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The study of the hypoglycemic action of extracts from bearberry leaves under experimental insulin resistance in rats

Type 2 diabetes mellitus (DM2) has been increasing steadily all over the world. A large number of medicinal plants that have the hypoglycemic effect are known, but, unfortunately, currently there is very limited choice of antidiabetic herbal medicines.

Aim. To design the experiment in order to study the hypoglycemic effect of polyphenolic extracts from bearberry (*Arctostaphylos uva-ursi*) leaves under the experimental insulin resistance (IR) in rats.

Materials and methods. The experimental IR was induced by dexamethasone injections (Dex) and feeding with a high-fructose diet (HFD). Male outbred albino rats were randomized depending on the purpose of the experiment. As the study objects 50 % ethanolic polyphenol extracts obtained from bearberry leaves with addition of arginine (PE50_arg) and cysteine (PE50_cys) were selected. The oral glucose tolerance test (OGTT) was performed in all experimental groups of animals.

Results. Dex had a more pronounced effect on tolerance to glucose compared to the HFD. It was shown that PE50_arg and PE50_cys after two weeks of administration revealed the ability to decrease the blood glucose level in rats, as well as reduce IR development and improve tolerance to glucose under the experimental IR. The hypoglycemic activity found did not much differ from the action of Metformin, but exceeded the activity of Arphazetin. These results can be the evidence of activation of glucose utilization processes, and it, in turn, indicates the insulin sensitivity improvement due to the action of the extracts studied. The data obtained indicate that the corrective effect of arginine and cysteine on signal transduction processes in insulin target cells plays an important role in the IR treatment.

Conclusions. Bearberry leaves are the promising raw material for creating an anti-diabetic drug. Thus, it is necessary to further study the mechanisms of regulation of metabolic disorders when introducing new polyphenolic extracts.

Key words: insulin resistance; bearberry; oral glucose tolerance test; diabetes mellitus type 2; hypoglycemic action

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Дослідження гіпоглікемічної дії екстрактів з листя мучниці звичайної за експериментальної інсулінорезистентності у щурів

Захворюваність на цукровий діабет 2-го типу (ЦД2) постійно зростає у всьому світі. Було знайдено велику кількість лікарських рослин, які чинять гіпоглікемічну дію, але, на жаль, на теперішній час існує дуже обмежений вибір рослинних протидіабетичних лікарських препаратів.

Мета дослідження. Цей експеримент був розроблений для вивчення гіпоглікемічного ефекту поліфенольних екстрактів з листя Мучниці звичайної (Arctostaphylos uva-ursi) за експериментальної інсулінорезистентності (ІР) у щурів.

Матеріали та методи. Експериментальну ІР викликали ін'єкціями дексаметазону та годуванням з високим вмістом фруктози (HFD). Щурів-альбіносів чоловічої статі було розподілено по групах залежно від мети експерименту. В якості об'єктів дослідження були відібрані 50 % етанольні поліфенольні екстракти, які були отримані з листя Мучниці звичайної з додаванням аргініну (PE50_arg) та цистеїну (PE50_cys). Пероральний тест на толерантність до глюкози (OGTT) проводили у всіх експериментальних групах тварин.

Результати. Ін'єкції дексаметазону чинили більш виражений вплив на толерантність до глюкози порівняно з HFD. Було показано, що PE50_arg та PE50_cys після двох тижнів введення виявили здатність знижувати рівень глюкози в крові щурів, послаблювати розвиток ІР та послаблювати толерантність до глюкози за експериментальної ІР. Виявлена гіпоглікемічна активність мало відрізнялася від дії метформіну, але перевищувала активність арфазетину. Ці результати можуть бути відображенням активізації процесів утилізації глюкози, що, в свою чергу, вказує на поліпшення чутливості до інсуліну завдяки дії екстрактів. Отримані дані свідчать про те, що коригуючий вплив аргініну та цистеїну на процеси передачі сигналу в клітинах-мішенях інсуліну відіграє важливу роль у лікуванні ІР.

Висновки. Листя Мучниці звичайної є багатообіцяючою сировиною для створення антидіабетичного лікарського препарату. Таким чином, необхідно подальше вивчення механізмів регуляції метаболічних порушень за введення отриманих поліфенольних екстрактів.

Ключові слова: інсулінорезистентність; мучниця звичайна; пероральний тест на толерантність до глюкози; цукровий діабет 2 типу; гіпоглікемічна дія

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Исследование гипогликемического действия экстрактов, полученных из листьев толокнянки обыкновенной, при экспериментальной инсулинорезистентности у крыс

Заболеваемость сахарным диабетом 2-го типа (СД2) постоянно возрастает во всем мире. Было найдено большое количество лекарственных растений, которые имеют гипогликемическое действие, но, к сожалению, на сегодняшний день существует очень ограниченный выбор растительных противодиабетических лекарственных препаратов.

Цель исследования. Этот эксперимент был разработан для изучения гипогликемического эффекта полифенольных экстрактов из листьев Толокнянки обыкновенной (Arctostaphylos uva-ursi) при экспериментальной инсулинорезистентности (ИР) у крыс.

Материалы и методы. Экспериментальную ИР вызывали инъекциями дексаметазона (Dex) и диетой с высоким содержанием фруктозы (HFD). Самцы крыс-альбиносов были распределены по группам в зависимости от цели эксперимента. В качестве объектов исследования были отобраны 50 % этанольные полифенольные экстракты, полученные из листьев Толокнянки обыкновенной с добавлением аргинина (PE50_arg) и цистеина (PE50_cys). Пероральный тест на толерантность к глюкозе (OGTT) проводили во всех экспериментальных группах животных.

Результаты. Инъекции дексаметазона имели более выраженное влияние на толерантность к глюкозе по сравнению с HFD. Было показано, что PE50_arg и PE50_cys после двух недель введения проявили способность снижать уровень глюкозы в крови крыс, ослаблять развитие ИР и снижать толерантность к глюкозе по экспериментальной ИР. Обнаруженная гипогликемическая активность мало отличалась от действия метформина, но превышала активность арфазетина. Эти результаты могут быть свидетельством активизации процессов утилизации глюкозы, что, в свою очередь, указывает на улучшение чувствительности к инсулину благодаря действию экстрактов. Полученные данные свидетельствуют о том, что корректирующее воздействие аргинина и цистеина на процессы передачи сигнала в клетках-мишенях инсулина играет важную роль в лечении ИР.

Выводы. Листья Толокнянки обыкновенной являются многообещающим сырьем для создания антидиабетического лекарственного препарата. Таким образом, необходимо дальнейшее изучение механизмов регуляции метаболических нарушений при введении новых полифенольных экстрактов.

Ключевые слова: инсулинорезистентность; толокнянка обыкновенная; пероральный тест на толерантность к глюкозе; сахарный диабет 2 типа; гипогликемическое действие

Diabetes mellitus type 2 (DM2), a metabolic disease, spreads rapidly across our planet, encompassing a growing population. Medical statistics shows that every fifth inhabitant on the Earth is either already have DM2 or diabetes would develop within next 10 years. Multiple factors, such as heredity, age, body weight, stress, nutrition, hypodynamia, smoking, can be the cause for DM2 development [1]. It should be noted that the DM2 and associated pathologies develop for a rather long time with latent symptoms. At this early period, when the fasting blood glucose (BG) level remains normal due to hyperinsulinemia, the functional activity of beta-cells changes and with increasing glucose tolerance lead to the state of insulin resistance (IR) when the increased production of insulin is not enough to overcome it [2]. Beta-cells suppression is increasing, the insulin synthesis is declining and relative insulin deficiency is already in full swing with all the consequences. Therefore, it is important to know not only the fasting BG level, but also it is necessary to measure glycemia after meals or after a special glucose load. Therefore, the oral glucose tolerance test (OGTT) is important for the early DM2 diagnosis [3].

The purpose of DM2 treatment is to achieve and maintain a condition, in which the manifestation of the disease and the likelihood of complications are minimal, while the quality of life is as high as possible. Thus, glucose-lowering oral drugs currently used in clinical practice are represented by several groups that differ from each other not only in the mechanism of action, but also by their mechanisms of side effects, and it should be taken into account when choosing a drug for therapy. The use of herbal medicines can minimize the side effects of chemotherapy and affect all sides of the pathogenetic process. A large number of medicinal plants that have the hypoglycemic effect have been used for a long time in traditional medicine [4]. But, unfortunately, currently there is very limited choice of antidiabetic herbal medicines. Therefore, it is necessary to use products, which effectiveness has been proven to date by evidence-based medicine.

The **aim** of the works was to design the experiment in order to study the hypoglycemic effect of polyphenolic extracts from bearberry (*Arctostaphylos uva-ursi*) the experimental IR in rats.

Materials and methods

Male outbred three-months-old albino rats, 96 in total, were purchased from the vivarium of the Central Research Laboratory of the National University of Pharmacy (NUPh). In order to induce the experimental IR we used two different models. The glucocorticoid-induced IR was developed by daily intraperitoneally administration of dexamethasone (15 mkg/kg/day) for 5 weeks (Dex) [5]. The diet-induced IR was caused by “watering” with 20 % fructose water solution (with free access) during

Table

Glycemic variation and oral glucose tolerance test under the experimental insulin resistance compared to administration of pure extract (PE50), arginine (PE50_arg) and cysteine (PE50_cys) in healthy animals

Groups	Blood glucose level (mmol/l) at various time intervals				
	0 min	30 min	60 min	90 min	120 min
Intact control	4.07±0.35	5.84±0.64	7.21±0.85	5.08±0.79	3.78±0.56
PE50	4.03±0,54	5.47±0.65	7.07±0.77	6.42±0.71	4.59±0.49
PE50_arg	4.05±0.66	5.35±0.58	6.81±0.74	5.78±0.67	4.47±0.51
PE50_cys	4.04±0.57	5.51±0.63	7.03±0.69	5.93±0.72	4.57±0.53
HFD	7.12±0.64[a]	10.61±0.71[a]	11.88±0.98[a]	10.11±0.84[a]	8.61±0.83[a]
Dex	9.01±0.59[a]	17.20±0.81[a]	19.87±0.93[a]	15.49±0.75[a]	12.21±0.63[a]

Note. Values are expressed as mean ± SEM from 6 rats; a – $p<0.05$ vs IC group.

7 weeks – high-fructose diet (HFD) [6]. As the study objects 50 % ethanolic polyphenol extracts obtained from bearberry leaves with addition of arginine (PE50_arg) and cysteine (PE50_cys) and a pure extract (PE50) in the dose of 100 mg/kg b.w. were selected [7]. All these substances were developed at the Pharmacognosy Department of the NUPh under the supervision of professor Koshevoy O. M. As the reference drugs Arphasetin infusion (arph) in the recommended dose recalculated for rats (18 ml/kg b.w.) and Metformin (met) in the dose of 100 mg/kg b.w. were selected [8].

Animals were randomly divided into 16 experimental groups (n = 6 rats) as follows: 1 – healthy animals, intact control (IC); 2-4 – healthy animals taken PE50, PE50_arg, PE50_cys, respectively, (groups specified as PE50, PE50_arg, PE50_cys); 5 – animals with IR induced by HFD (specified as HFD); 6 – animals with IR induced by dexamethasone injection (specified as Dex); 7-11 – animals fed with HFD and beginning from the 5th week of the experiment administered PE50, PE50_arg, PE50_cys, arph and met, respectively, for 2 weeks (groups specified as HFD_PE50, HFD_PE50_arg, HFD_PE50_cys, HFD_arph, HFD_met); 12-16 – animals injected with Dex and beginning from the 5th week of the experiment administered PE50, PE50_arg, PE50_cys, arph and met, respectively, for 2 weeks (groups specified as Dex_PE50, Dex_PE50_arg, Dex_PE50_cys, Dex_arph, Dex_met).

The oral glucose tolerance test (OGTT) was performed in all experimental groups of animals. When conducting OGTT the blood samples were taken in 0, 30, 60, 90 and 120 min after oral administration of glucose solution (3 g/kg b.w.) via gastric tube [9]. Blood samples were obtained by gingival vein punction [10]. The blood glucose (BG) concentration was determined using a "One Touch Select" glucometer (LifeScan, USA). The areas under the curves (AUC) were calculated using the trapezoidal rule [11]. The IR development was confirmed by measuring the immunoreactive insulin level and the fasting blood plasma glucose level in 5 weeks and 7 weeks of the experiment [6].

All manipulations were performed according to the "Protocol of Amendment to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986, as amended, 1998), the Law of Ukraine "On protection from cruelty to animals" (dated 15.12.2009, No. 1759-VI), and the European Union Directives 2010/10/63 EU about animal experiments. All results were expressed as mean ± SEM (standard error of mean). The data were analyzed using STATISTICA 6. The value of $p<0.05$ was considered significant.

Results and discussion

The HFD and Dex groups of rats showed a significant BG level elevation in fasting state compared to normal animals (Table). The OGTT conducted confirmed the IR development in HFD group of animals since we observed a considerable increase in glucose levels not only on the 30th, 60th and 90th min of the experiment, but even by 120th min the glucose level did not return to the initial level. At the same time, administration of the polyphenolic extracts studied to healthy animals did not affect significantly this index.

However, the oral glucose load revealed some difference in the process of glucose utilization (Table). Thus, PE50_arg and PE50_cys administration caused a significant difference on the 90th min of OGTT in the BG level compared to IC group; it was caused by the probable stimulation of glucose uptake by cells.

Nevertheless, we were interested in studying the effect of the substances under research on glucose tolerance under IR experimentally induced. OGTT with AUC calculation is an informative test for assessing the potential hypoglycemic activity.

Fig. 1 presents the results of OGTT in rats with Dex induced IR and when administering polyphenolic extracts.

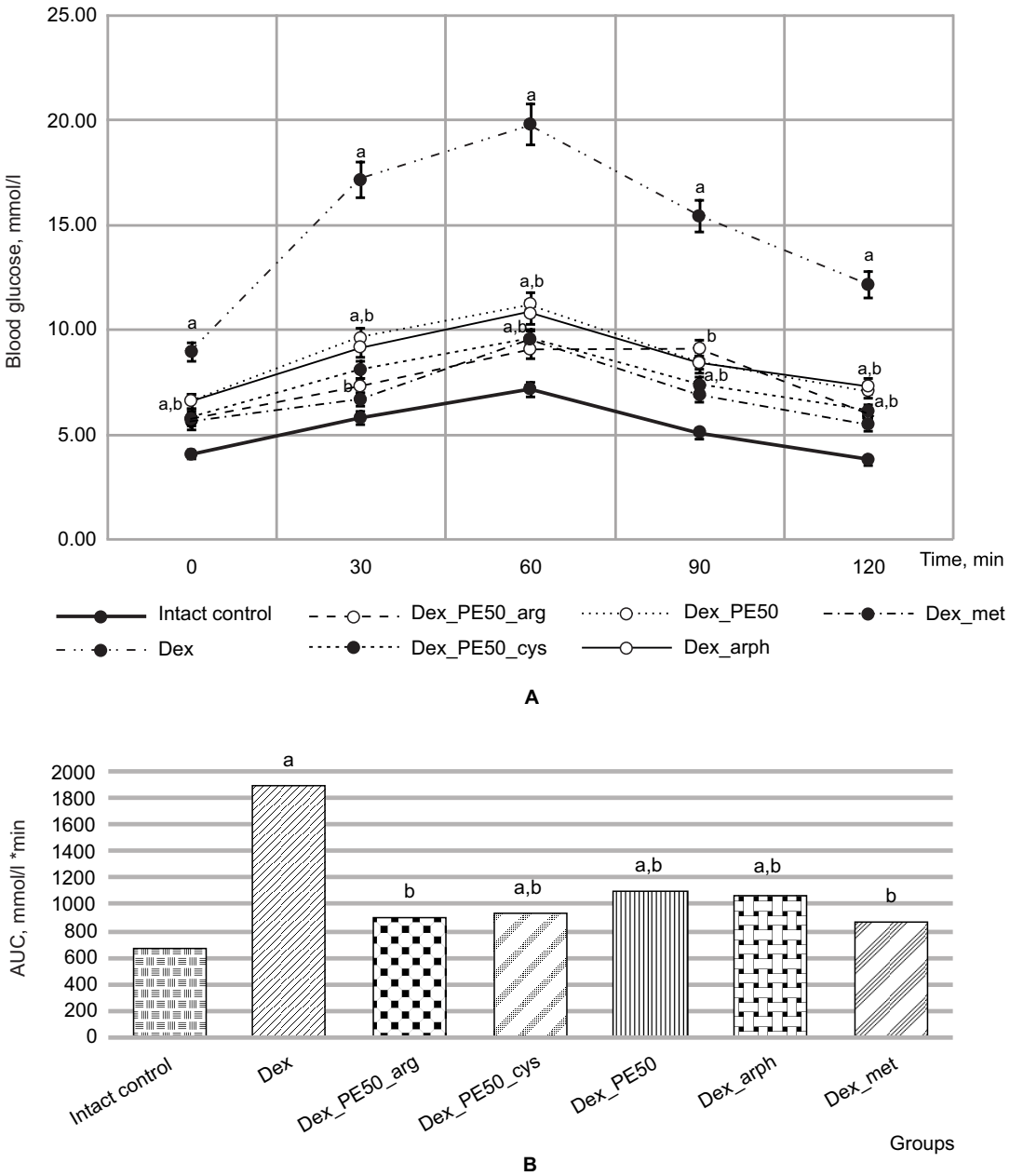

Fig. 1. OGTT and AUC under dexamethasone induced IR in rats in 2 weeks after administration of PE50, PE50_arg and PE50_cys
Note. a<0.05 vs IC group; b<0.05 vs Dex group.

During OGTT in Dex group the glucose concentration maximized on the 60th min of the experiment, and by the 120th min remained significantly higher than the initial level, indicating the presence of IR. It was found that the AUC value in Dex group rats was at least 3 times more than the corresponding area in IC. It should be also noted that the oral administration of the substances studied for 14 days in Dex_PE50_arg and Dex_PE50_cys groups of rats led to a significant decrease in the BG concentration by 36.5 % and 35.1 %, respectively. The effect observed exceeded the effect of PE50 (26.45 %) and approached the result that was observed in Dex_met group (38.2 %).

The maximum BG increase in the experimental groups was observed on the 60th min after glucose load, however, in rats that received PE50_arg and PE50_cys these indices were significantly lower compared to Dex group by 54.2 % and 51.8 %, respectively. Moreover, in the 90th min of the experiment the BG level in the groups mentioned significantly decreased, and in the 120th min it reached the initial level.

In HFD group (Fig. 2), the basal glucose level was significantly, in 1.69, times, higher than the values of the intact control. It was reflected in the AUC area that was twice more than of intact animals. PE50_arg and PE50_cys administration to IR animals normalized glucose levels. At the same time, the effect observed exceeded the effect of arph and was comparable with the action of met. OGTT in HFD_arg and HFD_cys groups showed that the BG elevation

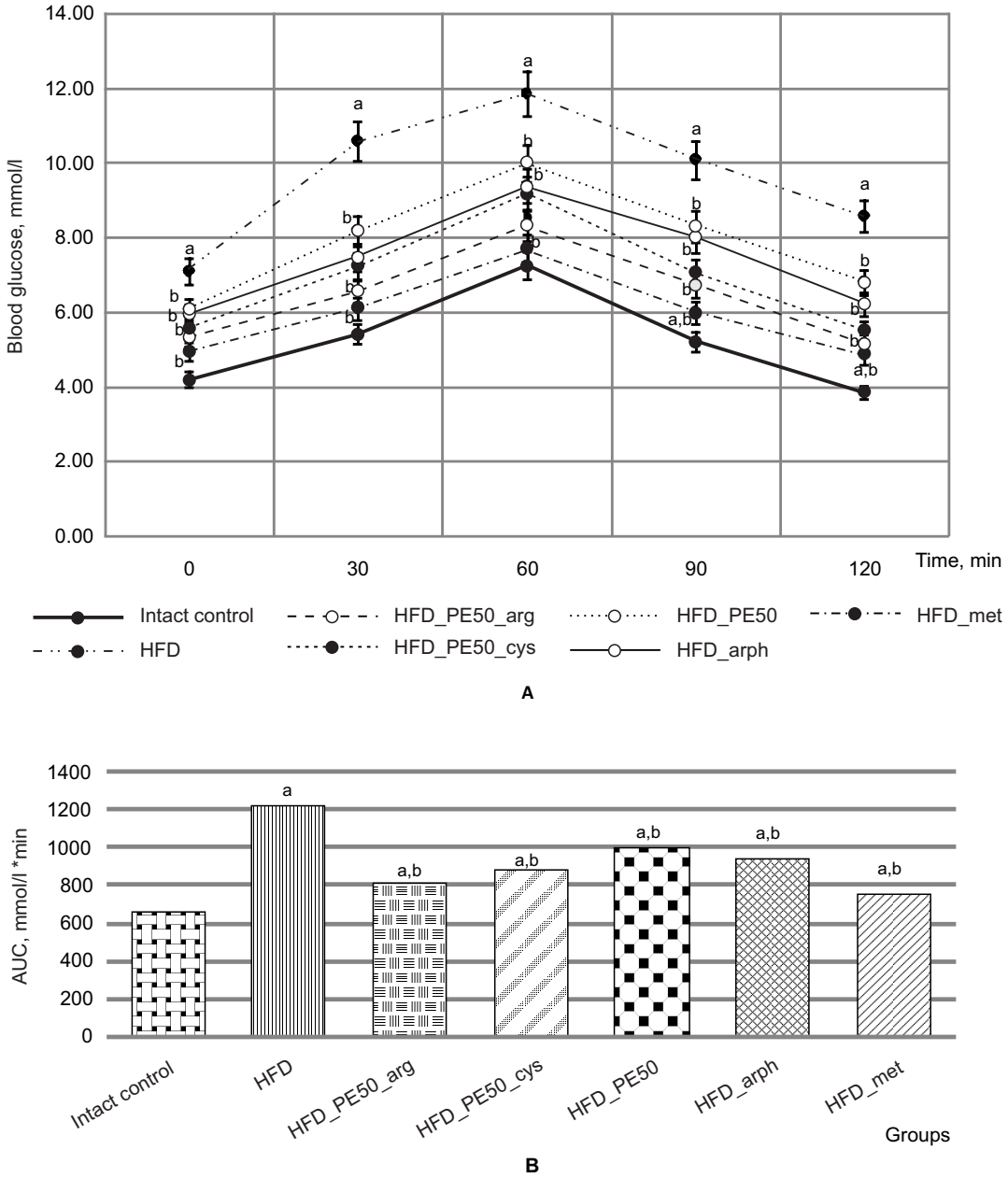

Fig. 2. OGTT and AUC under the high-fructose diet induced IR in rats in 2 weeks after administration of PE50, PE50_arg and PE_cys
Note. a<0.05 vs IC group; b<0.05 vs HFD group.

determined on the 30th and 60th min was significantly lower compared to HFD group, and by the 120th min decreased to the initial level. The effect of PE50_arg and PE50_cys observed by the 120th min after the glucose load was significantly higher than the same indicator of PF50 extract without amino acids. Therefore, OGTT showed the BG lowering on the 30th, 60th and 120th min of the test, indicating a significant decrease in the AUC area (Fig. 2).

Dexamethasone injections had a more pronounced effect on the glucose content compared to the HFD fructose diet, but it should be remembered that both models were effective. The general tendency observed when taking extracts from bearberry leaves studied showed that in 120 min they reduced BG to the initial level unlike the BG concentration that still kept higher in IR untreated animals.

These results can be the evidence of activation of glucose utilization processes, and it, in turn, indicates the insulin sensitivity improvement due to the action of the extracts studied. The effect observed is mediated by the presence of polyphenolic components that stimulate glucose uptake into cells, as well as the presence of amino acids that normalize signal transduction processes, which improve the insulin sensitivity of target cells.

CONCLUSIONS

1. The experimental study of antidiabetic properties of extracts from bearberry leaves has been performed under the experimental IR. The data obtained indicate that the corrective effect of arginine

and cysteine on signal transduction processes in insulin target cells plays an important role in the IR treatment.

2. It has been shown that PE50_arg and PE50_cys after two weeks of administration revealed the ability to decrease the blood glucose level in rats, as well as reduce IR development and improve tolerance to glucose under the experimental IR. The hypoglycemic activity has been found to be not much different from the action of Metformin, but exceeds the activity of Arphazetin.

3. Bearberry leaves are the promising raw material for creating an anti-diabetic drug. Thus, further study of the new polyphenolic extracts obtained on improving metabolic disorders is necessary.

Conflict of interests: authors have no conflict of interests to declare.

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