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RESEARCH ARTICLE

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Glycoprotein levels and oxidative lung injury in experimental diabetes: effect of oxovanadium(IV) complex based on thiosemicarbazone

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ABSTRACT

Diabetes mellitus (DM) is chronic and metabolic disorder, which is mainly attributed by hyperglycemia. Vanadium salts and their oxo-complexes have been shown to possess insulin-mimetic and anti-diabetic activities in animal models and diabetic patients. The main goal of this study was to investigate the protective effect of oxovanadium(IV) complex based on thiosemicarbazone (VOL) [L: (N(1)-2,4-dihydroxybenzylidene-N-(4)-2-hydroxybenzylidene-S-methyl-isothiosemicarbazidato-oxovanadium(IV)] on glycoprotein components levels and oxidative lung injury of streptozotocin (STZ)-induced diabetic rats. Male Swiss albino rats were separated into four groups. Group I ($n = 5$): Control (normal) animals, Group II ($n = 5$): Control animals administered with VOL, Group III ($n = 6$): STZ-induced diabetic animals, and Group IV ($n = 5$): STZ-induced diabetic rats treated with VOL. VOL was given to the experimental animals by gavage at a dose of 0.2 mM/kg body weight every day for 12 days. Diabetes was induced by single intraperitoneal injection of STZ (65 mg/kg body weight). On the 12th day, lung tissue samples were taken. Glycoprotein components, advanced oxidation protein products, protein carbonyl, hydroxyproline levels, and prolidase, arginase, xanthine oxidase, catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase and adenosine deaminase activities significantly increased whereas aryl esterase, paraoxonase-1, carbonic anhydrase, Na^+/K^+-ATPase activities remarkably decreased in lung tissue of diabetic rats. Treatment with VOL reversed these effects showing a beneficial effect. The present study shows that VOL has a protective effect against diabetes-induced lung damage as well as on abnormal glycoprotein component levels.

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Diabetes mellitus; oxovanadium(IV) complex; lung tissue; glycoprotein content; oxidative stress parameters

Introduction

Diabetes mellitus (DM) is one of the most common metabolic disorders, which is mainly attributed by hyperglycemia (Domingo and Gómez 2016) and endocrine-related ailments characterized by disturbances of carbohydrate, protein and fat metabolism, associated with absolute or relative deficiency in insulin secretion by pancreatic β-cells, insulin action, or both (Azam et al. 2018). The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs such as the eyes, kidneys, lung, heart, and liver (Sekiou et al. 2019; American Diabetes Association 2020). Lung tissues are target organs in DM (Rajasurya et al. 2020). Glycoproteins are carbohydrate linked protein macromolecules found in the cell surface (Pari and Rathinam 2016). They play an important role in membrane transport, cell differentiation and recognition, absorption of macromolecules, adhesion of macromolecules to cell surface, excretion (Connelly et al. 2016), inflammation and pathological process in various diseases (Sujithra et al. 2019). Increased levels of glycoprotein in DM may also be a predictor of angiopathic complications (Konukoglu et al. 1999).

Vanadium is a transition metal that is very common in nature. Vanadium salts and their oxo-complexes have been shown to possess insulin-like abilities by various researchers (Amin et al. 2000; Crans 2000; Mehdi et al. 2006; Bastos et al. 2008). To date, various compounds of vanadium have been synthesized, and their potential therapeutic effects on progressive and degenerative diseases such as DM have been investigated (Willsky et al. 2013). In addition, anti-cancer, anti-thrombotic, anti-atherosclerotic and anti-hypertensive studies have been conducted on these vanadium complexes (Liu et al. 2016; Naglah et al. 2019). Under physiological conditions, their oxo-complexes exhibit redox properties and act as cofactor for enzymes in blood sugar metabolism, lipid and cholesterol metabolism and hormone production (Jyothy 2018). It has been revealed by Crans (2015) that vanadium compounds have an important role in the regulation of blood glucose levels as phosphatase and phosphorylase inhibitors. It is suggested that they may be used in the treatment of many metabolic diseases and cancer (Naso et al. 2013; Wang et al. 2014; Crans et al. 2019; Treviño et al. 2019; Treviño and González-Vergara 2019; Bai et al. 2020; Treviño and Díaz 2020). Thiosemicarbazones are an important class of ligands for metal complexes because of biological and

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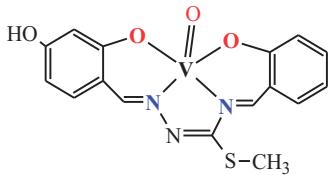


Figure 1. The oxovanadium(IV) complex with tetradentate thiosemicarbazone (VOL).

therapeutic properties such as anti-oxidant (Ramachandran et al. 2012; Bal-Demirci et al. 2015), cytotoxic (Bal et al. 2007; Lu et al. 2012; Chaves et al. 2019), anti-diabetic (Yanardag et al. 2009; Tunali et al. 2021), anti-malarial and anti-bacterial (de Oliveira et al. 2008; Katsipis et al. 2021), anti-viral (Pelosi et al. 2010), and anti-protozoa (Benítez et al. 2009, 2011).

An oxovanadium complex alone or combined with some metal atoms has been well-designed and synthesized by several research groups (Bal Demirci et al. 2006; Benítez et al. 2009; Lu et al. 2012) and these complexes have been widely investigated for their toxicity (Rivas-García et al. 2020; Ertik et al. 2021), anti-oxidative and anti-inflammatory properties (El-Deen et al. 2019; Liu et al. 2021), and hypoglycemic effects (Kongot et al. 2020; Szklarzewicz et al. 2021). More so, the insulin-mimetic properties of various oxovanadium complexes VO(L) (where L = O_4, N_2O_2, N_2S_2, S_4, S_2O_2, and N_4) have been evaluated both *in vivo* and *in vitro* (Yanardag et al. 2009; Bharathi et al. 2020).

It is known that oxidative stress caused by overproduction of free radicals plays crucial role in many diseases, such as DM that results from the pathogenesis of many organ injuries (Newsholme et al. 2016). The aim of this study was to investigate the protective effect of an oxovanadium(IV) complex based on thiosemicarbazone, VOL, on glycoprotein components levels and oxidative lung injury of streptozotocin (STZ)-induced diabetic rats. VOL complex was obtained through 4-hydroxysalicylaldehyde-S-methyl-isothiosemicarbazone and salicylaldehyde in presence of vanadyl sulfate by template reaction (Figure 1).

Materials and methods

Chemicals and apparatus

All chemicals were of the highest purity. Unless otherwise stated, all chemicals were supplied from Merck Chemical Company (Darmstdat, Germany) and/or Sigma-Aldrich Chemical Company (St. Louis, MO, USA). STZ was purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, USA). IR spectra of the compounds were recorded on Cary 630 FTIR spectrometer with Diamond ATR from Agilent.

Starting material

4-hydroxysalicylaldehyde-S-methyl-isothiosemicarbazone was prepared by refluxing reaction of 4-hydroxysalicylaldehyde (1.0 g, 7.2 mmol) with S-methyl-isothiosemicarbazide (0.78 g, 7.4 mmol) in ethanol (25 mL). After 4 hours, the precipitated powder with pinkish-cream color was filtered, and washed with ethanol (Yanardag et al. 2009). Yield 91% (1.48 g), m.p: 180–181 °C.

VOL: The complex was obtained from 4-hydroxysalicylaldehyde-S-methyl-isothiosemicarbazone and salicylaldehyde in the presence of $VOSO_4{\cdot}5H_2O$ in 1:1:1 molar ratio by literature method (Yanardag et al. 2009). The physical properties of amorphous brown powder were controlled. Yield: 72%, m.p: >380 °C.

Animals and experimental design

In the experiments, male Swiss albino rats were used. The rats which are 3–3.5 months old were randomly divided into four groups. Group I ($n = 5$): Control (normal) animals, Group II ($n = 5$): Control animals administered with VOL, Group III ($n = 6$): STZ-induced diabetic animals, and Group IV ($n = 5$): STZ-induced diabetic rats treated with VOL. Experimental diabetes was induced by a single intraperitoneal injection of STZ (65 mg/kg body weight). The STZ was dissolved in a freshly prepared 0.01 M citrate buffer (pH 4.5). VOL of 0.2 mM/kg body weight daily dose was administered by gavage technique to rats for 12 days, after the experimental animals were made diabetic (Yanardag et al. 2009). On day 12, the lung tissues were taken under ether anesthesia from animals that were fasted overnight.

The experiments were reviewed and approved by the Animal Care and Use Institute's Committees of Istanbul University. They were maintained under standard environmental conditions and fed with laboratory pellet chow and given water *ad libitum*.

Biochemical analyses

For biochemical analyses, lung samples were dissected out and immediately washed in ice-cold with 0.9% saline and homogenized in 0.9% saline with a glass homogenizer to make up to 10% homogenate (*w/v*). The homogenates were centrifuged, and the clear supernatants were used for protein, glycoproteins and enzymatic analyses. Lung sialic acid levels were assessed by the method of Lorentz et al. (1986). Hexosamine and hexose levels were evaluated according to Winzler (1955). Fucose levels were assayed by the method described by Zacharias and Shettles (1948). Advanced oxidized protein products (AOPP), protein carbonyl content (PC), and hydroxyproline levels and prolidase activity were determined according to Witko-Sarsat et al. (1996), Levine et al. (1990), Reddy and Enwemeka (1996) , and Chinard (1952), respectively. Arginase (AR), aryl esterase (ARE), paraoxonase1 (PON1), and xanthine oxidase (XO) activities were estimated by the methods of Geyer and Dabich (1971), Gan et al. (1991), Furlong et al. (1988), and Corte and Stirpe (1968), respectively. Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-S-transferase (GST) activities were done by the methods of Aebi (1984), Mylroie et al. (1986) , Paglia and Valentine (1967) and modified by Wendel (1981), Beutler (1971), and Habig and Jakoby (1981), respectively. Adenosine deaminase (ADA), carbonic anhydrase (CA) and sodium/

potassium ATPase (Na^+/K^+-ATPase) activities were assessed according to methods published previously by Karker (1964), Verpoorte et al. (1967), and Ridderstap and Bonting (1969), respectively. The protein content in the supernatants was estimated by the method of Lowry using Bovine Serum Albumin (BSA) as standard (Lowry et al. 1951).

Statistical analyses

The results of the current study were evaluated by using GraphPad Prism Software, version 6.01 (San Diego, USA). Data were stated as mean ± standard deviation (SD) by 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.

Results

VOL complex was obtained via template synthesis method as previously synthesized by Yanardag et al. (2009). Outcomes of body weights and fasting blood glucose levels of diabetic animals have been previously published with respect to the effects of newly synthesized VOL complex on the pancreas (Yanardag et al. 2009).

Lung tissue sialic acid, hexosamine, hexose, and fucose levels were presented in Table 1. When compared with control group, all of glycoprotein components were significantly increased in diabetic group ($p < 0.05$). VOL given to the diabetic group resulted in remarkable decrease in the levels of lung tissue glycoproteins ($p < 0.05$) (Table 1).

Lung tissue AOPP, PC and hydroxyproline levels and prolidase activity were shown in Table 2. All these parameters were significantly increased in diabetic group when compared with control group ($p < 0.05$). On the contrary, VOL treatment to the diabetic group led to significant decrease in the AOPP, PC and hydroxyproline levels and prolidase activity ($p < 0.05$) (Table 2).

Lung tissue AR, ARE, PON1and XO activities were presented in Table 3. There was a significant increase in AR and XO activities of diabetic group as compared with control group ($p < 0.05$, $p < 0.005$). However, administration of VOL to the diabetic group caused a significant decrease in both AR and XO activities ($p < 0.05$, $p < 0.0001$). On the other hand, ARE and PON1 activities were significantly decreased as compared to the control group ($p < 0.05$, $p < 0.001$). Treatment with VOL reversed these effects

Table 1. Lung tissue sialic acid, hexosamine, hexose, and fucose levels of all groups of rats.

Groups	Sialic Acid (μmol SA/mg protein)	Hexosamine (μg Glucosamine/mg protein)	Hexose (mg Hexose/mg protein)	Fucose (μg Fucose/mg protein)
Control	20.13 ± 2.15	4.87 ± 1.31	1.53 ± 0.56	2.28 ± 0.09
Control + VOL	25.31 ± 2.04	5.01 ± 1.70	1.61 ± 0.75	1.69 ± 0.84
Diabetic	44.53 ± 6.92[a]	15.81 ± 3.26[a]	3.47 ± 0.68[a]	11.63 ± 0.91[a]
Diabetic + VOL	20.75 ± 5.35[b]	4.38 ± 1.72[b]	0.81 ± 0.35[b]	1.86 ± 0.96[b]
P_{ANOVA}	0.0001	0.001	0.0001	0.0001

Data were presented as mean ± SD.
SD: standard deviation; ANOVA: analysis of variance; VOL: oxovanadium(IV) complex; SA: sialic acid.
One-way ANOVA followed by Tukey's comparison test was employed.
[a]$p < 0.05$ versus control group; [b]$p < 0.05$ versus diabetic group

Table 2. Lung tissue AOPP, PC, hydroxyproline levels, and prolidase activities of all groups of rats.

Groups	AOPP (pmol/mg protein)	PC (nmol/mg protein)	Hydroxyproline (μmol /mg protein)	Prolidase (U/mg protein)
Control	3.43 ± 0.68	12.07 ± 2.72	140.47 ± 6.35	14.66 ± 1.57
Control + VOL	2.66 ± 0.49	8.24 ± 1.59	146.95 ± 8.72	21.34 ± 4.12
Diabetic	8.38 ± 0.79[a]	20.12 ± 4.30[a]	274.59 ± 7.58[a]	36.99 ± 6.93[a]
Diabetic + VOL	2.79 ± 1.12[b]	7.80 ± 2.17[b]	196.03 ± 22.96[b]	18.02 ± 2.69[b]
P_{ANOVA}	0.0001	0.0001	0.0001	0.0001

Data were presented as means ± SD.
SD: standard deviation; ANOVA: analysis of variance; VOL: oxovanadium(IV) complex; AOPP: advanced oxidized protein products; PC: protein carbonyl.
One-way ANOVA followed by Tukey's comparison test was employed.
[a]$p < 0.05$ versus control group; [b]$p < 0.05$ versus diabetic group

Table 3. Lung tissue AR, ARE, PON1, and XO activities of all groups of rats.

Groups	AR (μmol urea/mg protein)	ARE (kU/g protein)	PON1 (U/g protein)	XO (U/g protein)
Control	1.40 ± 0.45	3.04 ± 0.71	18.43 ± 4.37	5.30 ± 0.97
Control + VOL	1.13 ± 0.28	2.43 ± 0.25	14.99 ± 2.97	4.35 ± 0.71
Diabetic	2.93 ± 0.92[a]	1.39 ± 0.58[a]	7.86 ± 1.85[c]	9.13 ± 1.61[e]
Diabetic + VOL	1.22 ± 0.35[b]	2.25 ± 0.24[b]	15.83 ± 2.47[d]	4.08 ± 0.81[d]
P_{ANOVA}	0.001	0.011	0.0001	0.0001

Data were presented as means ± SD.
SD: standard deviation; ANOVA: analysis of variance; VOL: oxovanadium(IV) complex; AR: arginase; ARE: aryl esterase; PON1: paraoxonase1; XO: xanthine oxidase.
One-way ANOVA followed by Tukey's comparison test was employed.
[a]$p < 0.05$ versus control group; [b]$p < 0.05$ versus diabetic group; [c]$p < 0.001$ versus control group; [d]$p < 0.0001$ versus diabetic group; [e]$p < 0.005$ versus control group.

Table 4. Lung tissue CAT, SOD, GPx, GR, and GST activities of all groups of rats.

Groups	CAT (U/mg protein)	SOD (U/g protein)	GPx (U/g protein)	GR (U/g protein)	GST (U/g protein)
Control	8.23 ± 3.56	23.91 ± 12.55	20.82 ± 6.10	19.66 ± 8.12	36.18 ± 1.64
Control + VOL	7.24 ± 2.12	26.45 ± 8.26	16.70 ± 3.15	46.87 ± 22.46	34.95 ± 3.41
Diabetic	26.01 ± 3.61[a]	70.05 ± 23.58[a]	37.86 ± 4.84[a]	62.82 ± 6.29[d]	101.33 ± 4.83[d]
Diabetic + VOL	2.34 ± 0.21[b]	16.03 ± 4.22[b]	15.59 ± 0.49[c]	16.24 ± 4.62[e]	33.43 ± 3.78[e]
P_{ANOVA}	0.002	0.011	0.0001	0.038	0.0001

Data were presented as means ± SD.
SD: standard deviation; ANOVA: analysis of variance; VOL: oxovanadium(IV) complex; CAT: catalase; SOD: superoxide dismutase; GPx: glutathione peroxidase; GR: glutathione reductase; GST: glutathione-S-transferase.
One-way ANOVA followed by Tukey's comparison test was employed.
[a]$p < 0.05$ versus control group; [b]$p < 0.05$ versus diabetic group; [c]$p < 0.001$ versus diabetic group; [d]$p < 0.0001$ versus control group; [e]$p < 0.0001$ versus diabetic group.

Table 5. Lung tissue ADA, CA, and Na^+/K^+-ATPase activities of all groups of rats.

Groups	ADA (U/g protein)	CA (U/mg protein)	Na^+/K^+-ATPase (nmol P_i/mg protein/h)
Control	55.10 ± 12.13	12.65 ± 1.56	19.29 ± 3.32
Control + VOL	61.95 ± 9.12	10.70 ± 0.55	16.75 ± 3.32
Diabetic	94.12 ± 13.99[a]	7.92 ± 0.95[c]	10.99 ± 2.39[c]
Diabetic + VOL	48.57 ± 6.60[b]	12.72 ± 0.80[d]	21.06 ± 4.60[d]
P_{ANOVA}	0.0001	0.0001	0.011

Data were presented as means ± SD.
SD: standard deviation; ANOVA: analysis of variance; VOL: oxovanadium(IV) complex; ADA: adenosine deaminase; CA: carbonic anhydrase; Na^+/K^+-ATPase: sodium/potassium ATPase.
One-way ANOVA followed by Tukey's comparison test was employed.
[a]$p < 0.001$ versus control group; [b]$p < 0.0001$ versus diabetic group; [c]$p < 0.05$ versus control group; [d]$p < 0.05$ versus diabetic group

showing a beneficial effect of vanadium ($p < 0.05$, $p < 0.0001$) (Table 3).

CAT, SOD, GPx, GR, and GST activities of lung tissue homogenates are shown in Table 4. As seen in Table 4, in comparison with control group, all the anti-oxidant enzyme activities of diabetes group were remarkably raised ($p < 0.05$, $p < 0.0001$). By contrast, administration of VOL to diabetic group led to remarkable decrease in the activities of these enzymes ($p < 0.05$, $p < 0.001$, $p < 0.0001$) (Table 4).

Lung tissue ADA, CA, and Na^+/K^+-ATPase activities are presented in Table 5. According to Table 5, ADA activity in diabetes group was notably increased ($p < 0.001$), while CA and Na^+/K^+-ATPase activities in this group were significantly decreased ($p < 0.05$) as compared to the control group. After VOL treatment, ADA activity was obviously decreased ($p < 0.0001$), but CA and Na^+/K^+-ATPase activities were significantly increased ($p < 0.05$) (Table 5).

Discussion

In the current study, the effect of an oxovanadium(IV) complex based on thiosemicarbazone, VOL, on glycoprotein components levels and oxidative lung injury of STZ-induced diabetic rats was investigated.

It is well documented that diabetes may give rise to elevated catabolic reactions which in turn associated with increased blood glucose levels and loss in body weight in both patients and STZ-induced animal models (Yanardag et al. 2009; Dandona et al. 2014; Ebaid et al. 2020; Tunali et al. 2021).

Tissue glycoprotein content in both experimental diabetes on animal model and human diabetic subjects are reported to be elevated due to abnormal glycoprotein metabolism (Sacan et al. 2016; Tian and Zhen 2019). In this study, we observed elevated levels of sialic acid, hexosamine, hexose, and fucose in lung tissue of diabetic rats. Increase in the levels of these glycoprotein components may be due to high serum glucose levels and insulin deficiency or insufficient secretion of insulin (Patti et al. 1999). VOL treatment in diabetic rats reversed the alterations in the glycoprotein components toward near normal levels. According to these results, it can be suggested that VOL decreases glycoprotein levels in lung because of it anti-hyperglycemic effects (Yanardag et al. 2009).

Direct oxidation of amino acid residues of proteins by reactive oxygen species (ROS) through free radicals give rise to formation of aldehydes and ketones known as carbonyl-containing derivatives (Gryszczyńska et al. 2017). Exceeding the neutralization capacity of ROS during oxidative stress conditions may result in oxidation of specific amino acid residues of protein such as lysine, arginine and proline. Moreover, oxidation (hydroxylation, nitration, chlorination of aromatic groups, etc.) of functional groups of proteins can lead to conversion of some amino acid residues to carbonyl derivatives (Hecker and Wagner 2018). In the present study, AOPP and PC levels remarkably increased in diabetic animals as compared to control animals. These results indicate that the amino acid residues are affected by oxidative stress. Outcomes obtained from this study were in agreement with the findings of Sacan et al. (2016). On the other hand, the decline in the levels of AOPP and PC of diabetic + VOL group may indicate the beneficial effects of VOL on the highly oxidative conditions in the lung tissues of diabetic animals.

Prolidase is the enzyme that has iminopeptidase activity, which possesses regulation and recycling function in collagen degradation. The biological function of prolidase is to split C-terminal amino acid proline or hydroxyproline in collagen (Zareba and Palka 2016). Prolidase not only acts as a

main regulatory enzyme in collagen metabolism, but also plays a crucial role in the stability of collagen in tissue repairing system. For this reason, prolidase and hydroxyproline serve as a biochemical marker for oxidative damage in diabetic models (Caetano et al. 2016). Therefore, both elevated prolidase activity and hydroxyproline content in tissues, especially diabetes-induced lung damage indicates the deposition of collagen (Hemmati et al. 2018). In the present findings, prolidase activity and hydroxyproline content in STZ-induced rats were elevated statistically as compared with control rats. Conversely, administration of VOL to the diabetic group remarkably reversed these effects. The decrease in prolidase activity as well as hydroxyproline content may be due to the anti-oxidative and insulin-mimetic effect of VOL against oxidative damage. These results concur with that of studies published by Yanardag et al. (2009) and Sacan et al. (2016).

AR is an enzyme that generates L-ornithine and urea from L-arginine. Additionally, it has been stated that AR also shows activity in some tissues other than liver, such as kidney, brain and lung. Its catalytic activity is increased in some diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (Maarsingh et al. 2008). In our study, AR activity in diabetic lung tissue was higher than that of control group. Since oxidative stress is a distinctive feature for many diseases, especially diabetes, elevation of AR activity may be due to increased oxidative stress in diabetic rats. Thus, ROS resulting from oxidative stress may be a key mediator for elevated AR levels in diabetic conditions (Kiss et al. 2014). Because several vanadium(IV) complexes had shown potent anti-diabetic effects (Yanardag et al. 2009; Naglah et al. 2019), VOL supplementation to diabetic group gave rise to obvious decrease in AR activity in our study.

PON1, synthesized in hepatic tissue, is the enzyme that shows lactonase/arylesterase activities as well as organophosphatase activity (Li et al. 2014). Besides, it has been revealed that PON1 shows anti-inflammatory effect and is able to stimulate the anti-oxidant enzymes (Wang et al. 2017). In the present study, PON1 and ARE enzyme activities in diabetic groups were notably decreased. It was reported that these enzymes activities in STZ-diabetic animals had shown a remarkable diminishment when compared with control animals (Ozgun et al. 2019). In diabetic animals, decline in the activities of PON1 and ARE may be due to oxidative stress caused by ROS and hyperglycemia. On the other hand, VOL + diabetic group showed a notable increase in these enzyme activities. This finding may be the results of insulin-mimetic and anti-oxidant effects of VOL (Sheela et al. 2013; Bharathi et al. 2020). Another anti-oxidant enzyme, XO, plays a pivotal role in purine nucleoside metabolism by catalyzing the conversion of hypoxanthine to xanthine as well as oxidation of xanthine to uric acid. Apart from this, XO enzyme is responsible for generation of free radicals such as superoxide anion radical (Wang et al. 2017). XO activity in diabetic group was elevated as compared to control rats. Oppositely, VOL administration to diabetic rats caused a decrease in XO activity. The reason for the elevation of the XO activity may reflect lung tissue injury caused by excess amounts of ROS, this finding may directly represent the degree of lung damage due to oxidative stress.

ROS are not only generated continuously in respiration system of organisms, but also detoxified by endogenous anti-oxidant enzymes such as CAT, SOD, GPx, GR and GST (Ighodaro and Akinloye 2018). In the current study, all these enzyme activities were increased in diabetic rats as compared with control rats. Our findings were consistent with the results of Sacan et al. (2016) and Đurašević et al. (2019). Elevation of the activities of these defensive enzymes may be explained as adoption to excessive production of ROS caused by diabetic conditions in rats (Gezginci-Oktayoglu et al. 2014). VOL treatment in diabetic rats resulted in decrease in these enzyme activities. As can be clearly seen from the current findings, oxidative stress in lung tissue has increased in diabetic conditions, whereas VOL treatment has resulted in better restoration of all enzyme activities than the control group via its anti-oxidative effect. Similarly, in a study examining the effects of both vanadyl sulfate and oxovanadium(IV) bipyridine complex on diabetic albino mice, it was stated that the oxovanadium complex was more effective than inorganic vanadium in the restoration of impaired anti-oxidant capacity (El-Shafey and Elsherbiny 2020).

ADA is a polymorphic enzyme which plays a fundamental role in purine nucleoside metabolism. ADA also catalyzes the irreversible and hydrolytic deamination of adenosine to inosine as well as deoxyadenosine to deoxyinosine, respectively (Larijani et al. 2016). This enzyme is suggested to be a good biomarker of cell-mediated immune system (Sapkota et al. 2017). It is reported that ADA is considered to be crucial enzyme for regulating insulin action on glucose metabolism (Turkal et al. 2016). Moreover, estimation of ADA activity is an important tool for screening tuberculosis, autoimmune diseases, and DM (Niraula et al. 2018). It has been reported that ADA activities increased in liver, kidney, and lung tissues of STZ-induced diabetic rats, respectively (Gezginci-Oktayoglu et al. 2014; Sacan et al. 2016). In the current study, similar results were seen in ADA activity in diabetic group. The increase in ADA activity was reverted by VOL administration. The decrease in ADA activity may be due to the insulin mimetic effect of vanadium compound (Pillai et al. 2013).

CA catalyzes the reversible hydration of gaseous CO_2 to carbonic acid, which dissociates to give hydrogen carbonate above neutral pH. CA is involved in gluconeogenesis, lipogenesis, and ureagenesis (Rahman et al. 2019). Thus, it has been stated that the increase in CA activity is associated with many pathologic processes including diabetes (Ibrahim et al. 2016). According to our data, there was a decline of CA activity in the lung tissue of the diabetic rats, which is in accordance with previous report (Sacan et al. 2016). In diabetic conditions, cells are exposed to a higher glucose concentration. In this case, the activity of CA may have decreased as a result of glycosylation of this enzyme (Kondo et al. 1987), whereas CA activity was seen much higher in VOL + diabetic group as compared with diabetic group.

Na^+/K^+-ATPase is an integral membrane enzyme that is ubiquitously found in animal cells. It plays a crucial role in

maintaining electrolyte balance in cells via exporting three Na^+ ions and imports two K^+ ions across the plasma membrane using the energy released during the hydrolysis of one ATP molecule to ADP and inorganic phosphate (Pi) (Kaločayová et al. 2015). The degree of peroxidation of lipid and/or protein molecules in cell membrane is associated with decrease in the Na^+/K^+-ATPase activity (de Lores Arnaiz and Ordieres 2014). According to our findings, Na^+/K^+-ATPase decreased in STZ-induced diabetic group. Decrease in Na^+/K^+-ATPase activity may be due to the redox-sensitive properties of Na^+/K^+-ATPase, which can be regulated by levels of intracellular ROS (Yan et al. 2016). Treatment with VOL to diabetic group statistically increased Na^+/K^+-ATPase activity.

Vanadium compounds have been shown to be effective against many types of disease including diabetes type 2, cancer, endemic tropical diseases, bacterial infections and HIV infections (Mehri 2020).

According to the obtained results, diabetes induces oxidative stress and disrupts the anti-oxidant defense system in the lungs of rat tissue. This study emphasized the improvement in lung tissue glycoprotein and the carbonylation of proteins contents and the recovery of anti-oxidant enzyme systems of STZ-induced diabetes by VOL chelate. As a consequence, the present study shows that the VOL chelate has a protective effect against diabetes-induced lung damage and on abnormal glycoprotein component levels.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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