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## INFLUENCE OF *CITRULLUS COLOCYNTHIS* (L.) SHRAD. EXTRACT ON GLUCOSE LEVEL, LIPID METABOLISM AND OXIDATIVE HOMEOSTASIS PARAMETERS OF ANIMALS UNDER EXPERIMENTAL DIABETES MELLITUS

**Topicality.** Diabetes mellitus is one of the most common chronic diseases. Among the methods of diabetes treating, phytotherapy occupies the remarkable place. Phytoproducts, as an alternative to synthetic drugs, are becoming increasingly popular due to the ability to exhibit multi-vector effects on the organism of the patient and to act in a complex manner.

**The aim** of the study was to investigate the hypoglycemic, hypolipidemic and antioxidant activity of *Citrullus colocynthis* dry extract, as a representative of medicinal plants with antidiabetic action.

**Materials and methods.** Hypoglycemic, hypolipidemic and antioxidant activity of *C. colocynthis* extract was investigated on Wistar rats with the model of type 2 diabetes mellitus. The plant extract was administered at doses of 50 mg/kg and 100 mg/kg, a reference drug "Arphazetyn" at a dose of 18 ml/kg for 28 days. The level of glucose was determined at the beginning and at the end of the experiment, the parameters of lipid (cholesterol, triglycerides, LDL, VLDL, HDL) and oxidative homeostasis (malonic dialdehyde, catalase, superoxidisedismutase) – on the last day of the study.

**Results and discussion.** It has been established that *C. colocynthis* extract exhibits dose-dependent hypoglycemic and hypolipidemic effects. The most pronounced activity the plant extract exhibits at a dose of 100 mg/kg: lowers blood glucose levels as well as elevated parameters of lipid metabolism and increases the level of HDL. At a dose of 100 mg/kg it increases the activity of antioxidant enzymes, thereby reducing the level of malonic dialdehyde. The reference drug is inferior to the effectiveness of the *C. colocynthis* extract for all of these parameters.

**Conclusions.** According to results of the study, *C. colocynthis* extract has hypoglycemic, hypolipidemic and antioxidant effects.

**Key words:** *C. colocynthis*; type 2 diabetes; antioxidant activity; hypolipidemic action; *C. colocynthis* dry extract

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### Вплив екстракту *Citrullus colocynthis* (L.) shrad. на рівень глюкози, параметри ліпідного обміну та оксидативного гомеостазу тварин за умови експериментального цукрового діабету

**Актуальність.** Цукровий діабет – одне з найпоширеніших хронічних захворювань. Серед методів терапії цукрового діабету чинне місце посідає фітотерапія. Фітозасоби як альтернатива препаратам синтетичної природи набувають все більшої популярності завдяки здатності проявляти різновекторний вплив на організм хворого і діяти комплексно.

**Метою** даної роботи було дослідження гіпоглікемічної, гіполіпідемічної та антиоксидантної активності сухо-го екстракту плодів *Citrullus colocynthis* як одного з представників лікарських рослин із протидіабетичною дією.

**Матеріали та методи.** Гіпоглікемічну, гіполіпідемічну та антиоксидантну активність екстракту *C. colocynthis* досліджували на щурах лінії Вістар з моделлю цукрового діабету 2 типу. Рослинний екстракт вводили в дозах 50 мг/кг та 100 мг/кг, препарат порівняння «Арфазетин» у дозі 18 мл/кг – впродовж 28 діб. Рівень глюкози визначали на початку та в кінці експерименту, параметри ліпідного (холестерин, тригліцериди, ЛПНЩ, ЛПДНЩ, ЛПВЩ) та оксидативного гомеостазу (малоновий діальдегід, каталаза, супероксиддисмутаза) – в останній день дослідження.

**Результати та їх обговорення.** Встановлено, що екстракту плодів *C. colocynthis* притаманна дозозалежна гіпоглікемічна та гіполіпідемічна дія. Найбільш виражену активність рослинний екстракт проявляє при дозі 100 мг/кг: знижує рівень глюкози крові, а також підвищує показники ліпідного обміну і збільшує рівень ЛПВЩ. У дозі 100 мг/кг екстракт *C. colocynthis* сприяє збільшенню активності антиоксидантних ферментів, тим самим зменшує рівень малонового діальдегіду. За всіма зазначеними показниками препарат порівняння поступається ефективністю дії екстракту *C. colocynthis*.

**Висновки.** Відповідно до результатів проведених досліджень екстракт плодів *C. colocynthis* володіє гіпоглікемічною, гіполіпідемічною та антиоксидантною дією.

**Ключові слова:** *C. colocynthis*; цукровий діабет 2 типу; антиоксидантна активність; гіполіпідемічна дія; сухий екстракт плодів *C. colocynthis*

Г. Р. Ламазян

### Влияние экстракта *Citrullus colocynthis* (L.) shrad. на уровень глюкозы, параметры липидного обмена и оксидативного гомеостаза животных в условиях экспериментального сахарного диабета

**Актуальность.** Сахарный диабет – одно из самых распространенных хронических заболеваний. Среди методов терапии сахарного диабета весомое место занимает фитотерапия. Фитосредства как альтернатива препаратам синтетической природы приобретают все большую популярность благодаря способности проявлять разновекторное влияние на организм больного и действовать комплексно.

**Целью** работы было исследование гипогликемической, гиполипидемической и антиоксидантной активности сухого экстракта плодов *Citrullus colocynthis* как одного из представителей лекарственных растений с противодиабетическим действием.

**Материалы и методы.** Гипогликемическую, гиполипидемическую и антиоксидантную активность экстракта *C. colocynthis* исследовали на крысах линии Вистар с моделью сахарного диабета 2 типа. Растительный экстракт вводили в дозах 50 мг/кг и 100 мг/кг, препарат сравнения «Арфазетин» – в дозе 18 мг/кг в течение 28 суток. Уровень глюкозы определяли в начале и в конце эксперимента, параметры липидного (холестерин, триглицериды, ЛПНП, ЛПОНП, ЛПВП) и оксидативного гомеостаза (малоновый диальдегид, каталаза, супероксиддисмутаза) – в последний день исследования.

**Результаты и их обсуждение.** Установлено, что для экстракта плодов *C. colocynthis* свойственно дозозависимое гипогликемическое и гиполипидемическое действие. Наиболее выраженную активность растительный экстракт проявляет при дозе 100 мг/кг: снижает уровень глюкозы крови, а также повышенные показатели липидного обмена и увеличивает уровень ЛПВП. В дозе 100 мг/кг способствует увеличению активности антиоксидантных ферментов, тем самым уменьшает уровень малонового диальдегида. По всем указанным показателям препарат сравнения уступает по эффективности действия экстракту *C. colocynthis*.

**Выводы.** Согласно результатам проведенных исследований экстракт плодов *C. colocynthis* обладает гипогликемическим, гиполипидемическим и антиоксидантным действием.

**Ключевые слова:** *C. colocynthis*; сахарный диабет 2 типа; антиоксидантная активность; гиполипидемическое действие; сухой экстракт плодов *C. colocynthis*

## INTRODUCTION

Diabetes mellitus (DM) is a disease that's characterized by an increase of blood glucose level due to primarily carbohydrate and also lipid and protein metabolism disorders [1].

In the presence of diabetes plasma lipids level also increases contributing to the development of cardiovascular complications which are the main cause of disability and mortality in patients. The accumulation of a valuable amount of lipids in diabetes is mediated by insulin deficiency and insulin resistance [2].

DM is accompanied by an increase in the level of prooxidant factors and a decrease in antioxidant protection of the organism, which leads to the development of oxidative stress (OS) [3]. Glucose oxidation induced by hyperglycemia initiates peroxide oxidation of membrane lipids (POL) and non-enzymatic glycosylation of proteins which in turn leads to the production of reactive oxygen species (ROS) [4]. Excessive production of free radicals (FR) causes damage of cellular structures [1]. Islands of Langerhans differ by a low content of antioxidant enzymes, so they are especially sensitive to the ROS [5, 6].

Due to the increasing of diabetes prevalence and the costs this illness bears, the interest in alternative therapies of this pathology is also increasing. The results of numerous studies on experimental animals with DM models confirm the therapeutic value of phytochemicals.

One of medicinal plants (MP) which possesses anti-diabetic activity is *Citrullus colocynthis* (*colocynth*) – representative of the *Cucurbitaceae* family [7]. It is known that colocynth contains significant amount of phenolic compounds and flavonoids in various morphological parts [8]. Their content is associated with the presence of hypoglycemic, hypolipidemic and antioxidant activity in *C. colocynthis* medicinal plant raw material (MPRM) [9, 10, 11].

**The aim** of the study is to investigate the hypoglycemic, hypolipidemic and antioxidant activity of colocynth fruits dry extract on the model of type 2 DM.

## MATERIALS AND METHODS

Experimental studies have been carried out in accordance with strategies of the Directive of the European Parliament and the Council of the EU 2010/63/EC of 22.09.2010 on the protection of animals used for scientific purposes, the Order of the Ministry of Health of Ukraine No. 944 of 14.12.2009. "On Approval of the Procedure for the Pre-clinical Study of medicines and examination of materials for preclinical study of medicinal products", Law of Ukraine No. 3447-IV of 21.02.2006. "On the Protection of Animals from Cruel Treatment".

The object of pharmacological research was *C. colocynthis* fruit dry extract.

Studies of the antidiabetic activity were performed on the model of type 2 DM induced by administration of nicotinamide (NA) (Sigma-Aldrich, USA) at a dose of 230 mg/kg body weight intraperitoneally 15 minutes prior to intravenous injection of streptozotocine (STZ) (Sigma-Aldrich, USA) at a dose of 65 mg/kg [12]. The extract was used at doses of 50 mg/kg, 100 mg/kg body weight of the animal. "Arphasetyn" (PJSC "Likravny", Ukraine) was used as a reference drug at a dose of 18 ml/kg.

The glucose level was measured after 1 day and 28 days after DM model reproduction by the GOD/POD/PAP method ("Diagnosticum Zrt" kit) on the semi-automatic biochemical analyzer BS-3000M (China) [13].

Lipid profiles (cholesterol (Chol), triglyceride (TrG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL)) were studied using biochemical kits Cholesterol PAP, Triglycerides PAP, LDL Cholesterol, VLDL Cholesterol, HDL Cholesterol produced by "Diagnosticum Zrt" (Hungary) at the end of the experiment [13].

Indicators of oxidative homeostasis (malonic dialdehyde, catalase, superoxidedismutase) were determined on the 28-th day of study in the liver homogenate of animals with a DM model [14, 15, 16]. As a reference drug, an antioxidant with a known mechanism of action, NAC – N-acetylcysteine at a dose of 1.5 g/kg was used.

**Experimental design.** Wistar rats were divided into five groups: Control – healthy rats which were given water for injection per os, Model – rats with DM model, receiving water for injection per os, Model + DE *C. colocynthis* 50 mg/kg – animals with DM model which were administered *C. colocynthis* dry extract at a dose of 50 mg/kg per os, predissolved in water for injection, Model + DE *C. colocynthis* 100 mg/kg – animals with DM model which were administered *C. colocynthis* dry extract at a dose of 100 mg/kg per os, predissolved in water for injection, Model + A 18 ml/kg – animals with DM model, which were administered “Arfazety” per os, prepared in accordance with the instructions for the drug use.

Results are expressed as mean (M) ± error of mean (± m). Statistical comparison was performed by Student's test. The results were considered statistically significant if  $p < 0.05$ .

### RESULTS AND DISCUSSION

The results of the study showed (Table) that the administration of STZ with the simultaneous administration of nicotinamide (HA) induces stable and moderate hyperglycemia that significantly increases with time – in case of model group. However, prophylactic and therapeutic administration for 28 days of *C. colocynthis* extract at doses of 100 mg/kg and 50 mg/kg contributes to the reduction of hyperglycemia to a significantly lower level than reference drug does.

A plant extract (Table) exhibits a more pronounced hypoglycaemic effect at a dose of 100 mg/kg than at a dose of 50 mg/kg, so the sugar-reducing activity of the *C. colocynthis* extract is dose-dependent. Up to the 28-th day of observation glucose level decreased by 54 %, 46 % and 40 % in relation to the model and by 33 %, 25 % and 17 % in relation to the level of glycemia of the first day in groups of model + DE *C. colocynthis* 100 mg/kg, model + DE *C. colocynthis* 50 mg/kg, model + A 18 ml/kg respectively.

The value of “effective dose” differs from the researchers as well as the selection of *C. colocynthis* MPRM and the extract from its, which exhibits the highest antidiabetic activity.

It was found out that *C. colocynthis* fruits ethanol extract at a dose of 50 mg/kg results in a decrease of hyperglycemia in experimental rats [17]. The hypoglycemic effect of colocynth pulp and seed extracts was found in an experi-

ment in rabbits at a dose of 100 mg/kg [18, 19]. Lakshmi B. et al. established the presence of a hypoglycemic effect in colocynth seed alcohol extract at a dose of 250 mg/kg, while Jeyanthi K. A. revealed hypoglycemic activity in *C. colocynthis* seed water extract at a dose of 300 mg/kg. Salami M. et al. observed a significant hypoglycemic effect of the colocynth pulp suspension in normal rats after a single dose of 30 mg/kg, while at doses of 10 mg/kg and 90 mg/kg plant remedy did not show a significant sugar-reducing action. Dose-dependent activity was established for colocynth pulp methanol extract in streptozotocin-induced diabetic mice (CTZDM), which were administered the extract in doses of 250 mg/kg and 500 mg/kg [23].

Agarwal V. found that the most pronounced hypoglycemic effect in aloxane-induced diabetic rats has the colocynth roots aqueous extract at a dose of 200 mg/kg in comparison with its chloroform and alcohol ones, and according to Marwat S. K. the best antidiabetic activity was shown by *C. colocynthis* seed aqueous and butanol extracts. Clinical trials of 50 patients with type 2 diabetes over a 2-month period showed a significant reduction in HbA1c and glucose levels in the group of patients treated with capsules from colocynth at a dose of 100 mg/kg [26].

Scientists in in vitro studies have shown that insulinotropic activity is the basis of the hypoglycemic effect of pulp and seed extracts, as well as colocynth seed oil [27, 28]. In vivo plant extracts contribute to the preservation and regeneration of  $\beta$ -cells of the pancreas in streptozotocin-induced diabetic rats and also reduced insulin resistance [28-32], stimulate secretion of insulin by viable pancreatic  $\beta$ -cells [33]. The hypoglycemic effect of colocynth is also achieved through stimulation of glycolytic enzymes and reduction of gluconeogenesis enzymes activity [21, 34, 35]. It was revealed that colocynth pulp water-alcohol extract at a dose of 50 mg/kg exhibits antidiabetic effect by reducing the level of proinflammatory cytokines TNF- $\alpha$  and IL-6, which are synthesized by adipocytes of experimental animals with obesity and contributed to the development of insulin resistance [36]. One of the mechanisms of hypoglycemic action of *C. colocynthis* can be considered the ability to positively influence on the formation of glycogen stores in the liver of animals with experimental DM, and increasing the dose of extract from 100 mg/kg to 200 mg/kg did not affect the severity of the effect [37]. We also found no significant difference

Table

#### EFFECT OF *C. COLOCYNTHIS* EXTRACT ON GLUCOSE LEVEL DYNAMIC IN RAT'S BLOOD (M ± m)

| The term of observation | Blood glucose level, mmol/L (M ± m) in different groups |                  |  |   |                      |
|-------------------------|---|------------------|--|---|----------------------|
|                         | Control   | Model            | Model + DE <i>C. colocynthis</i> , 100 mg/kg | Model + DE <i>C. colocynthis</i> , 50 mg/kg | Model + A, 18 ml/kg  |
| 1 day                   | 4.80 ± 0.30   | 9.36 ± 0.43*     | 9.04 ± 0.40*                                 | 9.30 ± 0.57*                                | 9.40 ± 0.60*         |
| 28 days                 | 4.13 ± 0.28   | 13.07 ± 0.5*/*** | 6.06 ± 0.30*/**/****                         | 7.03 ± 0.39*/**/****                        | 7.79 ± 0.35*/**/**** |

Notes: \* – relative to control ( $p \leq 0.05$ ); \*\* – relative to model ( $p \leq 0.05$ ); \*\*\* – relative to the 1-st day ( $p \leq 0.05$ ); \*\*\*\* – relative to “Arphasetyn” ( $p \leq 0.05$ ).

in the hypoglycemic activity of *C. colocynthis* dry extract at doses of 100 mg/kg and 200 mg/kg in original studies on the aloxane model of DM in rats.

There are controversial opinions of scientists regarding biologically active substances (BAS), which determine the antihyperglycemic effect of *C. colocynthis*. After conduction of a comparative study of alkaloid, glycoside and saponin extracts at a dose of 50 mg/kg in normoglycemic rabbits it was found that hypoglycemic activity is characteristic for the last two extracts to a greater extent to saponin one [38]. Contrary to these results Benmehdi H. showed that the saponozide extract at a dose of 20 mg/kg reduces glucose levels only in diabetic rats. According to Singh L. the colocynth extract contains free amino acids (AA) that induce secretion of insulin from isolated pancreatic islets. Some scientists argue that flavonoids have the ability to stimulate the synthesis of insulin in vitro [41], including apigenin [42] and quercetin [43]. In literary sources it is described that MPRM of colocynth is reach in flavonoids [10, 44-47]. Among the flavones isoorientin and isovitexin [9] have been identified in it. The latter one has a hypoglycemic effect and stimulates insulin secretion [11].

It has been established that reproduction of model of DM in animals results in significant elevation of Chol TrG LDL VLDL and on the contrary reduction of HDL levels (Fig. 1). Thus the Chol value in model group was  $1.81 \pm 0.05$  mmol/L versus  $1.60 \pm 0.05$  mmol/L in the control group, TrG –  $1.37 \pm 0.11$  mmol/L versus  $1.04 \pm 0.15$  mmol/L, LDL –  $0.54 \pm 0.02$  mmol/L versus  $0.36 \pm 0.04$  mmol/L, VLDL –  $0.64 \pm 0.06$  mmol/L versus  $0.46 \pm 0.05$  mmol/L, HDL –  $0.41 \pm 0.07$  mmol/L versus  $0.83 \pm 0.08$  mmol/L respectively. After 28 days of prophylactic and therapeutic administration of the herbal extract at doses of 50 mg/kg and 100 mg/kg, there were a significant decrease of elevated indices and increase of HDL. Moreover the severity of the hypolipidemic effect regarding VLDL and TrG in-

creased with an increase in the dose of *C. colocynthis* extract. Under the influence of herbal extract at a dose of 100 mg/kg the level of VLDL decreased in 1.8 times ( $0.35 \pm 0.01$  mmol/L) in relation to model group ( $0.64 \pm 0.06$  mmol/L) and was significantly lower than in control group ( $0.46 \pm 0.05$  mmol/L). The administration of the *C. colocynthis* dry extract at a dose of 50 mg/kg resulted in 1.5-fold decrease of VLDL level ( $0.44 \pm 0.05$  mmol/L) compared with the model group, almost to the level of VLDL in the control group of animals. The plant extract at a dose of 100 mg/kg causes a decrease in TrG from  $1.37 \pm 0.11$  mmol/L in the model group to a value of  $0.77 \pm 0.02$  mmol/L which is lower ( $p < 0.05$ ) than in the control group. At the same time, the plant extract at a dose of 50 mg/kg caused a decrease in TrG only to a value of  $0.95 \pm 0.08$  mmol/L, significantly higher than the previous one. The hypolipidemic activity of the plant extract exceeded the activity of the reference drug "Arphasetyn".

Administration of *C. colocynthis* dry extract during 28 days at doses of 100 mg/kg and 50 mg/kg to rats with a model of DM caused a significant decrease in plasma Col – to  $1.66 \pm 0.03$  mmol/L and  $1.68 \pm 0.03$  mmol/L, LDL level – to  $0.37 \pm 0.07$  mmol/L and  $0.40 \pm 0.03$  mmol/L respectively, and led to an increase in HDL – to  $0.85 \pm 0.09$  mmol/L and  $0.71 \pm 0.08$  mmol/L, respectively. Unlike the herbal extract, the reference drug did not reduce LDL level.

*C. colocynthis* extracts have a positive effect on the altered lipid metabolism parameters under conditions of the experimental type 1 DM (aloxane and streptozotocin) and other states that induce hyperlipidemia. They contribute to lowering of LDL, VLDL, TrG, Chol, free fatty acids (FFA) and increasing of HDL levels. Different parts of colocynth, including the fruits, exhibit hypolipidemic activity in the dose range from 50 to 400 mg/kg [33, 35, 49, 50].

Abe I. et al. supposed that catechin selectively inhibits squalene dioxidase, an enzyme that participates in

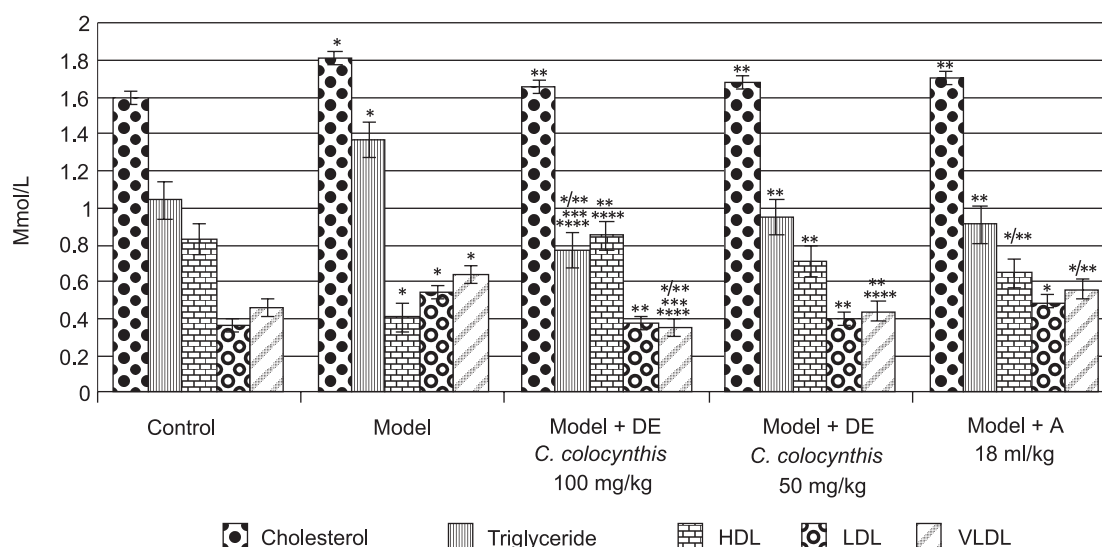
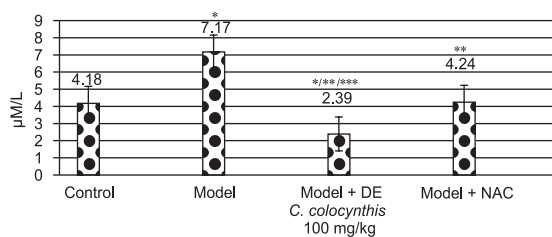


Fig. 1. Dynamic of plasma lipids level in rats of different experimental groups

Notes: \* – relative to control ( $p \leq 0.05$ ); \*\* – relative to model ( $p \leq 0.05$ ); \*\*\* – between groups Model + DE *C. colocynthis* 100 mg/kg and Model + DE *C. colocynthis* 50 mg/kg ( $p \leq 0.05$ ); \*\*\*\* – relative to "Arphasetyn" ( $p \leq 0.05$ )



**Fig. 2.** Concentration of MDA in liver homogenate in rats of experimental groups

Notes: \* – relative to control ( $p \leq 0.05$ ); \*\* – relative to model ( $p \leq 0.05$ ); \*\*\* – between groups Model + DE *C. colocyntis* 100 mg/kg and Model + NAC ( $p \leq 0.05$ ).

the synthesis of cholesterol. Harada U. et al explained the hypolipidemic effect of *C. colocyntis* by enhancing the process of  $\beta$ -oxidation of fats in the liver.

It is considered that presence of saponins leads to a decrease in cholesterol through inhibition of its absorption, development of diarrhea caused by increased intestinal motility [49, 53].

Taking into account previous studies of hypoglycemic and hypolipidemic effects of plant extract, the most effective experimental dose of 100 mg/kg was chosen to determine the parameters of oxidative homeostasis.

It was found (Fig. 2) that the index of intensity of oxidative stress (OS) – malonic dialdehyde (MDA) in liver homogenate of diabetic rats was significantly higher ( $7.17 \pm 0.83 \mu\text{M/L}$ ) than in control group ( $4.18 \pm 0.58 \mu\text{M/L}$ ) – in 1.7 times ( $p \leq 0.05$ ).

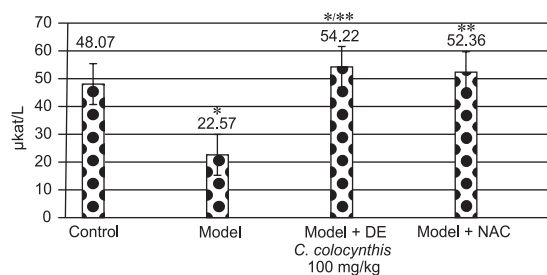
Administration of the *C. colocyntis* dry extract at a dose of 100 mg/kg caused a significant decrease in MDA in tissues: in comparison with model group – in 3 times, and in relation to control group – in 1.7 times, to a value of  $2.39 \pm 0.18 \mu\text{M/L}$ . Administration of NAC led to a decrease in the MDA only in comparison with model group – in 1.7 times (to  $4.24 \pm 0.74 \mu\text{M/L}$ ), which was practically equal to the same indicator in control group.

MDA is mainly formed as a result of POL of membranes, that leads to the destruction of these membranes.

To evaluate intracellular protection from highly toxic oxygen radicals, production of which grows in conditions of DM, the level of antioxidant enzymes in the liver homogenate of experimental rats in particular the level of catalase (CAT), was measured.

The diagram (Fig. 3) presents data of the CAT activity in rats of experimental groups.

During catalase activity analysis, it was found that in model group the enzyme level is  $22.57 \pm 1.67 \mu\text{kat/L}$ . It was observed that due to diabetes the activity of catalase significantly reduces – in 2.1 times ( $p < 0.05$ ) relative to control group ( $48.07 \pm 2.51 \mu\text{kat/L}$ ). Administration of *C. colocyntis* extract at a dose of 100 mg/kg leads to an increase in catalase activity in 2.4 times – to  $54.22 \pm 2.67 \mu\text{kat/L}$  in relation to the model group. Administration of NAC produces an effective increase in catalase activity in the rat with a model of DM to  $52.36 \pm 2.52 \mu\text{kat/L}$ , which is not statistically different from the control ( $p < 0.05$ ).



**Fig. 3.** CAT activity in liver homogenate in rats of experimental groups

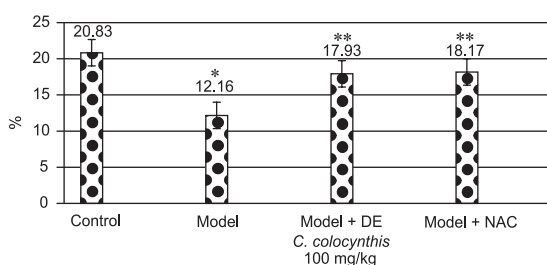
Notes: \* – relative to control ( $p \leq 0.05$ ); \*\* – relative to model ( $p \leq 0.05$ ).

Thus, the activity of catalase in the liver homogenate of rats with experimental diabetes induced by administration of STZ with the simultaneous administration of nicotinamide is reduced almost twice. Oral administration of *C. colocyntis* dry extract at a dose of 100 mg/kg increased activity of the enzyme even above the control level.

Under the experimental DM, the level of another antioxidant enzyme superoxidodismutase (SOD) is significantly reduced (Fig. 4): in model group the SOD value was  $12.16 \pm 1.92 \%$  which is in 1.7 times less than in control group ( $20.83 \pm 2.40 \%$ ).

In animals that were received a plant extract at a dose of 100 mg/kg the enzyme activity increased almost to the level of the enzyme activity in the control group ( $17.93 \pm 1.7 \%$ ). The severity of the effect of *C. colocyntis* dry extract on the level of SOD was not inferior to the reference drug ( $18.17 \pm 1.63 \%$ ). In relation to model group the enzyme activity significantly increased: in model + DE *C. colocyntis* 100 mg/kg group – in 1.47 times and in NAC group – in 1.49 times. Values of SOD in these groups did not differ against each other.

Hyperglycemia promotes the decrease of activity and synthesis of antioxidant enzymes by glycosylation process [54]. Due to DM there are POL and decrease of antioxidant enzymes activity take place. *C. colocyntis* methanol extract restores the normal activity of SOD, CAT and glutathione and reduces the level of OS-marker – MDA. *In vitro* the herbal substance exhibits dose-dependent antiradical activity. An increase in the level of antioxidant enzymes after the use of colosynth by diabetic rats may be induced by stimulation of their biosynthesis or



**Fig. 4.** SOD activity in liver homogenate in rats of experimental groups

Notes: \* – relative to control ( $p \leq 0.05$ ); \*\* – relative to model ( $p \leq 0.05$ ).

by antiradical activity of *C. colocynthis* extract [55]. It is considered that the antioxidant activity of MPRM *C. colocynthis* is induced by phenolic compounds [9, 56].

One way or another, the effect of *C. colocynthis* extracts is dose-dependent [33]. And as the data from literary sources show, the dosage for each type of extract or medical form of colosynth may vary; some extracts are more effective, others are less effective, but it is undeniable that *C. colocynthis* MPRM possesses antioxidant activity [3, 7, 8, 17, 23, 24, 49, 57, 58]. Hussaina A. I. established the relationship between the part of MP colocynth and the severity of antioxidant and antiradical activity. He showed that alcohol extract of colocynth leaves is more effective than alcohol extracts of roots and fruits, which is explained by the higher content of flavonoids and phenolic compounds in the leaves of *C. colocynthis*.

Zaree A. B. found that the use of *C. colocynthis* fruit extract could prevent and reduce the risk of diabetes, reducing OS symptoms and lowering glycemia.

### CONCLUSIONS

1. *C. colocynthis* exerts a dose-dependent hypoglycemic and hypolipidemic effects in rats with a model of type 2 DM, more pronounced than the reference drug.
2. Administration of herbal extract to rats with a model of DM contributes to the correction of the oxidative stress by increasing the activity of antioxidant enzymes: catalase and superoxide dismutase, and reducing the level of malonic dialdehyde.

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