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**INFLUENCE OF THE HERBAL MIXTURES
ON THE FUNCTIONAL STATE OF THE LIVER
IN DEXAMETHASONE-INDUCED INSULIN RESISTANT RATS**

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Diabetes mellitus is one of WHO's priority issues. It requires immediate resolution as the epidemiological situation is gaining alarming proportions – the number of diabetic patients is increasing every year along with the number of deaths and disabilities due to the development of micro- and macro-angiopathies. According to the official information of International Diabetes Federation (2019), the number of patients is projected to increase to 642 million by 2040 [1].

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 development of the pathological processes cascade – 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 formation of oxidative stress, which leads to the development and progression of diabetic angiopathies [1, 2].

Therefore, the optimization of pharmacotherapy, search and study of new drugs with hypoglycemic activity for the prevention and treatment of this disease and its dangerous complications is a top issue of pharmacy and medicine.

One of these areas is using herbal remedies, either as monotherapy for the prevention or in the mild stages of the disease or in the combination with traditional therapy in more severe forms of the disease. Phytotherapy is a justified method for the prevention and treatment because it has some advantages, such as relatively low toxicity, mild pharmacological effects and possibility to be used for long periods without significant side-effects, and it often well combines with synthetic drugs, has a complex activity through a number of biologically active compounds [3, 4]. 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 [3, 5].

Thus, the aim of our research was to study the influence of some herbal mixtures on the functional state of the liver in dexamethasone-induced insulin resistant rats.

The objects of study were the herbal antidiabetic mixtures No. 3 (*Urtica dioica* leaf, *Cichorium intybus* roots, *Rosa majalis* fruits, *Elymus repens* rhizome, *Taraxacum officinale* roots) No. 4 (*Arctium lappa* roots, *Elymus repens* rhizome, *Zea mays* columns with stigmas, *Helichrysum arenarium* flowers, *Rosa majalis* fruits), No. 7 (*Inula helenium* rhizome with roots, *Helichrysum arenarium* flowers, *Zea mays* columns with stigmas, *Origanum vulgare* herb, *Rosa majalis* fruits, *Taraxacum officinale* roots), No. 13 (*Cichorium intybus* roots, *Elymus repens* rhizome, *Helichrysum arenarium* flowers, *Rosa majalis* fruits, *Zea mays* columns with stigmas), No. 19 (*Urtica dioica* leaf, *Taraxacum officinale* roots, *Vaccinium myrtillus* leaf, *Rosa majalis* fruits, *Mentha piperita* herb), which are used in folk medicine for the treatment and prevention of diabetes mellitus type 2 [6]. It was used the herbal raw materials harvested in June – August 2019 in Ternopil region and Carpathians (*Vaccinium myrtillus* leaf) (Ukraine) during the study.

The samples of 10 g of each powdered herbal mixture were put into a 100 mL conical flask, was added 120 mL of distilled water to each. The aqueous extracts were obtained by heating in the boiling water bath for 30 min. 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.

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 $22 \pm 1^\circ\text{C}$, 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 [7].

Induction of insulin resistance by dexamethasone was performed according to the previously described protocol [8] 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 (KRKA, Slovenia) (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 (Lek S.A., Poland) (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.*). At the end of the experiment, rats were sacrifice by decapitation after anesthesia with Sodium thiopental (Abbott Park, IL, USA) and the blood was collected.

Determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity was performed using commercial kits (Filisit-Diagnostyka, Ukraine).

The values were expressed as mean \pm 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 $p<0.05$.

The administration of dexamethasone at a dose of 1 mg/kg/day for 15 days to linear rats caused the disorders of functional activity of the liver due to the increase of the activity of hepatic transaminases ALT and AST, which was 38 % and 42 % higher than in rats from the Control group. The administration of aqueous extracts of the herbal mixtures and metformin to dexamethasone-induced insulin resistant rats reduced ALT and AST activity almost to the values of the Control group. The extracts of the herbal

mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 significantly reduced the ALT activity by 26 %, 25 %, 23 %, 25 % and 31 %, respectively, and AST activity by 42 %, 35 %, 38 %, 42 % and 42 %, respectively. The introduction of metformin showed similar results to the investigated herbal extracts, as the reduction in ALT and AST activity was 32 % and 34 % compared with DEXA group.

The results from the present study showed that aqueous extracts of the herbal mixtures No. 3, No. 4, No. 7, No. 13 and No. 19 possess potential hepatoprotective effect and reduce the disorders of functional activity of the liver, which was caused by dexamethasone administration.

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