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ACUTE TOXICITY STUDIES OF AQUEOUS EXTRACTS OF PLANT ANTIDIABETIC MIXTURES

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Abstract

An important step in preclinical studies of potential drugs is to determine their safety. Therefore, the aim of present study was to investigate an acute toxicity of PAMs: sample 1) *Urtica dioica* leaf, *Cichorium intybus* roots, *Rosa majalis* fruits, *Elymus repens* rhizome, *Taraxacum officinale* roots; sample 2) *Arctium lappa* roots, *Elymus repens* rhizome, *Zea mays* columns with stigmas, *Helichrysum arenarium* flowers, *Rosa majalis* fruits; sample 3) *Inula helenium* rhizome with roots, *Helichrysi arenarium* flowers, *Zea mays* columns with stigmas, *Origanum vulgare* herb, *Rosa majalis* fruits, *Taraxacum officinale* roots; sample 4) *Cichorium intybus* roots, *Elymus repens* rhizome, *Helichrysum arenarium* flowers, *Rosa majalis* fruits, *Zea mays* columns with stigmas; sample 5) *Urtica dioica* leaf, *Taraxacum officinale* roots, *Vaccinium myrtillus* leaf, *Rosa majalis* fruits, *Mentha piperita* herb, which were used in Ukrainian folk medicine for the prevention and treatment of DM type 2.

The study was performed on albino rats weighing between 340 g and 380 g by single intragastric administration of aqueous extracts of PAMs at a dose of 30 mL/kg.

The results showed that PAMs, do not show toxic effects and belong to VI toxicity class, LD50> 15000 mL/kg. Therefore, the obtained experimental data characterize all five PAMs as safe and promising for further in-depth pharmacological studies.

Keywords: *antidiabetic herbal mixture, acute toxicity, diabetes mellitus*

Introduction

Herbal medicine has long been a source of medicines, and for many years there have been many attempts to use plant remedies to treat diabetes mellitus (DM) [1, 2, 3]. In addition, the number of scientific publications regarding phytomedicine and type 2 diabetes is continuously increasing [4, 5, 6, 7].

Among the possible mechanisms of action of natural products in DM, such as inhibition of α-glucosidase and α-amylase, effects on glucose uptake and glucose transporters, increased insulin secretion and proliferation of pancreatic β-cells have been studied in depth [8, 9, 10, 11].

Particular attention deserves the mixtures of different medicinal plants [12, 13, 14, 15], because such phyto-compositions are expected to have more biologically active substances that influence on different links of the pathogenetic mechanism of DM development and its complications [16, 17, 18, 19, 20].

Plant biocompounds have a wide range of pharmacological action and a variety influencing mechanisms on the DM and diabetic angiopathies development [22, 23, 24, 25, 26, 27, 28].

However, often herbal preparations contain several compounds that have toxic properties [29, 30, 31, 32, 33]. This can lead to poisoning or the occurrence and exacerbation of side effects from an overdose.

That is why an important step in preclinical studies of potential drugs is to determine their acute toxicity [34].

Therefore, the aim of our study was to investigate an acute toxicity of plant antidiabetic mixtures (PAMs): a) *Urtica dioica* leaf, *Cichorium intybus* roots, *Rosa majalis* fruits, *Elymus repens* rhizome, *Taraxacum officinale* roots; b) *Arctium lappa* roots, *Elymus repens* rhizome, *Zea mays* columns with stigmas, *Helichrysum arenarium* flowers, *Rosa majalis* fruits; c) *Inula helenium* rhizome with roots, *Helichrysi arenarium* flowers, *Zea mays* columns with stigmas, *Origanum vulgare* herb, *Rosa majalis* fruits, *Taraxacum officinale* roots; d) *Cichorium intybus* roots, *Elymus repens* rhizome, *Helichrysum arenarium* flowers, *Rosa majalis* fruits, *Zea mays* columns with stigmas; e) *Urtica dioica* leaf, *Taraxacum officinale* roots, *Vaccinium myrtillus* leaf, *Rosa majalis* fruits, *Mentha piperita* herb, which were used in Ukrainian folk medicine for the prevention and treatment of DM type 2 [35, 36, 37, 38, 39].

Methods

Plant materials: The herbal raw materials, harvested from June to August 2019 in the Ternopil region and Carpathians (*Vaccinium myrtillus* leaf) (Ukraine), were used. After harvesting, the raw materials were dried, graind and stored according to the general GACP requirements [40]. The plants were identified by Prof. S. M. Marchyshyn [41, 42, 43, 44, 45, 46, 47]. The voucher specimens of herbal raw materials have been deposited in Herbarium of Pharmacognosy with Medical Botany Department, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.

Five different PAMs with reliable hypoglycemic activity established during the screening tests [48] were used for the study. The composition of PAMs is given in Table 1.

Extraction procedure: The samples of PAMs were grinded into a powder by laboratory mill. Then 10 g of powdered PAMs were put into a 100 mL conical flask and 120 mL of distilled water were added. The aqueous extracts were obtained by heating in the boiling water bath for 30 min. The extracts of PAMs 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 PAMs were stored at 4 °C for further use [49, 50, 51, 52, 53].

Experimental Protocol: The study was performed on albino rats weighing between 340 g and 380 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.* Before intragastric administration of aqueous extracts of PAMs, rats were fasted overnight, and they were allowed to eat only 3 hours after the introduction of extracts. 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 [54]. All protocols for animals' experiment were approved by the animal ethical committee of I. Horbachevsky Ternopil National Medical University.

Route of administration: the route of administration was by oral gavage (per os, p.o.) in accordance with the main route of intake of an aqueous extract of PAMs by humans for medicinal purposes [55].

Acute toxicity test: Rats were randomly divided into six groups comprising 8 animals in each group (n=8). Group I (Control): received distilled water (30 mL/kg, p.o.) once and experimental groups II-VI received aqueous extracts of PAMs (30 mL/kg, *p.o.*) in small portions.

Observations of animals were carried out for two weeks after administration of the test extracts.

At the end of the experiment, rats were sacrifice by decapitation after anesthesia with Sodium thiopental (Abbott Park, IL, USA) and investigated macroscopic changes of internal organs, weighed them and calculated mass coefficients. Criteria for assessing acute toxicity was the clinical picture of intoxication: death of animals, their general condition, changes in body weight [56, 57, 58].

Statistical analysis: Statistical evaluation was carried out with StatView. Data were expressed as mean ± SEM. Statistical differences were evaluated by One-way ANOVA.

Results and Discussion

Studies have shown that after intragastric administration of an aqueous extracts of PAMs at a dose of 30 mL/kg, all animals survived, their physiological condition was satisfactory: the animals were tidy, active, reaction to sound and pain stimuli and the processes of urination and defecation were normal, respiratory disorders and seizures were not observed, the condition of the mucous membrane of the nose and mouth was normal. No side effects were observed after the introduction of studied extracts of PAMs. External examination of the skin and mucous membranes of the physiological openings did not reveal signs of irritation, inflammation or other manifestations of pathological processes. The internal organs of the experimental animals did not differ from the control animals in size, color and consistency. The mass coefficient of internal organs of rats did not change significantly, and fluctuations in the mass of internal organs in groups were within the physiological norm (Table 2).

Determination of the dynamics of animals' body weight showed that the introduction of overdoses of the studied aqueous extracts of PAMs did not lead to negative changes in body weight of rats both in relation to the original data and in comparison, with the data of the Control group. On the contrary, a positive dynamics of body weight was observed, which indicates the absence of toxic effects of the studied extracts on general trophic processes with a single excess of the conditionally therapeutic dose of PAMs.

Thus, according to the results of the study, it was established that aqueous extracts of PAMs at a dose of 30 mL/kg do not lead to death of animals, do not affect the mass coefficients of internal organs, indicating the absence of toxic effects of PAMs at the maximum dose and characterizes them as relatively harmless substances (toxicity class VI, LD50> 15000 mL/kg) (Table 3).

Conclusions

It was conducted the study of acute toxicity activity of PAMs: sample 1) *Urtica dioica* leaf, *Cichorium intybus* roots, *Rosa majalis* fruits, *Elymus repens* rhizome, *Taraxacum officinale* roots; sample 2) *Arctium lappa* roots, *Elymus repens* rhizome, *Zea mays* columns with stigmas, *Helichrysum arenarium* flowers, *Rosa majalis* fruits; sample 3) *Inula helenium* rhizome with roots, *Helichrysi arenarium* flowers, *Zea mays* columns with stigmas, *Origanum vulgare* herb, *Rosa majalis* fruits, *Taraxacum officinale* roots; sample 4) *Cichorium intybus* roots, *Elymus repens* rhizome, *Helichrysum arenarium* flowers, *Rosa majalis* fruits, *Zea mays* columns with stigmas; sample 5) *Urtica dioica* leaf, *Taraxacum officinale* roots, *Vaccinium myrtillus* leaf, *Rosa majalis* fruits, *Mentha piperita* herb, which were used in Ukrainian folk medicine for the prevention and treatment of DM type 2.

The results of the study showed that PAMs, do not show toxic effects after single intragastric administration at a dose of 30 mL/kg in rats and belong to the group of relatively harmless substances - VI toxicity class, LD50> 15000 mL/kg.

Therefore, the obtained experimental data characterize all five PAMs as safe and promising for further in-depth pharmacological studies.

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Table 1. Composition of plant antidiabetic mixtures

PAMs	Plant component	Portion in the mixture, %	Relative ratio
Sample 1	*Urtica dioica* leaf	26.32	5
	Cichorium intybus roots	26.32	5
	Rosa majalis fruits	21.05	4
	Elymus repens rhizome	15.79	3
	Taraxacum officinale roots	10.52	2
Sample 2	*Arctium lappa* roots	26.32	5
	Elymus repens rhizome	26.32	5
	Zea mays columns with stigmas	21.05	4
	Helichrysum arenarium flowers	15.79	3
	Rosa majalis fruits	10.52	2
Sample 3	*Inula helenium* rhizome with roots	10.0	1
	Helichrysi arenarium flowers	20.0	2
	Zea mays columns with stigmas	20.0	2
	Origanum vulgari herb	20.0	2
	Rosa majalis fruits	20.0	2
	Taraxacum officinale roots	10.0	1
Sample 4	*Cichorium intybus* roots	26.32	5
	Elymus repens rhizome	26.32	5
	Helichrysum arenarium flowers	21.05	4
	Rosa majalis fruits	15.79	3
	Zea mays columns with stigmas	10.52	2
Sample 5	*Urtica dioica* leaf	20.0	1
	Taraxacum officinale roots	20.0	1
	Vaccinium myrtillus leaf	20.0	1
	Rosa majalis fruits	20.0	1
	Mentha piperita herb	20.0	1

Table 2. Dynamics of changes in internal organs after intragastric administration of aqueous extracts of PAMs (30 mL/kg, *p.o.*). Values are expressed as mean ± SEM, n=8

Group of animals		Mass coefficients of internal organs							
		Liver	Kidneys	Heart	Lung	Spleen	Adrenal glands	Thymus	Testicles
Group I (Control group)		3.18 ±0.20	0.66 ±0.03	0.31 ±0.01	0.54 ±0.02	0.40 ±0.03	0.014 ±0.001	0.07 ±0.00	0.94 ±0.03
Experimental groups	Group II (PAM 1)	3.13 ±0.11	0.66 ±0.02	0.30 ±0.01	0.57 ±0.07	0.37 ±0.03	0.014 ±0.000	0.07 ±0.01	1.05 ±0.04
	Group III (PAM 2)	3.17 ±0.18	0.69 ±0.03	0.32 ±0.01	0.56 ±0.04	0.43 ±0.02	0.015 ±0.001	0.08 ±0.00	0.95 ±0.04
	Group IV (PAM 3)	3.14 ±0.11	0.67 ±0.02	0.31 ±0.01	0.58 ±0.07	0.38 ±0.03	0.015 ±0.000	0.08 ±0.01	1.04 ±0.04
	Group V (PAM 4)	3.16 ±0.18	0.67 ±0.03	0.32 ±0.01	0.57 ±0.04	0.41 ±0.02	0.014 ±0.001	0.07 ±0.00	0.95 ±0.03
	Group VI (PAM 5)	3.17 ±0.21	0.66 ±0.02	0.30 ±0.01	0.55 ±0.02	0.42 ±0.02	0.014 ±0.001	0.07 ±0.00	0.96 ±0.04

Table 3. Lethal Dose (LD50) of aqueous extracts of PAMs (30 mL/kg, *p.o.*)

Group of animals	n	Dosage, mL/kg	Number of animals that died / number of animals that survived	Toxicity class	Degree of toxicity	LD50, mL/kg
Group II (PAM 1)	8	30,0	0/8	VI class	relatively harmless substances	>15000
Group III (PAM 2)	8		0/8			
Group IV (PAM 3)	8		0/8			
Group V (PAM 4)	8		0/8			
Group VI (PAM 5)	8		0/8			