EFFECT OF DI-μ-HYDROXO-BIS (QUERCETINATOOXOVANADIUM(IV)) COMPLEX ON ALLOXAN-INDUCED DIABETIC RATS

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Abstract

Diabetes mellitus is a metabolic disease characterized by hyperglycemia and excess mobilization of fatty acids. The effect of the vanadium complex di-μ-hydroxo-bis(quercetinatooxovanadium(IV)) (HOBQOV) on blood glucose and serum lipid levels was studied on alloxan-induced diabetic rats, and compared to that of vanadyl sulphate and metformin as reference substances. The diabetic rats were treated with the vanadium complex (0.4 mmol/kg body weight/day) for a period of 15 days. The blood glucose level was monitored daily, whereas the blood lipid profile was evaluated at the end of the treatment period. The administration of the vanadium complex restored to near normal the increased levels of blood glucose and blood lipid concentration. The results are encouraging for the consideration of the studied oxovanadium complex as a promising anti-diabetic drug.

Rezumat

Diabetul zaharat este o boală metabolică, caracterizată de hiperglicemie şi mobilizare excesivă a acizilor graşi. Efectul complexului vanadiului di-μ-hydroxo-bis(quercetinatooxovanadium(IV)) (HOBQOV) asupra glucozei sanguine şi lipidelor serice a fost evaluat într-un model de diabet aloxanic, indus la sobolani, faţă de substanţele de referinţă sulfatul de vanadil şi metformin. Şobolanii diabetici au fost trataţi cu complexul vanadiului cu doza de 0.4 mmol/kg corp timp de 15 zile. Glicemia animalelor a fost monitorizată zilnic, iar profilul lipidic a fost evaluat la finalul tratamentului. Administrarea de HOBQOV a adus aproape de normal valorile glicemiei şi lipidelor serice. Rezultatele obţinute sunt încurajatoare pentru continuarea cercetărilor asupra complexului de oxovanadiu ca un promiţător medicament antidiabetic.

Keywords: HOBQOV; Hypoglycemic activity, Hypolipidemic activity

Introduction

Diabetes mellitus is a chronic disease caused by relative or absolute deficiency of insulin associated with disorders in the metabolism of glucose and fatty acids. As consequences, hyperglycemia, alteration in carbohydrate and lipid metabolism, and vascular and neurological complications are the major pathological conditions associated with diabetes mellitus [12]. Although development of oral drugs for the treatment of diabetes mellitus was focused mainly on organic molecules such as biguanides and thiazolidinediones derivatives, in the last years there is an incoming interest for the inorganic compounds with insulin mimetic activity.

Since 1980 the insulin-mimetic effect of vanadate was observed *in vitro* [21,5], and five years later was demonstrated *in vivo* [7] on streptozotocin (STZ) diabetic rats. Since the vanadate is poorly absorbed from gastrointestinal tract and has a therapeutic dose near to the toxic level [11,4], the further studies were oriented toward other vanadium compounds. Vanadyl sulphate is less toxic than sodium vanadate [18] and has also an insulin-like effect in rats with STZ-induced diabetes [20]. Because vanadyl sulfate is not well absorbed, the next step in this research area was the development of complexes of VOL_2 type, with high thermodynamic stability, an adequate balance of hydro/lipophilicity, and low toxicity.

Among the promising insulin-mimetic agents, bis(maltolato) oxovanadium(IV) [$VO(maltolato)_2$] (BMOV), bis(ethylmaltolato) oxovanadium(IV) [$VO(ethylmaltolato)_2$] [13,23], oxobis(picolinato) vanadium(IV) (VOPA), bis(methylpicolinato) oxovanadium(IV) (VOMPA) [14,19] bis*(*biguanidato*)* oxovanadium*(*IV*)*, [$VO(big)_2$], bis(N',N'-dimethylbiguanidato) oxovanadium(IV), [$VO(metf)_2$], bis(beta-phenethylbiguanidato*)* oxovanadium*(*IV*)*, [$VO(phenf)_2$] [26] and bis(allixinato) oxovanadium(IV) [$VO(alx)_2$] [1] were extensively studied regarding their chemical and pharmacological properties.

The beneficial effects of vanadium compounds on diabetic impaired lipid metabolism were also reported [10-15].

The present study was designed to investigate the hypoglicemic and antilipidemic effects of a new complex of VO(II) with quercetin in alloxan-induced diabetic rats. The complex di-μ-hydroxo-bis(quercetinatooxo vanadium(IV)), [$(VO(Querc))_2(\mu\text{-}OH)_2]\cdot 4H_2O$ (HOBQOV) was designed so that the molecule associates oxovanadium (IV) ion and quercetin ligand, a natural flavonol reported to exerts itself antidiabetic [25] and hypolipidemic effects [9].

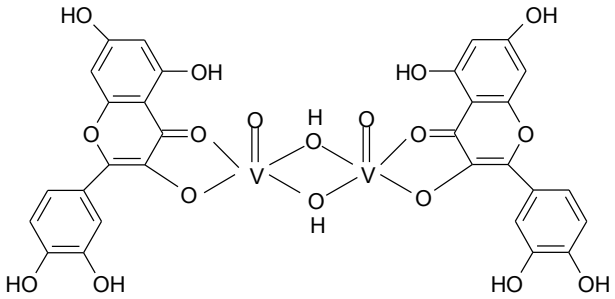

Figure 1
Structure of di-μ-hydroxo-bis(quercetinatooxovanadium(IV)) (HOBQOV)

Diabetes was induced by alloxan, a well-known and widely used experimental model with a positive time/response ratio [6]. The daily dose of 0.4 mmol/kg/day, administered by gavage, was chosen so that it represents less than 1/20 of LD_{50} and it is in concordance with previous studies which used vanadium compounds at a daily dose of 0.1 – 0.8 mmol/kg/day/p.o. [10, 24]. General evaluation of hypoglycemic and hypolipidemic effects of tested compound were carried out by monitoring the blood glucose level and the main pathogenic blood parameters of hyperlipidemy: high density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG). The study was conducted with 2 reference substances, vanadyl sulphate, the first oxovanadium(IV) salt tested for their insulin-mimetic activity [20], and metformin, an widely used oral antidiabetic drug [3, 8].

Materials and Methods

Reagents and chemicals

The complex HOBQOV was prepared according to previously reported procedure [2]**.** Alloxan monohydrate and 1,1-dimethylbiguanide hydrochloride (Metformin) where purchased by Sigma-Aldrich. All chemicals were of analytical grade and used without further purification.

Animals

Male Wistar rats weighing 189.29±27.66 g from the Cantacuzino Institute, Bucharest, Romania were used. The rats were housed in plastic cages in an air-conditioned animal room and fed on granulated food with free access to water. The temperature and relative humidity were continuously monitored using a thermohygrometer. The temperature was between 20ºC and 22ºC and the relative humidity was generally maintained at 35-45%.

All procedures were carried out in accordance with the Directive 86/609/EEC of 24th November 1986, on the protection of animals used for experimental and other scientific purposes.

Induction of diabetes

Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate 13% (w/v) in a saline solution at a dose of 130 mg/kg body weight (b.w.). Blood samples were collected 48 hours later and venous glucose levels were determined to confirm the development of diabetes. Of the 80 rats receiving alloxan, 66.25% were found to be diabetic (blood glucose > 200 mg/mL), with 478.32± 103.32mg/dl venous blood glucose. From the diabetic animals 100% were found to be with severe diabetes (blood glucose > 250 mg/mL) and considered to have a beta cells necrosis equivalent to a pancreatectomy [6]. Blood samples (in fasting conditions) from the tail vein of the rat were collected by puncture and blood glucose levels were analyzed using BioLand G-423 glucometer, BioLand Technology LTD, for identifying the hyperglycemic and diabetic animals.

Biochemical analysis

Daily venous glucose determination was carried out using a commercial kit for glucose monitoring, BioLand G-423 glucometer, BioLand Technology LTD. At the end of the treatment biochemical analysis was made with diagnostic kits for determination of Glucose, Total cholesterol, HDL-cholesterol, LDL-Cholesterol, Tryglycerides concentration (Liquick Cor) from Cormay and a Cormay biochemical analyzer.

Experimental design

The acute toxicity studies on the vanadyl-quercetin complex (data not published) have found no lethal effect following the oral administration of a 16 mmol/kg b.w. dose, at rodents.

The animals were randomly separated into 5 groups of 10 rats:

- normal rats (N) treated with water 1mL/100 g b.w. for 15 days;
- diabetic rats (D) treated with water 1mL/100 g b.w. for 15 days;
- diabetic rats treated with HOBQOV complex (HOBQOV) 0,4 mmol/kg b.w., aqueous suspension 0,4 mmol % for 15 days;
- diabetic rats treated with vanadyl sulfate (V) 0,4 mmol/kg b.w., aqueous solution 0,4 mmol % for 15 days;
- diabetic rats treated with metformin (M) 100mg /kg b.w., solution 1 % for 15 days.

All substances were administered orally, by gavage, the corresponding volume was 1mL/100g b.w. The animals received the substances daily at 10 a.m. The venous blood glucose levels (in fasting conditions) were measured daily at 9:30 a.m. The animals were sacrificed in day 15 of treatment, 1hour and 30 minutes after the substances administration and blood samples were collected for whole blood glucose and lipidic profile (triglyceride, HDL-cholesterol, LDL-cholesterol) measurements.

Statistical analysis

The results are expressed as mean ± standard deviation. The statistical analysis was performed using StatSoft, Inc. (2004). STATISTICA (data analysis software system), version 7. (www.statsoft.com). All results for the applied statistical methods have a 90% confidence interval.

Results and Discussion

Body weight

In Figure 2, the body weight evolution of each group of the animals is presented. Following the substances administration, the body weight evolution of the animals from diabetic groups untreated or treated with HOBQOV, vanadyl sulphate and metformin shown significant changes compared to the normal group (ANOVA, $p<0.05$). There is no significant changes for the animals within each group (ANOVA, $p>0.05$).

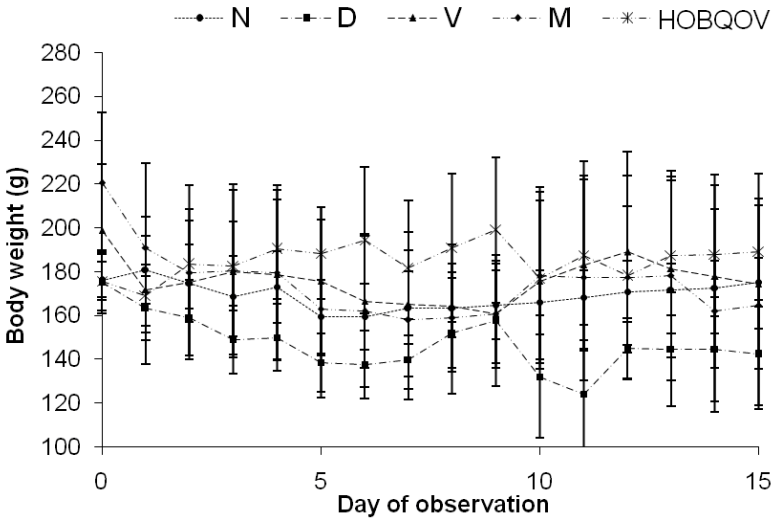

Figure 2

Mean body weight evolution during the experiment.
N - normal rats, D - diabetic rats, V - diabetic rats treated with vanadyl sulfate, M - diabetic rats treated with metformin

At the end of treatment, the mean body weight for diabetic rats and for diabetic rats treated with vanadyl sulphate was smaller compared to the normal rats. For the diabetic rats treated with HOBQOV and metformin, an increase of mean body weight was observed. The decrease of body weight is considered as a sign of vanadium toxicity [12]. On the other side, the enhancement of body weight indicates that the vanadium increases glucose metabolism and thus enhances the body weight [16].

Blood Glucose

The data for the venous blood glucose levels during the experiment are shown in Table I and graphically represented in Figure 2. The percent venous blood glucose evolution reported to day 1 of observation, is shown in Table II and in Figure 4.

For all treated groups (with HOBQOV, vanadyl sulphate and metformin) the venous blood glucose decrease was statistically significant compared to diabetic group starting with the third day (t Test, $p<0.05$).

The treatment decreased the venous glucose level, however the venous blood glucose values were statistically higher compared to those of the normal group during the experiment (t Test, $p<0.05$).

In the fifteenth day of the experiment, the venous blood glucose values for the groups treated with HOBQOV and with metformin were statistically decreased compared to those of group treated with vanadyl sulphate (t Test, $p<0.05$).

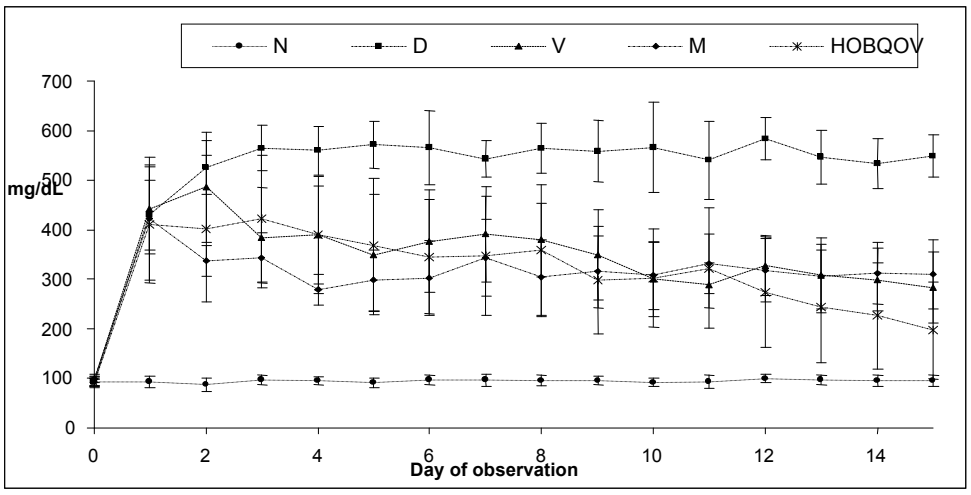

Figure 3

Mean blood glucose level during the experiment

N - normal rats, D - diabetic rats, V - diabetic rats treated with vanadyl sulfate, M - diabetic rats treated with metformin

Table I

Mean venous blood glucose levels (mg/dL) for the groups

group	N	D	HOBQOV	V	M
before alloxan /Day 0	93.00 ± 8.39	92.40± 10.37	91.60± 7.871	96.10± 11.65	98.40± 6.85
48 hours after aloxan /Day1	92.29± 11.57	429.80 ± 70.57	410.50 ± 117.5	441.70 ± 90.46	422.80± 124.33
Day 2	88.10± 13.50	525.40± 54.64	401.40± 148.46	486.10± 111.91	337.10± 30.59
Day 3	97.00± 9.29	565.10± 45.45	422.40± 128.67	383.20± 100.73	343.70± 49.70
Day 4	95.00± 8.64	559.40± 50.25	389.60± 118.45	389.00± 98.70	279.20± 31.11
Day 5	91.00± 10.52	571.50± 47.14	369.30± 134.31	349.90± 120.83	298.10± 61.08
Day 6	97.00± 9.11	565.40± 74.26	345.70± 114.85	377.30± 103.89	303.10± 75.81
Day 7	96.10± 11.82	542.50± 37.07	347.10± 120.3	390.20± 96.77	343.90± 77.36
Day 8	95.40± 10.49	564.40± 51.04	358.00± 133.15	379.20± 74.58	303.70± 76.12
Day 9	95.90± 9.30	558.60± 61.70	298.40± 107.99	348.90± 91.48	315.40± 72.09
Day 10	92.00± 9.35	565.50± 91.09	302.20± 99.117	300.00± 74.19	308.00± 69.04
Day 11	92.40± 13.72	540.40± 78.04	322.50± 121.01	288.00± 46.01	331.10± 60.59
Day 12	99.90± 9.56	583.30± 42.48	274.10± 111.46	328.20± 60.41	317.60± 64.28
Day 13	96.60± 10.08	547.00± 54.83	245.80± 113.13	308.30± 76.12	305.80± 65.22
Day 14	94.70± 11.66	533.70± 50.65	226.90± 107.75	299.60± 62.25	311.70± 61.78
Day 15	94.90± 11.33	548.60± 43.08	196.70± 97.148	282.40± 72.10	310.60± 70.34

Table II

Mean % venous blood glucose evolution reported to day 1 of observation*)

group\day of observation	N	D	HOBQOV	V	M
2	-4.49	22.23	-2.19	10.06	-20.27
3	5.11	31.47	2.82	-13.23	-18.72
4	2.94	30.14	-5.15	-11.93	-33.95
5	-1.39	32.97	-10.12	-20.80	-29.49
6	5.11	31.54	-15.86	-14.62	-28.31
7	4.18	26.22	-15.51	-11.51	-18.68
8	3.41	31.31	-12.87	-14.04	-28.18
9	3.87	30.01	-27.36	-21.02	-25.41
10	-0.31	31.57	-26.46	-32.08	-27.16
11	0.15	25.72	-21.52	-34.80	-21.69
12	8.20	35.69	-33.28	-25.71	-24.90
13	4.64	27.25	-40.30	-30.21	-27.70
14	2.63	24.16	-44.96	-32.18	-26.28
15	2.79	27.62	-52.09	-36.03	-26.55

*) % evolution = (day of observation – day 1 of observation)/ day 1 of observation*100)

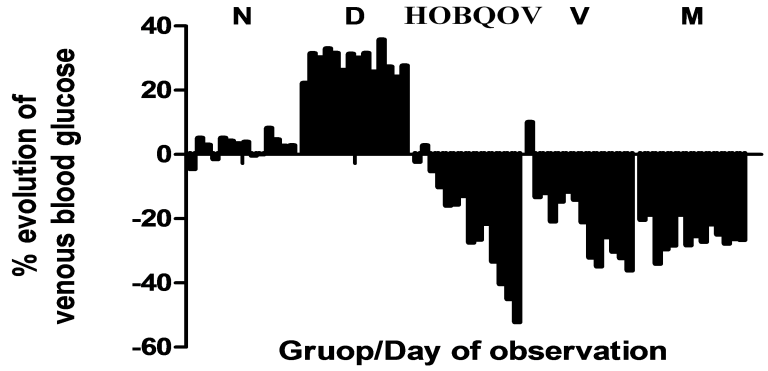

Figure 4
The daily venous blood glucose evolution during the experiment compared to the first day

At the end of experiment, the lowest glucose concentration of was observed for the diabetic rats treated with HOBQOV group (data are shown in Table III).

Table III
Whole blood glucose at the end of the experiment

	N	D	HOBQOV	V	M
Mean±SD(mg/dL)	106.31±7.73	381.11±52.61	129.63±18.99	212.32±33.88	260.45±40.92
t-test. p					
Group vs N		p<0.05	p<0.05	p<0.05	p<0.05
Group vs D			p<0.05	p<0.05	p<0.05
HOBQOV vs V; M				p<0.05	p<0.05
V vs M					p<0.05

All the compounds administered proved a hypoglycemic effect by decreasing the glucose level, still without normalizing it.

Compared to diabetic group (diabetic control), HOBQOV, vanadyl sulphate and metformin decreased the glucose levels of diabetic rats ($p<0.05$). However, the values observed were different ($p<0.05$) from the normal group.

The hypoglycemic effect was calculated as % of reduction in whole blood glucose level reported to diabetic group using the formula: (D group mean value – Treated group value)/ D group mean value *100). The result indicates a percent decrease of 65.99 ±4.98 for HOBQOV, of 44.29±8.89 for vandyl sulphate, and of 31.66±10.74 for metformin, respectively.

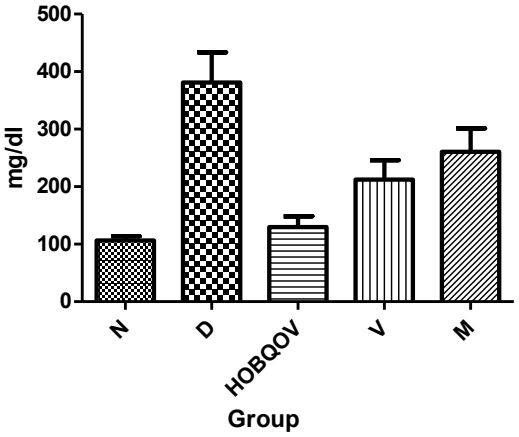

Figure 5
Mean whole blood glucose levels at the end of the treatment

Lipidic profile

The lipidic profile was evaluated at the end of the treatment and expressed as total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels.

Total cholesterol

At the end of experiment, the groups of treated animals had the values of total cholesterol lower than those of diabetic animals ($p<0.05$), but higher than those of normal group ($p<0.05$) (Table IV and Fig. 6).

Table IV
Total cholesterol

Total cholesterol	N	D	HOBQOV	V	M
Mean±SD(mg/dL)	76.83±2.83	128.80±6.86	84.07±6.18	104.10±10.90	85.84±5.01
t-test (90% CI).p					
Group vs N		p<0.05	p<0.05	P<0.05	p<0.05
Group vs D			p<0.05	p<0.05	p<0.05
HOBQOV vs V; M				P<0.05	p>0.05
V vs M					p<0.05

The lowering effect was calculated as % of reduction in total cholesterol level reported to diabetic group using the formula: (D group mean value – Treated group value)/ D group mean value *100. The result indicates a % decrease of 34.73±4.80 for HOBQOV, of 19.18±8.46 for vanadyl sulphate, and of 33.36±3.89 for metformin, respectively.

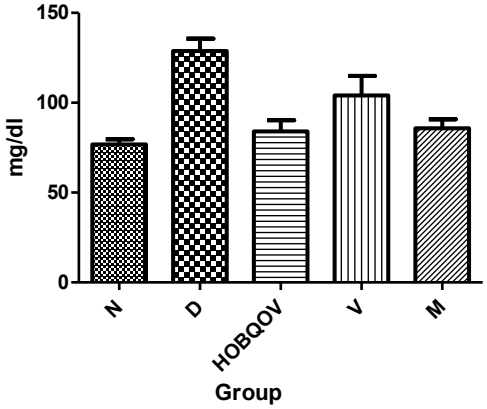

Figure 6
Mean total cholesterol levels at the end of the experiment

HDL-cholesterol
HDL-cholesterol was determinate also at the end of the experiment (Table V, Fig. 7).

Table V
Serum HDL-cholesterol levels

	N	D	HOBQOV	V	M
Mean±SD(mg/dL)	30.02±4.30	17.66±6.58	38.56±4.39	28.24±9.33	39.58±3.41
t-test (90% CI).p					
Group vs N		p<0.05	p<0.05	p>0.05	p<0.05
Group vs D			p<0.05	p<0.05	p<0.05
HOBQOV vs V; M				p<0.05	p>0.05
V vs M					p<0.05

Compared to diabetic group group, HOBQOV, vanadyl sulphate and metformin increased the HDL-cholesterol levels ($p<0.05$). The values observed for HOBQOV and for metformin were different ($p<0.05$) from the normal group. For the group treated with vanadyl sulphate, the results indicated the normalization ($p>0.05$) of the HDL-cholesterol values in comparison with normal group.

The effect was calculated as % of variation in HDL-cholesterol level reported to diabetic group with the formula: (D group mean value – Treated group value)/ D group mean value *100. The result indicates a % increase of 118.39±24.84 for HOBQOV, of 59.93±52.84 for vanadyl sulphate, and of 124.13±19.29 for metformin, respectively.

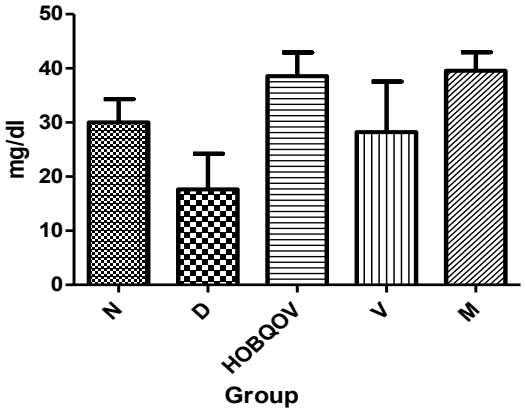

Figure 7
Mean HDL-cholesterol levels at the end of the treatment

LDL-cholesterol
The data obtained for LDL-cholesterol at the end of the experiment are presented in Table VI and in Figure 8.

Table VI
Serum LDL-cholesterol levels

LDL-cholesterol	N	D	HOBQOV	V	M
Mean±SD(mg/dL)	25.39±1.34	83.78±2.46	25.98±1.14	30.59±4.32	25.59±1.93
t-test (90% CI).p					
Group vs N		p<0.05	p>0.05	P<0.05	p>0.05
Group vs D			p<0.05	p<0.05	p<0.05
HOBQOV vs V; M				P<0.05	p>0.05
V vs M					p>0.05

All the compounds decreased the LDL-cholesterol concentration. HOBQOV, vandyl sulphate and metformin decreased the LDL-cholesterol levels ($p<0.05$) in comparison with diabetic group.

The treatment with HOBQOV lead to a normalized LDL-cholesterol level ($p>0.05$); the effect was similar to that of metformin ($p>0.05$).

The lowering effect was calculated as % of reduction in LDL-cholesterol level reported to diabetic group, with the formula: (D group mean value – Treated group value)/ D group mean value *100. The result indicates a % decrease of 68.99±1.39 for HOBQOV, of 63.49±5.16 for vanadyl sulphate, and of 69.46±2.31 for metformin, respectively.

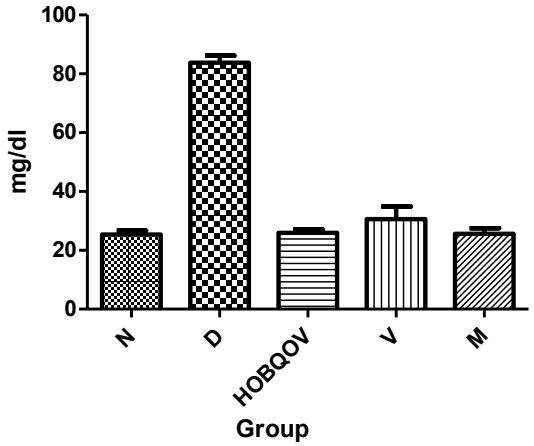

Figure 8
Mean LDL Cholesterol levels at the end of the exeperiment

Triglycerides values
The results of triglyceride concentration at the end of experiment are presented in Table VII and in Figure 9.

Table VII
Serum triglycerides values

TG	N	D	HOBQOV	V	M
Mean±SD(mg/dL)	69.32±4.74	162.77±5.24	63.33±6.85	70.38±5.08	68.06±3.57
t-test (90% CI).p					
Group vs N		p<0.05	p>0.05	p>0.05	p>0.05
Group vs D			p<0.05	p<0.05	p<0.05
HOBQOV vs V; M				p<0.05	p>0.05
V vs M					p>0.05

All the compounds proved to lower the elevated TG to a normal level ($p>0.05$).

Compared to diabetic group HOBQOV, vanadyl sulphate and metformin decreased the TG levels ($p<0.05$).

The effect calculated as % of reduction in TG level reported to D group (D group mean value – Treated group value)/ D group mean value *100) indicates a % decrease of 61.09±4.21 for HOBQOV, of 56.76±3.12 for vanadyl sulphate and of 58.19±2.20 for M, respectively.

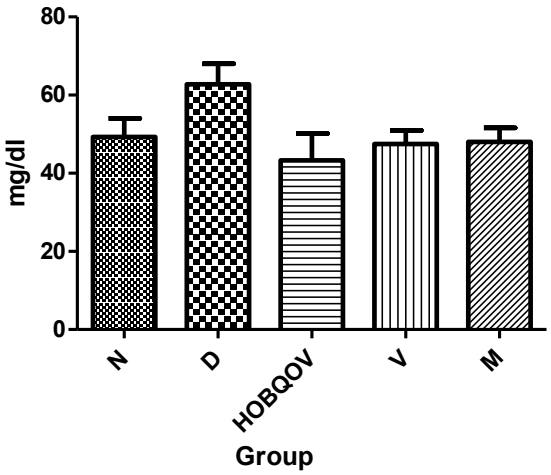

Figure 8
Mean TG levels at the end of the treatment

As a general remark, the complex HOBQOV has an effect of improvement of lipidic profile better than that of vanadyl sulphate and comparable with that of metformin. The amelioration of dislipidemia is in agreement with previous results obtained with oxovanadium(IV) chelates [12, 16, 17, 22, 27].

Conclusions

The vanadium complex with natural flavonoid quercetin (HOBQOV), tested in this study, had a statistically significant hypoglycemic activity in alloxan-diabetic rats. The effect was higher than that of oxovanadium(IV) sulphate and similar to metformin. Moreover, the tested substance has a positive impact on the lipidic profile. The decrease on the cholesterol values was significant compared to diabetic group. HOBQOV decreased the LDL-cholesterol and TG levels at the values compared to those of the normal group. The effect was also higher than that of oxovanadium(IV) sulphate and similar to metformin. After the treatment of diabetic animals with the novel HOBQOV complex the glucidic and lipidic profiles were improved in comparison to the untreated diabetic animals. The results obtained reveals that the complex HOBQOV is valuable for therapeutic application and there is a good premise for the long-term studies.

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