

**p < 0.01; ****p < 0.0001; VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4)hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); CAT: catalase; SOD: superoxide dismutase

Gastric tissue LDH, XO and CA activities for all the experimental groups are given in Figs. 5, 6. Compared to the control group, significantly higher LDH and XO activities (p<0.01; p<0.001, respectively) were observed in the non-treated diabetic group. The rise in the activity of these enzymes (LDH and XO) due to diabetes was significantly attenuated by VOL (p<0.01; p<0.0001, respectively) (Fig. 5). Similarly, the activity of CA was significantly elevated in the diabetic group as compared to control animals (p<0.0001). The 12 days VOL administration to diabetic animals significantly increased CA activity when compared to the non-treated hyperglycemic group (p<0.0001) (Fig. 6).

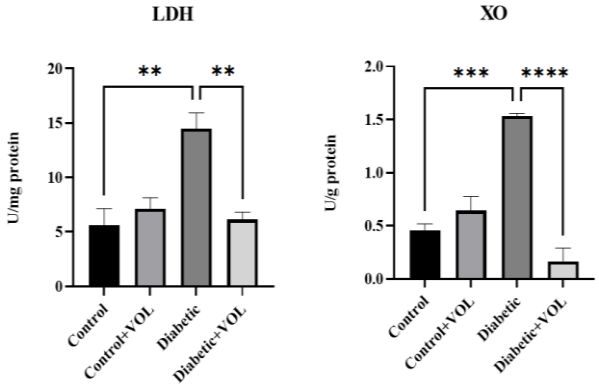

Figure 5. Effects of VOL on gastric tissue LDH and XO activities in control and experimental animals

**p < 0.01; ***p < 0.001; ****p < 0.0001;

VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4) hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); LDH: lactate dehydrogenase; XO: xanthine oxidase

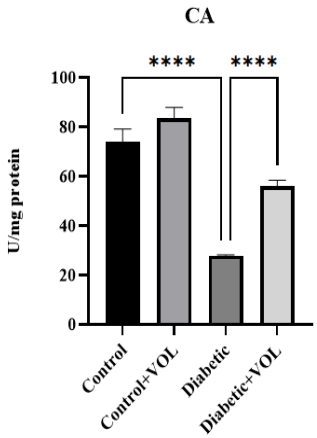

Figure 6. Effects of VOL on gastric tissue CA activity in control and experimental animals

****p<0.0001; VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4)hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); CA: carbonic anhydrase

The activities of GST, GPx and GR of the hyperglycemic group markedly decreased when compared to non-treated control animals (p<0.001; p<0.05; p<0.001). On the other hand, VOL treatment significantly increased the activities of these antioxidant enzymes in the diabetic rats when compared to the hyperglycemic animals (p<0.01) (Figure 7).

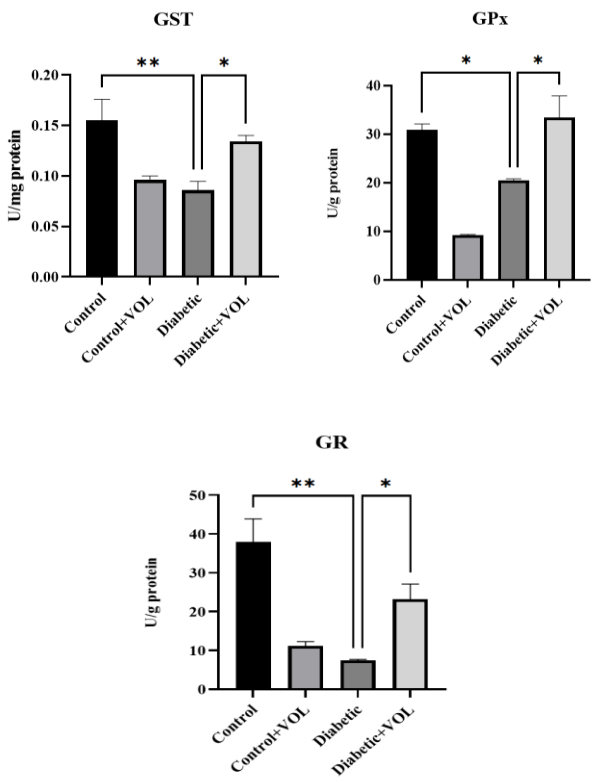

Figure 7. Effects of VOL on gastric tissue GST, GPx and GR activities in control and experimental animals

*p < 0.05; **p < 0.01; VOL: N (1)-2, 4-dihydroxybenzylidene-N-(4)hydroxybenzylidene-S-methyl thiosemicarbazidato-oxidovanadium (IV); GST: glutathione-S-transferase; GPx: glutathione peroxidase; GR: glutathione reductase

Oxidative stress has a very common effect on the emergence and the progression of diabetes, as well as its complications [42]. An abnormally increased level of free radicals can compromise the function of the antioxidant defense system. Thus, resulting in damage to the intra-cellular organelles, defective enzyme activities, increased lipid peroxidation levels, and insulin resistance. In general, oxidative stress may trigger the complications observed in the DM.

The present study was undertaken to assess the potential of an oxidovanadium (IV) complex as an antidiabetic and antioxidant agent in order to ameliorate defective biochemical parameters in the stomach tissue of diabetic rats.

The possible antidiabetic mechanism of vanadium and vanadium-based compounds has been described in several studies [43-45]. Vanadium mimics insulin action, thereby resulting in the mediation of phosphorylation of certain downstream targets, such as the activation of phosphatidylinositol 3'-kinase (PI3K), and the stimulation of phosphatidylinositol phosphate synthesis. In general, the mimic action of these compounds leads to the regulation of glucose transport, glycogen synthesis and gluconeogenesis [22].

It can also restore pancreatic beta cells, as observed in our previous research [20, 21], and by Gao et al. [46]. However, the administration of the VOL complex to diabetic rats resulted in a significant gain of body weight, a decrease in blood glucose levels, as well as significant regeneration of pancreatic beta cells [21]. These findings support the fact that VOL had hypoglycemic property [12].

As a stimulant for insulin secretion, GSH plays an important role in glucose performance. GSH level is relevant for the balance between oxidation and the reduction cycles. In the present study, decreased GSH levels of the diabetic animals might be attributed to changes in the GSH metabolism following increased blood glucose levels [47]. The induction of diabetes either with STZ or alloxan resulted in an increased level of thiobarbituric acid reactive substances (TBARS), which is indirect evidence of increased free radical production [42]. Therefore, preventing the formation of hydroxyl radicals would be an effective way to reduce hydroxyl-induced damage. In the present study, VOL significantly increased stomach GSH levels and decreased LPO formation in diabetic rats. These findings are in agreement with the previous work [48]. This may be due to the effect of the oxidovanadium (IV) complex on blood glucose lowering effect, as well as the increase in gastric antioxidant capacity in diabetic rats.

Diabetes is tightly associated with the formation of glycation end products (AGEs) and AOPP in different tissues [49]. While AGEs are the result of non-enzymatic glucose-protein reactions

alongside lipids and nucleic acids, AOPP is an indicator of albumin damage due to oxidative stress [30].

AGEs and AOPP levels are reported to be elevated in diabetic conditions due to micro/macrovascular complications and albuminuria [50-53]. In the present study, STZ induced diabetes resulted in an increased gastric AOPP levels, as well as NEG level [49]. Vanadium administration normalized the levels of AOPP and NEG via its antidiabetic effect.

Besides high lipid peroxidation, disrupted CAT and SOD activities are associated with increased production of O^{2-} and cellular radical level [53]. High production and the accumulation of free radicals disrupt intracellular antioxidant levels and decrease GSH level. Under such circumstances, the activities of GSH metabolizing enzymes such as GPx, GR and GST are reduced [11]. ROS and other reactive species are directly moped up/scavenged by GSH via the indirect activities of GPx, GR and GST. The proton released as a result of the oxidation of GSH enables the reduction of H_2O_2 to water by GPx.

Therefore, decreased GSH level is accompanied by reduction of H_2O_2 and accumulation of hydroxyl radicals which are responsible for the oxidative damage of cells. On the other hand, accumulating GSSG is reduced to GSH by GR in the presence of NADPH, so as to be reutilized for the detoxification of ROS [54]. The decreased activity in all glutathione-related enzymes (GPx, GR and GST) observed in the hyperglycemic group of the present study, can be either due to decreased intracellular GSH concentration or increased GSH consumption by GPx [55]. In addition to restoring the impaired activities of glutathione metabolizing enzymes, oral VOL treatment also restores CAT and SOD activities in the STZ-induced diabetic group.

CA and its isozymes are found in significant amounts in the stomach tissue because they are related to the secretion of gastric acid. Stomach Parietal cells are responsible for the production of gastric acid. The hydrochloric acid produced by these cells occurs via a mechanism dependent on the hydration of carbon dioxide to carbonic acid (catalyzed by CA) [56]. Depending on the increase in blood glucose concentration, stomach CA activity decreases. According to Speeckaert et al. [57], hyperglycemia and insulin resistance can increase the level of anaerobic conversion, lactic acid accumulation in red blood cells. This can cause a decrease in the level of CAIII protein, thus preventing oxygen from binding to hemoglobin while triggering increased HbAlc levels. Parallel to these findings, decreased CA activity in stomach tissue of diabetic animals was observed in the present study. VOL significantly increased the activity of CA in the diabetic treated group. On the other hand, LDH and XO levels (two important tissue damage markers) were observed to be elevated in diabetic gastric tissue (Fig 5). While LDH catalyzes the reduction of pyruvate to the lactate without oxygen consumption, XO catalyzes the last two steps modulating the conversion of hypoxanthine to xanthine and then xanthine to uric acid. These metabolic pathways have been associated with oxidative stress and insulin resistance [58, 59]. In line with the current results, previous studies have shown that LDH and XO activities in diabetic stomach tissue increase [5]. In the current research, the increased activities of LDH and XO were significantly diminished in the diabetic + VOL group, to levels near that of the control groups.

4. Conclusion

Diabetic gastroenteropathy is an important complication that can lead to a high risk of death in diabetic patients. For this reason, the diagnosis of diabetic gastroenteropathy should be well observed and its complications outlined. In the present research, an oxidovanadium (IV) complex, VOL which was orally administered to diabetic STZ-rats may have exhibited its beneficial effect in the gastric tissue against oxidative stress damage caused by DM due to its hypoglycemic and antioxidant effects.

Article Information Form

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Authors' Contribution
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The Declaration of Conflict of Interest/ Common Interest
No conflict of interest or common interest has been declared by the authors.

The Declaration of Ethics Committee Approval
Experiments were approved by the Animal Care and Use Institute's Committee of Istanbul University, Türkiye.

The Declaration of Research and Publication Ethics
The authors of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

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