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# ANTIHYPERGLYCEMIC, HYPOLIPIDEMIC AND ANTIOXIDANT PROPERTIES OF THE HERBAL MIXTURES IN DEXAMETHASONE-INDUCED INSULIN RESISTANT RATS

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## Abstract

The herbal mixtures due to the wide range of biologically active substances can influence on various links of the pathogenetic mechanism of development of diabetes mellitus and its complications. The present study investigated the antihyperglycemic, hypolipidemic and antioxidant properties of the herbal mixtures in dexamethasone-induced insulin resistant rats. For research it was used the male albino rats of the Wistar strain. The pathology was modeled by intramuscular introduction of dexamethasone (1 mg/kg/day) to rats during 15 days. The aqueous extracts of the herbal mixtures (12 mL/kg/day) and standard drug – metformin (60 mg/kg/day) were orally administered during 15 days. The results of the study showed that the using of aqueous extracts of herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 has the ability to reduce the hyperglycemia ($p<0.05$) and to normalize the impaired glucose tolerance in dexamethasone-induced insulin resistant rats, relative to the untreated group with pathology. In addition, these extracts are improved the lipid profile by reducing the concentration of total plasma cholesterol, serum triglyceride, low density lipoproteins cholesterol and increasing the concentration of high density lipoproteins cholesterol ($p<0.05$), relative to dexamethasone group. Also, the studied herbal mixtures showed pronounced antioxidant activity by reducing the malonic dialdehyde content, increasing the content of the reduced form of glutathione in the blood and liver, increasing the activity of superoxide dismutase in the blood and liver and increasing the activity of catalase in the blood and reducing its activity in the liver ($p<0.05$) with respect to dexamethasone group.

**Keywords**: *diabetes mellitus, herbal mixtures, insulin resistant, dexamethasone*

## Introduction

Diabetes mellitus is a global social and medical problem caused by the rapid spread of the disease and the development of serious complications such as micro- and macroangiopathies, which significantly reduce the quality and life expectancy of patients [1]. According to the official data from the International Diabetes Federation (2019), the number of patients is projected to increase to 642 million by 2040 [2].

An important problem of pharmacovigilance is that existing pharmacotherapy can effectively reduce hyperglycemia, but it is not always able to stabilize fluctuations in glycemic values during the day and maintain it at an optimal level. This leads to the formation of a cascade of pathological processes - excessive glycation and inactivation of the body's antioxidant defense system, triggering the processes of free radical oxidation of lipids and, as a consequently, the development of oxidative stress, which leads to the development and progression of diabetic angiopathies [1, 3, 4]. In addition, a frequent trigger for the development of diabetic complications is a violation of the lipid profile, manifested by dyslipidemia, hypercholesterolemia and/or hypertriglyceridemia [1, 5]. Therefore, the optimization of pharmacotherapy, search and study of new drugs with antihyperglycemic, hypolipidemic and antioxidant activity for the prevention and treatment of this disease and its dangerous complications is a topical issue of pharmacy and medicine.

One such area is phytotherapy, as it has a number of advantages over traditional therapy with using oral synthetic agents, namely, it is low-toxic, has a mild pharmacological effect and can be used for long periods without significant side effects, is well combined with synthetic drugs, has a complex activity through a number of biologically active compounds [6, 7]. Particular attention deserve the combinations of different medicinal plants, because such herbal mixtures will have more biologically active substances that will influence on the all links of the pathogenetic mechanism of development of diabetes mellitus and its complications [8, 9].

Thus, for this purpose, it is advisable to study the antihyperglycemic, hypolipidemic and antioxidant properties in dexamethasone-induced insulin resistant rats of the investigated herbal mixtures, which are used in folk medicine for the prevention and treatment of diabetes mellitus type 2 in Ukraine [10], but do not have a scientific basis.

## Methods

**Plant materials:** It was used the herbal raw materials harvested in June – August 2019 in Ternopil region and Charpathians (*Vaccinium myrtillus* leaf) (Ukraine) during the study. After harvesting, the raw materials were dried, crushed and brought back to standard according to the general GACP requirements [11]. The plants were identified by Department of Pharmacognosy with Medical Botany, I.Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. Samples of herbal raw materials have been deposited in Departmental Herbarium for future record.

For the study were used the five different herbal mixtures with reliable antihyperglycemic activity established during the screening testing [12, 13, 14], which are used in folk medicine for the prevention and treatment of diabetes mellitus type 2 in Ukraine [11]. The compositions of the mixtures are given in Table 1.

**Extraction procedure:** The samples of 10 g of each powdered herbal mixture were put into a 100 mL conical flask and 120 mL of distilled water was added to each. The aqueous extracts were obtained by heating in the boiling water bath for 30 minutes. The extracts were filtered using Whatmann filter paper No. 1. Then the filtrates were evaporated by rotary evaporator and were lyophilized to dryness. The lyophilized powders of each herbal mixture were stored at 4 °C for further use.

**Drugs and chemicals:** Dexamethasone was purchased from KRKA, Slovenia, the standard drug – metformin SANDOZ® from Lek S.A., Poland, Sodium thiopental for anesthesia from Abbott Park, IL, USA. All chemicals that were used in the research were analytical graded.

**Experimental Animals:** The study was performed on male albino rats of the Wistar strain weighing between 180 g and 200 g, which were bred at the animal house of the Central Research Laboratory of I.Horbachevsky Ternopil National Medical University, where they were kept under appropriate conditions (at a constant room temperature of 22 ± 1°C, 40-70% humidity conditions and a 12-hour light/dark cycle). Throughout the experimental period, the animals received standard rat diet and water *ad libitum.* The animals were treated in accordance with the internationally accepted standard ethical guidelines for laboratory animal use and care as described in the European Community Guidelines [15]. All protocols for animals experiment were approved by the animal ethical committee of I.Horbachevsky Ternopil National Medical University.

**Induction of Insulin Resistance and Experimental Protocol:** Induction of insulin resistance by dexamethasone was performed according to the previously described protocol [16] with some modifications. Rats were randomly divided into eight groups of eight animals (n=8) each and received different treatments once daily for 15 days. Group I (Control): received per os (*p.o*) distilled water (12 mL/kg/day) and intramuscular (i.m.) injection of NaCl 0.9 % (1 mL/kg/day). Group 2 (DEXA) received daily intramuscular injection of dexamethasone (1 mg/kg/day) and distilled water (12 mL/kg/day, *p.o.*). Group III (DEXA+MET) received dexamethasone (1 mg/kg/day, i.m.) and the standard drug – metformin (60 mg/kg/day, *p.o.*). Group IV-VIII (DEXA+EHM) received dexamethasone (1 mg/kg/day, i.m.) and the aqueous extracts of the studied herbal mixtures (12 mL/kg/day, *p.o.*). The dose of dexamethasone (1 mg/kg/day) and metformin (60 mg/kg/day) was selected based on previous studies [16, 17]. The effective dose of herbal mixture extracts was established during the previous screening testing [12, 13, 14]. At the end of the experiment, rats were sacrifice by decapitation after anesthesia with Sodium thiopental and the blood and the liver were collected.

**Measurement of Oral Glucose Tolerance Test (OGTT):** Fasting blood glucose level (basal glycemia) was measured in tail blood samples after a 6 hours fasting on day 0 (before treatment) and day 15 (before the treatment of the day) by the glucose analyzer (glucometer Accuk-Check, Germany). OGTT was performed after the basal glycemia measurement by administering of glucose (3 g/kg, *p.o.*) on the 15-th day. Blood glucose levels were determined at 0, 30th, 60th and 120th minute after glucose load.

**Biochemical Analysis:** The obtained blood samples were centrifuged at 3000 rpm for 10 minutes. The resulting plasma was stored at -20 °C for further measurement. Liver samples were ground in Tris buffer (pH 7.4, 10 mM), centrifuged at 10 000 rpm for 15 minutes at 4 °C and the supernatant was used to assay tissue superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and malonic dialdehyde (MDA).

Lipid profile – total plasma cholesterol (TOT CHOL), high density lipoproteins cholesterol (HDL CHOL) and serum triglyceride (TG) were measured spectrophotometrically using the spectrophotometer Varian Cary 50 UV-Vis (USA) and commercial kits BioSistems (Spain). Atherogenic Index (AI) was calculated by the following formula: AI = (TOT CHOL - HDL CHOL) / HDL CHOL [18]. Low density lipoproteins cholesterol (LDL CHOL) concentration was determined according to the formula of Friedwald [19].

The beneficial effect of the herbal mixture extracts on oxidative stress was determined by assaying enzymatic and nonenzymatic antioxidant status. MDA level was determined by the method of Olszewska-Słonina et al. [20], GSH content as described by Giustarini et al. [21], SOD activity by the method of Serra et al. [22], and CAT activity as reported by Hadwan [23].

**Statistical Analysis:** The values were expressed as mean ± SEM. The data were analysed by using GraphPad Prism software version 5.03. The results were compared by using the ANOVA-One-Way test followed by *Mann-Whitney U test*. The difference was considered statistically significant at $p<0.05$.

## Results and Discussion

The administration of dexamethasone at a dose of 1 mg/kg/day for 15 days to linear rats caused the development of basal hyperglycemia, which was 60% higher than in rats from the Control group. The oral administration of aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 significantly was reduced the hyperglycemia induced by dexamethasone from 26% to 36% compared with the untreated group (DEXA). Metformin, which was used as positive control, was reduced glycemia by 43 % as compared to the DEXA group (Figure 1).

With the help of OTTG it is possible to detect the impaired glucose tolerance. The antihyperglycemic activity was evidenced by the ability of the studied objects to reduce glycemia at 30th minute of OTTG (during the maximum rise in blood glucose levels of experimental rats in response to oral carbohydrate load).The results of the OGTT showed that, 30 minutes after glucose load, the difference in blood glucose in rats receiving dexamethasone alone was 44% higher than that in healthy control animals. At the same time, the difference in blood glucose in rats receiving concomitantly dexamethasone and aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 were, respectively, 27%, 24%, 23%, 22% and 28% lower, as compared to that in the DEXA group. The difference in blood glucose in the metformin-treated animals was 31% lower than in the DEXA group. Two hours after glucose load, the reduction in glycemia was, respectively, 41%, 39%, 38%, 36% and 43% in the group, which has a treatment by aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19, as compared to that in the DEXA group. The introduction of metformin showed similar results as the investigated herbal extracts, as the reduction in blood glucose in animals was 47% compared with DEXA group (Figure 1).

The modeling of dexamethasone-induced insulin resistant caused a change in the lipid profile in rats, in particular, increasing the plasma concentration of TOT CHOL by 28% relative to the Control group. The administration of aqueous extracts of the herbal mixtures and metformin to dexamethasone-induced rats reduced TOT CHOL levels almost to control values. Concerning plasmatic TG, dexamethasone administration increased its level by 35%. The extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 as well significantly reduced the hypertriglyceridemia induced by dexamethasone by 34%, 31%, 19%, 23% and 34%, respectively. The introduction of metformin showed similar results as the investigated herbal extracts, as the reduction in plasmatic TG in animals was 28% compared with DEXA group. Dexamethasone significantly reduced the plasma concentration of HDL cholesterol and increased the plasma concentration of LDL cholesterol. The introduction of investigated extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 showed the decrease of plasmatic LDL cholesterol by 22%, 16%, 16%, 17% and 20% and the increase of plasmatic HDL cholesterol by 44%, 29%, 36%, 30% and 50%, respectively. In the group receiving metformin, the increase of twice was observed in plasma HDL cholesterol and the decrease in LDL cholesterol by 20% relative to DEXA group (Table 2).

The investigated extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 showed the ability to regulate the lipid metabolism, by reducing the AI by 60%, 52%, 52%, 49% and 66%, respectively, compared with metformin, which reduced the AI by 84 % relative to DEXA group (Figure 2).

Modeling of insulin resistance by administration of dexamethasone caused the development of oxidative stress in rats, which was manifested by changes in enzyme activity, namely an increasing the CAT activity by 25% in the blood and a decreasing it by 21% in the liver, an increasing the SOD by 47% in the blood and by 41% in the liver. The biological role of CAT is to degrade hydrogen peroxide, which is formed in cells under the action of flavoprotein oxidases (xanthine oxidase, glucose oxidase, monoamine oxidase) and to provide effective protection of cellular structures from destruction by hydrogen peroxide. This enzyme is a component of the complex enzymatic protection of the body from the action of toxic oxygen compounds [24, 25]. The extracts of the herbal mixtures No. 3 and No. 19 showed the best ability to reduce the activity of CAT in the blood by 16% and 18%, respectively, and to increase its activity by 17% and 19% in the liver,

respectively. SOD serves as an acceptor of free oxygen radicals, which inhibits the lipid peroxidation [25]. The oral administration of the studied herbal extracts caused a decrease in SOD activity by 29-34% in the blood and by 26-36% in the liver. Metformin eliminated the manifestations of oxidative stress by the reducing of CAT activity by 20% in the blood and increasing of it by 11% in the liver, reducing the activity of SOD by 32% in the blood and by 24% in the liver of rats (Table 3).

The administration of dexamethasone to experimental rats caused the accumulation of MDA by 43% in the blood and by 18% in the liver, which is indicated the activation of the lipid peroxidation. However, the aqueous herbal mixtures extracts showed the ability to reduce the MDA content by 19-31% in the blood, although in the liver the decrease in the MDA content was not so significant. Metformin showed similar results, as it reduced the concentration of MDA by 22% in the blood, and had little effect on reducing its concentration in the liver (Table 3).

Another important factor in assessing the state of the antioxidant defense system is to determine the content of the reduced form of glutathione (GSH). Induction of dexamethasone in rats caused a decrease in GSH content, indicating an imbalance between the antioxidant defense system and the lipid peroxidation processes, which is leading to the development of oxidative stress [25, 26]. During the study, it was established that the extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 have the ability to increase the concentration of GSH by 52%, 48%, 59%, 26% and 62% in the liver, respectively, but this effect on its concentration in the blood was not so pronounced. The administration of metformin did not change the concentration of GSH in the blood and liver in rats relative to DEXA group (Table 3).

Therefore, the oral administration of aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 has shown their ability to reduce the manifestations of hyperglycemia and to normalize the impaired glucose tolerance in dexamethasone-induced insulin resistant rats. In addition, these extracts have a positive effect on the regulation of the lipid metabolism by lowering TOT CHOL, TG and LDL CHOL and increasing HDL CHOL. Also, the studied herbal mixtures showed a pronounced antioxidant activity by reducing the content of MDA, increasing the content of GSH in the blood and liver, increasing the activity of SOD in the blood and liver and increasing the activity of CAT in the blood and reducing its activity in the liver in experimental rats.

## Conclusions

The results of the present study showed that aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 possess potential antihyperglycemic effects and reduce the development of impaired glucose tolerance, which was caused by dexamethasone administration. In addition, the investigated extracts have shown the ability to neutralize the manifestations of dyslipidemia and to regulate the balance between the antioxidant defense system and the the lipid peroxidation system. The powerful antihyperglycemic, hypolipidemic and antioxidant effects make these herbal mixtures promising tools for prevention and treatment of diabetes and its complications.

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**Table 1.** Composition of the herbal mixtures

| Herbal mixtures | Herbals | Quantity of herbals in mixtures, g |
|---|---|---|
| No. 3 | *Urtica dioica* leaf | 26.32 |
| | *Cichorium intybus* roots | 26.32 |
| | *Rosa majalis* fruits | 21.05 |
| | *Elymus repens* rhizome | 15.79 |
| | *Taraxacum officinale* roots | 10.52 |
| | | Total: 100.00 |
| No. 4 | *Arctium lappa* roots | 26.32 |
| | *Elymus repens* rhizome | 26.32 |
| | *Zea mays* columns with stigmas | 21.05 |
| | *Helichrysum arenarium* flowers | 15.79 |
| | *Rosa majalis* fruits | 10.52 |
| | | Total: 100.00 |
| No. 7 | *Inula helenium* rhizome with roots | 10.00 |
| | *Helichrysi arenarium* flowers | 20.00 |
| | *Zea mays* columns with stigmas | 20.00 |
| | *Origanum vulgari* herb | 20.00 |
| | *Rosa majalis* fruits | 20.00 |
| | *Taraxacum officinale* roots | 10.00 |
| | | Total: 100.00 |
| No. 13 | *Cichorium intybus* roots | 26.32 |
| | *Elymus repens* rhizome | 26.32 |
| | *Helichrysum arenarium* flowers | 21.05 |
| | *Rosa majalis* fruits | 15.79 |
| | *Zea mays* columns with stigmas | 10.52 |
| | | Total: 100.00 |
| No. 19 | *Urtica dioica* leaf | 20.00 |
| | *Taraxacum officinale* roots | 20.00 |
| | *Vaccinium myrtillus* leaf | 20.00 |
| | *Rosa majalis* fruits | 20.00 |
| | *Mentha piperita* herb | 20.00 |
| | | Total: 100.00 |

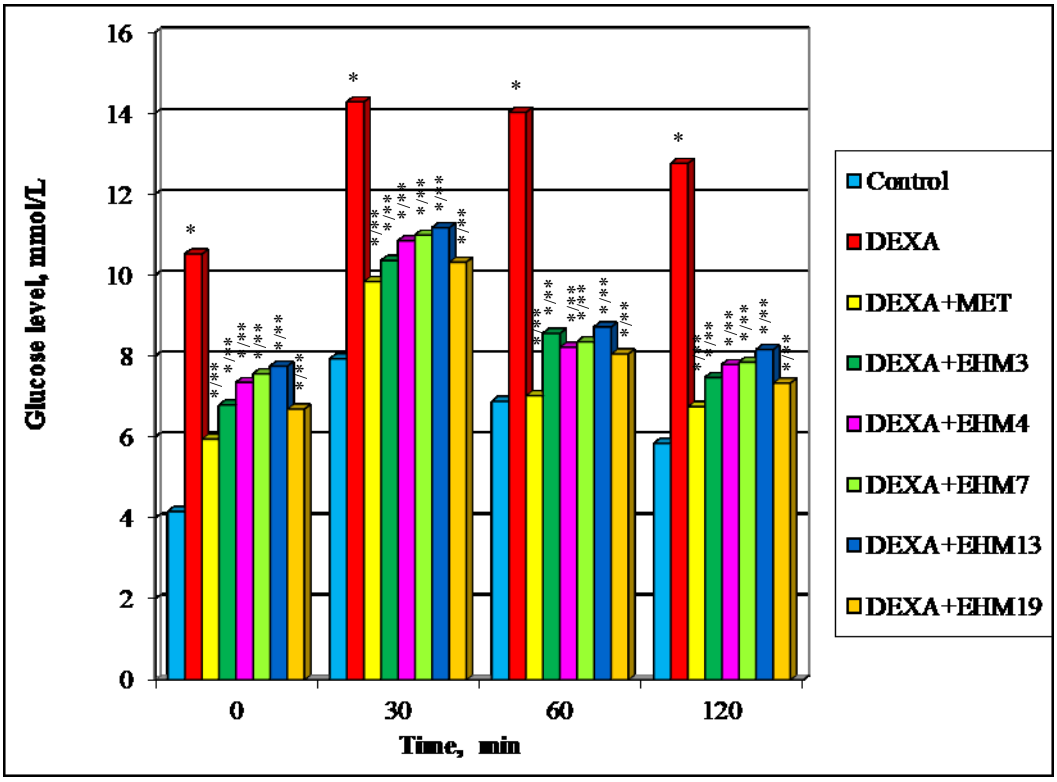


**Figure 1.** Effect of aqueous extracts of the herbal mixtures and the comparison drug metformin during OGTT in dexamethasone-induced insulin resistant rats on 15-th day of treatment. Values are expressed as mean ± SEM from 8 rats; * p<0.05 with respect to Control group; ** p<0.05 with respect to dexamethasone (DEXA) group.

**Table 2.** Effect of aqueous extracts of the herbal mixtures and the comparison drug metformin on the lipid profile in dexamethasone-induced insulin resistant rats.

| Para-meters (mmol/L) | Control | DEXA | DEXA+ EHM3, 12 mL/kg/day | DEXA+ EHM4, 12 mL/kg/day | DEXA+ EHM7, 12 mL /kg/day | DEXA+ EHM13, 12 mL/kg/day | DEXA+ EHM19, 12 mL/kg/day | DEXA+ MET, 60 mg/kg/day |
|---|---|---|---|---|---|---|---|---|
| TOT CHOL | 3.13±0.08 | 4.02±0.12 * | 3.24±0.13 ** | 3.21±0.09 ** | 3.37±0.21 ** | 3.36±0.15 ** | 3.09±0.19 ** | 3.08±0.13 ** |
| TG | 0.87±0,17 | 1.34±0,16 * | 0.89±0,26 ** | 0.92±0.15 ** | 1.09±0.11 */** | 1.03±0.17 */** | 0.89±0.09 ** | 0.83±0.09 ** |
| LDL CHOL | 2.12±0.17 | 2.87±0.16 * | 2.36±0.12 ** | 2.41±0.21 */** | 2.40±0.22 */** | 2.39±0.19 */** | 2.31±0.18 */** | 2.29±0.18 ** |
| HDL CHOL | 2.52±0.16 | 1.06±0.17 * | 1.53±0.15 */** | 1.37±0.19 */** | 1.44±0.11 */** | 1.38±0.13 */** | 1.59±0.21 */** | 2.11±0.18 */** |

Values are expressed as mean ± SEM from 8 rats; * p<0.05 with respect to Control group; ** p<0.05 with respect to dexamethasone (DEXA) group.

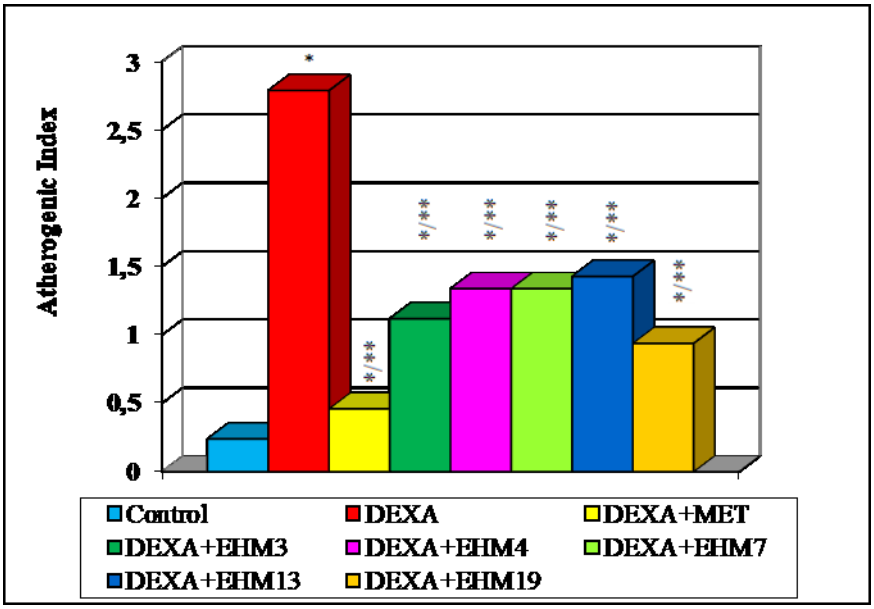


**Figure 2.** Effect of aqueous extracts of the herbal mixtures and the comparison drug metformin on the Aterogenic Index (AI) in dexamethasone-induced insulin resistant rats. Values are expressed as mean ± SEM from 8 rats; * p<0.05 with respect to Control group; ** p<0.05 with respect to dexamethasone (DEXA) group.

**Table 3.** Effect of aqueous extracts of the herbal mixtures and the comparison drug metformin on the antioxidant defense system in dexamethasone-induced insulin resistant rats.

| Parameters | Control | DEXA | DEXA+ EHM3, 12 mL/kg/day | DEXA+ EHM4, 12 mL/kg/day | DEXA+ EHM7, 12 mL/kg/day | DEXA+ EHM13, 12 mL/kg/day | DEXA+ EHM19, 12 mL/kg/day | DEXA+ MET, 60 mg/kg/ day |
|---|---|---|---|---|---|---|---|---|
| **In the blood** | | | | | | | | |
| **MDA, µmol/L** | 3.32±0.14 | 4.76±0.24 * | 3.75±0.26 */** | 3.93±0.22 */** | 3.87±0.31 */** | 3.99±0.36 */** | 3.64±0.29 */** | 3.47±0.21 ** |
| **CAT, U/L** | 14.12±0.37 | 17.72±0.34 * | 15.27±0.47 */** | 16.12±0.48 */** | 15.78±0.42 */** | 16.87±0.58 * | 15.02±0.87 ** | 14.48±0.61 ** |
| **SOD, U/L** | 4.85±0.38 | 6.57±0.26 * | 4.98±0.29 ** | 5.06±0.16 ** | 4.97±0.22 ** | 5.11±0.21 ** | 4.92±0.27 ** | 4.99±0.16 ** |
| **GSH, mmol/L** | 72.15±0.56 | 64.95±0.86 * | 71.64±0.86 ** | 70.85±0.97 ** | 70.19±0.69 ** | 69.91±0.95 ** | 73.38±0.57 ** | 67.78±0.93 |
| **In the liver** | | | | | | | | |
| **MDA, µmol/kg** | 4.62±0.24 | 5.46±0.21 * | 4.75±0.46 ** | 4.79±0.28 ** | 4.84±0.11 ** | 5.19±0.21 * | 4.69±0.17 ** | 4.89±0.26 ** |
| **CAT, U/kg** | 4.32±0.16 | 3.56±0.26 * | 4.18±0.23 ** | 4.15±0.22 ** | 4.17±0.31 ** | 4.09±0.16 ** | 4.24±0.29 ** | 4.01±0.21 */** |
| **SOD, U/kg** | 4.22±0.28 | 5.96±0.25 * | 4.37±0.15 ** | 4.39±0.16 ** | 4.64±0.36 */** | 4.72±0.35 */** | 4.39±0.16 ** | 4.82±0.18 */** |
| **GSH, mmol/kg** | 4.12±0.26 | 2.46±0.23 * | 3.75±0.41 */** | 3.63±0.17 */** | 3.92±0.42 ** | 3.11±0.31 */** | 3.99±0.23 ** | 2.59±0.22 * |

Values are expressed as mean ± SEM from 8 rats; * p<0.05 with respect to Control group; ** p<0.05 with respect to dexamethasone (DEXA) group.