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HYPOGLYCEMIC EFFECT OF *CYPERUS ESCULENTUS* L. TUBERS EXTRACT

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Abstract

Diabetes mellitus is a medical and social problem caused by the rapid spread of the disease and the development of serious complications. One of the areas is using herbal remedies, either as monotherapy for the prevention of diabetes mellitus type 2 or in the mild stages of this disease. Of great interest in this regard is *Cyperus esculentus* L., earthnut (chufa, earth almond) is a perennial tuberous plant of the sedge family (*Cyperaceae*). Chufa underground organs are used in pharmacology for the treatment and prevention of hypertension, diabetes, and varicose veins. The pharmacological study of the hypoglycemic effect of the tubers of *Cyperus esculentus* L. is relevant in order to create domestic new hypoglycemic drugs based on this plant. Studies of the hypoglycemic effect of a thick extract of earthnut tubers were performed in rats on a model of chronic hyperglycemia caused by prolonged administration of a high dose of dexamethasone. The results of the study of the hypoglycemic action of the studied extract and comparison drugs show, that there was a progressive increase in blood glucose by 28.2 % and 45.4 % on days 7 and 14, respectively against the background of dexamethasone administration. Eartnut tubers extract probably reduced glycemia, but complete normalization of blood glucose (on days 7 and 14 blood glucose levels were higher than baseline levels by 15.7 and 14.9 %, respectively) was not observed. On day 14 of the experiment, its effect exceeded Arfazetin and inulin and was comparable to metformin. Thus, it was found that a thick extract of earthnut tubers has a dose-dependent hypoglycemic effect and its conditionally effective dose can be considered 200 mg/kg. This dose may be recommended for further in-depth studies of this extract as a hypoglycemic agent.

Keywords: *Cyperus esculentus* L., tubers extract, hypoglycemic effect, diabetes mellitus, dexamethasone, Arfazetin, Metformin, inulin

Introduction

Diabetes mellitus, by definition of the World Health Organization, has gained the character of a non-communicable epidemic. Diabetes mellitus is a medical and social problem caused by the rapid spread of the disease and the development of serious complications such as angiopathies, which significantly reduce the quality and life expectancy of patients [1-4]. Pharmacotherapy increasingly takes into importance the centuries-old experience of folk medicine with the application of phytopreparations [5-7]. One of the areas is using herbal remedies, either as monotherapy for the prevention of diabetes mellitus type 2 or in the mild stages of this disease [8-11]. Therefore, the search for new drugs for the correction of metabolic disorders in this disease is a topical issue of pharmacy and medicine [12, 13]. This is quite justified because phytotherapy has a number of advantages over traditional therapy with synthetic drugs, namely, it is low-toxic, has a mild pharmacological effect, and can be used for a long period of time without significant side effects [14-16]. The search for medicinal plants with a long history of use and small side effects is of interest to our society [17, 18]. The basic appointment of using plants is the control of metabolic disorders, as plant metabolites are close to the metabolites of the human body [19-23].

Cyperus esculentus L., earthnut (chufa, earth almond) is a perennial tuberous plant of the sedge family (*Cyperaceae*). It is grown in Brazil, Spain, Africa and Portugal. In Ukraine, earthnut is cultivated on experimental and homestead plots [24, 25]. *Cyperus esculentus L.* is grown for its small, sweet, almond-shaped nodules, which are a source of edible oil. Tubers of earthnut formed at the roots have a hard shell and crispy flesh and a pleasant sweet taste. The use of chufa tubers in food has been known since ancient times, due to their high nutritional value. They contain: 20–25 % – lipids, 20–35 % – starch, 12–28 % – sugars, 5–9 % – proteins. The oil is used actually in food, in the processing industry and in medicine [26].

Tubers of earthnut are considered promising for the production of dietary, children's and special purposes, due to their content of biologically active substances. Chufa underground organs are used in pharmacology for the treatment and prevention of hypertension, diabetes and varicose veins [27].

The pharmacological study of the hypoglycemic effect of the tubers of *Cyperus esculentus* L. is relevant in order to create domestic new hypoglycemic drugs based on this plant.

Methods

Plant materials

Tubers of the *Cyperus esculentus* L. were collected at the experimental sites of the New Cultures Department of M. M. Hryshko National Botanic Garden of the NAS of Ukraine in Kyiv. The aerial part was harvested during a mass flowering period and tubers were collected in autumn after the death of aerial parts in 2018. The raw material was authenticated by Prof. Dzhamal Rakhmetov [28]. A voucher specimen was deposited in the herbarium at the Department of Pharmacognosy and Medical Botany, TNMU, Ternopil, Ukraine [29, 30]. The study plant material was dried using conventional method and stored in paper bags in a dry place [31-34].

Preparation of extract

About 100 g of dried tubers of the *Cyperus esculentus* L. were powdered with the help of a suitable crusher. It was taken in an extractor and extracted using 30 % ethanol as a solvent. The extract was concentrated under vacuum to half under volume and dried at a temperature of 50±2° C [35].

Animal models

The experiments were performed on 42 white Wistar rats weighing 175–215 g. The animals were kept in room having temperature 22 ± 2 ° C, and relative humidity of 44-55 % under 12/12 hour light and dark cycle with standard laboratory diet and water given ad libitum [36].

Pharmacological studies have been conducted in accordance with the rules and requirements of the "General Principles for the Work on Animals" approved by the I National Congress on Bioethics (Kyiv, Ukraine, 2001 and agreed with the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Council of Europe No 123, Strasbourg 1985), and the Law of Ukraine "On the

Protection of Animals from Cruelty" of 26.02.2006 [37-39].

The removal of animals from the experiment was carried out under light inhalation (ether) anesthesia by decapitation.

Acute toxicity studies

Studies of acute toxicity of thick extracts from the tubers of *Cyperus esculentus* L. were performed V. B. Prozorovskyi method [40] on 42 white nonlinear mice of both sexes weighing 21–25 g. Animals were divided into groups of (3 males and 3 females in each). Animals were injected intragastrically with test extracts in the dose range of 1000 mg/kg, 3000 mg/kg, and 5000 mg/kg. If the size of the extract exceeded 5 ml, the administration was performed in a fractional manner during the day [41]. At the end of the experiment (14 days), the mortality rate was determined in each group to calculate the average lethal dose (LD_{50}) [42].

Throughout the experiment, the survival of animals, consumption of food and water by them, as well as clinical manifestations of intoxication (if any): general condition, changes in body position, skin condition, the color of mucous membranes, and individual symptoms (lacrimation, diarrhea, changes in the color of urine and feces, drowsiness, convulsions) were observed. In case of death of animals, their autopsy was performed and macroscopic analysis of abdominal organs was performed in order to establish that the lethal outcome of the animal did not occur due to manipulation errors, as well as to determine the probable cause of death.

Study of the hypoglycemic effect of Cyperus esculentus L. *tubers extract*

Studies of the hypoglycemic effect of a thick extract from chufa (*Cyperus esculentus* L.) tubers were performed on 42 bisexual white linear rats of the *Wistar* population, weighing 175–215 g and aged 5 months. Animals for the experiment were divided into 6 groups of 7 animals each (n = 7). Group 1 was the control (IC), group 2 (CP) consisted of animals that received dexamethasone at a dose of 0.125 mg/kg, group 3 (CP+TEET) received dexamethasone and earthnut tubers dry extract 200 mg/kg, group 4 received dexamethasone and Arfazetin, group 5 received dexamethasone and metformin, group 6 received dexamethasone and inulin.

Acute hyperglycemia was caused by intraperitoneal administration of 40 % glucose solution at a dose of 2 g/kg. The blood glucose level was measured using BIONIME GM 550 glucometer.

The study of hypoglycemic action of chufa tubers extract and reference compounds – Arfazetin, Metformin and inulin was performed on a model of primary insulin resistance (dexamethasone hyperglycemia), which was caused by subcutaneous administration of Dexamethasone (KRKA, Slovenia), 0.125 mg/kg during 14 days.

Chufa tubers extract was studied at a dose of 200 mg/kg intragastrically once daily beginning from day 1 of glucocorticoid administration.

Metformin in the form of tablets Siofor BERLIN-CHEMI AG (MENARINI GROUP) (100 mg/kg), Arfazetin officinal herbal collection (PJSC "Viola", Ukraine) at a dose of 9 ml/kg, and inulin at a dose of 300 mg/kg administered in similar regimens were used as comparison drugs.

Blood glucose was determined using a glucometer on day 1 (baseline, before the administration of dexamethasone), as well as on day 7 and 14 of the experiment.

The obtained experimental data were processed by the methods of variation statistics (arithmetic mean and its standard error were calculated). For multiple comparisons of data with normal distribution, parametric one-way analysis of variance ANOVA was performed and Newman-Keuls method was used, and the data were presented as mean (M) and mean error (m). In other cases, comparisons of samples using the Mann-Whitney test were used. Differences between experimental groups were considered statistically significant at $p \leq 0.05$ [43]. A standard package of statistical programs Statistica, v. 6.0 (StatSoft Inc.) was used to perform mathematical calculations [44].

Results and Discussion

Study of acute toxicity of the extract from the tubers of Cyperus esculentus L.

In experimental animals, body weight was monitored on day 1 (before administration) and 14

days after intragastric administration of extracts (Table 1).

The obtained data show that a single intra-abdominal administration of the studied extracts to mice of both sexes at doses of 1000, 3000 and 5000 mg/kg did not affect the dynamics of body weight in comparison with the control. Experimental and control animals gained weight in accordance with physiological norms.

External examination of the animals showed no signs of pathological changes in their condition, the fur and skin are clean, the subcutaneous layer of adipose tissue is moderate, damage and inflammatory lesions were not observed on the mucous membranes and skin. Visual assessment of the condition of internal organs also showed no signs of pathological changes.

Survival and clinical observations. During the entire observation period the death of experimental animals wasn't registered after a single intraperitoneal oral administration of extracts (at doses of 1000, 3000 and 5000 mg/kg of body weight) in mice of both sexes. After administration of the test sample and until the end of the observation period, no deviations in appearance and toxic manifestations were observed. All animals were active, had smooth fur and clean skin.

The lack of mortality in animals suggests that the value of LD_{50} at enteral administration of both extracts exceeds the maximum dose used in the experiment, ie in mice LD_{50} > 5000 mg/kg. This value of LD_{50} allows including the studied extracts according to the classification by K. K. Sydorov to class VI of toxicity – almost harmless substances.

Study of the hypoglycemic effect of a thick extract of earthnut tubers

Studies of the hypoglycemic effect of a thick extract of earthnut tubers were performed in rats on a model of chronic hyperglycemia caused by prolonged administration of a high dose of dexamethasone. Diabetes caused by the administration of dexamethasone, allows you to reproduce the main pathogenetic mechanisms (disorders of secretion and action of insulin) observed in patients with type 2 diabetes at an early stage [45, 46]. The condition of chronic hyperglycemia was caused by subcutaneous administration to rats of a solution of dexamethasone at a dose of 0.125 mg/kg during 14 days. A thick extract of earthnut tubers (*Cyperus esculentus* L.) (TEET) was administered to experimental animals as an aqueous solution intragastrically at a dose of 200 mg/kg.

Experiments showed that administration of dexamethasone at a dose of 0.125 mg/kg for 14 days caused a decrease in body weight of animals.

Thus, the weight of CP rats on day 14 decreased by 13.74 % relative to the baseline (223.57±1.80) g and made (192.86 ± 2.14) g, and the average weight of animals that on the background of the introduction dexamethasone received TEET, decreased by 6.31 % relative to the initial weight (237.90±4.61) g and was (222.90±4.62) g (Table 2).

Rats, which on the background of CP received the comparison drug Metfomin, during the experiment had the lowest loss of average body weight, which was 3.35 %. The weight loss of rats treated with inulin on dexamethasone decreased by 5.33 %. The tea of herbal reference drug Arfazetin collection showed the smallest decrease of the catabolic effect of dexamethasone when used concomitantly – weight loss in rats decreased by 10.99 %.

According to the ability to prevent weight loss, the studied drugs can be arranged in the following sequence: dexamethasone < Arfazetin <TEET < inulin < metformin.

Table 3 shows the results of the study of the hypoglycemic action of the studied extract and comparison drugs. There was a progressive increase in blood glucose by 28.2 % and 45.4 % on days 7 and 14, respectively against the background of dexamethasone administration.

Eartnut tubers extract probably reduced glycemia, but complete normalization of blood glucose (on days 7 and 14 blood glucose levels were higher than baseline levels by 15.7 and 14.9 %, respectively) was not observed. On day 14 of the experiment, its effect exceeded Arfazetin and inulin, and was comparable to metformin.

On day 14 of the experiment, the average value of glycemia in rats treated with the studied extract of earthnut on the background of pathology was

(5.64±0.16) mmol/l, which is 14.90 % lower than the dynamics of blood glucose increase in group of rats CP, where the glucose level increased by 45.40 % relative to baseline (Fig. 1).

Conclusions

Thus, it was found that a thick extract of earthnut tubers has a dose-dependent hypoglycemic effect and its conditionally effective dose can be considered 200 mg/kg. This dose may be recommended for further in-depth studies of this extract as a hypoglycemic agent.

So, obtained by the proposed method, the plant substance in the form of a thick extract of earthnut tubers or chufa (*Cyperus esculentus* L.) is promising for the creation and use of drugs with a sufficiently pronounced hypoglycemic effect.

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Table 1. Dynamics of body weight of mice (g) after a single intra-abdominal administration of chufa tubers extract (M ± m; n=3)

Extract dose	Body weight on day 1	Body weight on day 14
Males		
Control	22.67±0.33	24.00±0.58
1000 mg/kg	23.33±0.88	24.00±0.58
3000 mg/kg	22.67±1.20	24.33±1.20
5000 mg/kg	23.0±1.00	23.33±0.67
Females		
Control	23.33±0.67	24.67±0.88
1000 mg/kg	23.67±0.88	25.0±1.00
3000 mg/kg	22.33±0.33	22.67±0.33
5000 mg/kg	21.33±0.33	22.00±0.58

Table 2. Influence of TEET on body weight of rats in the model of dexamethasone hyperglycemia (M ± m; n = 3)

Group of animals	Animal's weight on day 1	Animal's weight on day 14
IC	237.14±4.21	256.43±3.73 +8.18 %
CP	223.57±1.80	192.86±2.14 -13.74 %
CP + TEET (200 mg/kg)	237.90±4.61	222.90±4.62 -6.31 %
CP + Arfazetin	241.55±4.97	215.0±5.00 -10.99 %
CP + Metformin	235.0±4.76	227.14±6.97 -3.35 %
CP + Inulin	241.43±4.97	228.57±6.05 -5.33 %

Notes: IC – intact control;
CP – control pathology;
TEET – thick extract of earthnut tubers.

Table 3. Blood glucose level in rats with dexamethasone diabetes mellitus on the background of treatment with the studied drugs (M ± m, n = 7)

Group	Blood glucose level, mmol/l		
	Day 1 (baseline)	Day 7	Day 14
IC	5.03±0.08	4.96±0.13 (+1.20 %)	4.93±0.09 (+0.6 %)
CP	4.51±0.15	5.77±0.22• (+28,20 %)#	6.54±0.15• (+45.40 %)#
CP + TEET (200 mg/kg)	4.91±0.13	5.69±0.17• (+15.70 %)*	5.64±0.16• (+14.90 %)*
CP + Arfazetin	5.11±0.21	6.24±0.29• (+22.04 %)#	6.80±0.28• (+33.10 %)#
CP + Metformin	5.16±0.14	5.66±0.14• (+9.73 %)*	5.97±0.17• (+15.80 %)*
CP + Inulin	5.00±0.24	5.76±0.26• (+15.23 %)*	5.90±0.24• (+18.30 %)*

Notes: IC – intact control;

CP – control pathology;

TEET – thick extract of earthnut tubers;

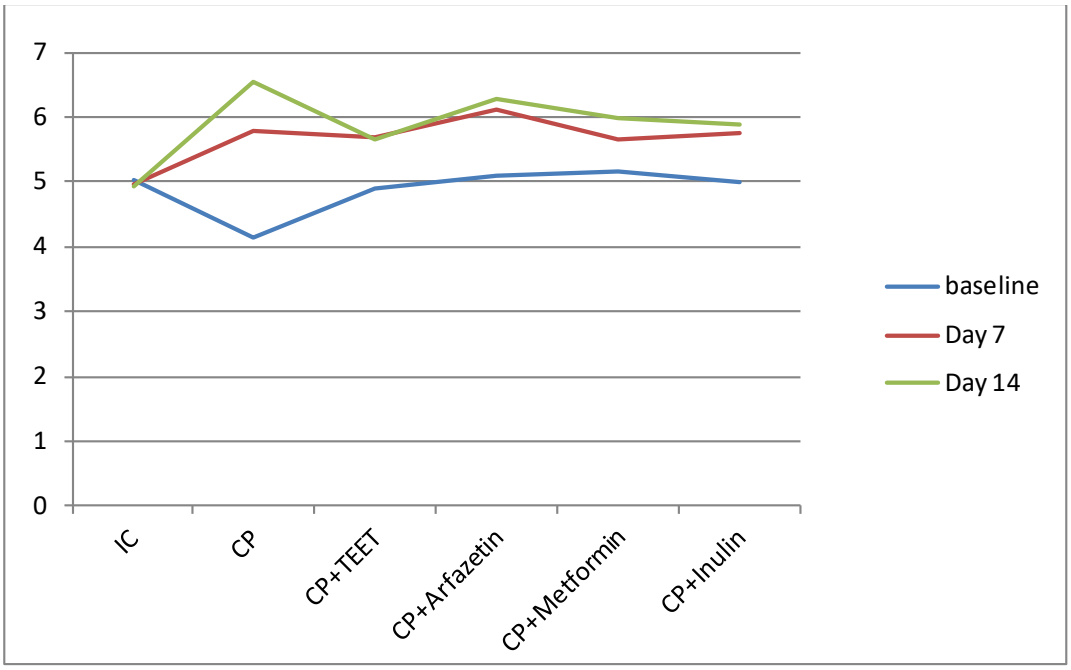
• - statistically significant differences ($p < 0.05$) relative to baseline in each group;

* statistically significant differences ($p < 0.05$) relative to control pathology (dexamethasone without correction);

- statistically significant differences ($p < 0.05$) relative to metformin;

The number in parentheses indicates the degree of increase in glycemia relative to baseline in each group.

Figure 1: Diagram of the effect of TEET and reference drugs on blood glucose in rats in a model of dexamethasone hyperglycemia



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