folia medica

Folia Medica 65(3):482-489
DOI: 10.3897/folmed.65.e83722

Original Article

Composition and Chronic Toxicity of Dry Methanol-Aqueous Extract of Wild-Growing *Satureja Montana*

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Received: 14 Mar 2022 ♦ **Accepted:** 28 Apr 2022 ♦ **Published:** 30 June 2023

Citation: Vilmosh N, Georgieva-Kotetarova M, Dimitrova S, Zgureva M, Atanassova PK, Hrischev PI, Kostadinova I. Composition and chronic toxicity of dry methanol-aqueous extract of wild-growing *Satureja Montana*. Folia Med (Plovdiv) 2023;65(3):482-489. doi: 10.3897/folmed.65.e83722.

Abstract

Introduction: *Satureja montana* is a wild growing medicinal plant, part of the Lamiaceae family. This herb is well known as a source of phenolic compounds, which can vary in a broad range depending on different factors and exert many pharmacological activities.

Aim: The aim of the study was to investigate the composition and chronic toxicity of dry extract of *Satureja montana*.

Material and methods: The composition was investigated by high-performance liquid chromatographic system with diode-array detector. To establish the chronic toxicity of dry extract of *Satureja montana* we used 40 eight-week-old male Wistar rats, treated orally with saline, olive oil (control groups), *Satureja montana* at a dose of 500 mg/kg bw, carvacrol – 500 mg/kg bw, and rosmarinic acid – 15 mg/kg bw. The animals were sacrificed at the end of the experiment and blood samples and organs for histological examination were obtained. Statistical analysis was performed with one-way analysis of variance (ANOVA) using IBM SPSS 19.0.

Results: Rosmarinic acid and small quantities of carvacrol were found in the dry extract of *Satureja montana*. Full blood count and the biochemical parameters ASAT, ALAT, uric acid, cholesterol, triglycerides, glucose and ionized Ca were in the reference values for 17+ weeks old male Wistar rats. The histological samples showed no signs of organ toxicity.

Conclusions: The main ingredient in the dry extract of *Satureja montana* is rosmarinic acid. The extract is not toxic after 90-days oral administration.

Keywords

biochemistry, carvacrol, histology, *Satureja montana*, rosmarinic acid, toxicity

INTRODUCTION

The prevalent part of the world population prefers using phyto-remedies or alternative medicine because of their efficacy and fewer adverse effects.[1] Herbal remedies are estimated to generate more than 80 billion dollars. The expected growth rate is around 18% per year, reaching incomes of US$ 550 billion by 2030.[2] However, very few herbal

species are investigated for the presence of various active ingredients and therapeutic uses.[3]

The Lamiaceae family is widely spread in the Mediterranean and sub-Mediterranean zones, Asia, both Americas, and some countries in Africa.[4] Many herbal genera, which are sources of essential oils rich in phenolic compounds, belong to this family.[5] One of these is the species *Satureja montana*.[6] This aromatic plant is spread in the Balkan peninsula and in the west regions of Republic of Bulgaria. [7,8] *Satureja montana* is rich in polyphenols, terpens and phenolic acids.[9,10]

The exact chemical composition varies in a broad range depending on the type of extract and location of the plants' growth. The essential oils of *Satureja montana* are rich in compounds like thymol and carvacrol.[11] Phenolic acids similar to rosmarinic, chlorogenic acids and their derivatives are mostly present in alcoholic extracts.[6,11,12]

The herb is well known in traditional medicine for the treatment of different conditions, affecting the gastrointestinal tract and pulmonary system.[9] In support of that, research shows that *Satureja montana* has many pharmacological activities, such as antioxidant, antibacterial, antifungal, anti-proliferative activities, due to the secondary metabolites in its composition.[9,11] Unfortunately, there aren't enough studies that examine the in vivo safety of *Satureja montana* and its active ingredients following repeated oral administration.

AIM

Our aim was to investigate the composition and chronic toxicity of the dry extract of *Satureja montana*.

MATERIALS AND METHODS

Extraction

Dried leaves of *Satureja montana* were bought from a herbal pharmacy in Plovdiv, Bulgaria. The extract was prepared by Veselino EOOD, Kazanlak, Bulgaria. Methanol-aqueous extraction in the ratio of 70:30 was used to obtain the extract, which was subsequently dried by a spray dryer at a temperature of 40°C until complete evaporation of both solvents.

Composition

The composition of dry extract of *Satureja montana* was analyzed in the Department of Bioorganic Chemistry, Faculty of Pharmacy, at the Medical University of Plovdiv. High-performance liquid chromatographic system with diode-array detector was used to identify and detect biologically active compounds in *Satureja montana*. According to the structure of the substances, a Hitachi C18 AQ column (250×4.6 mm, 5 μm) and a combination of suitable solvents were selected so as to ensure optimal separation. For qualitative and quantitative determination of rosmarinic acid, thymol, and carvacrol characteristic for *Satureja montana*, a mobile phase water with pH 3 (A) and organic phase 40 acetonitrile / 60 methanol (B) was used in the following gradient mode: 0-7 min 50A/50B; 7-14 min – 50A/50B – 20A/80B; 20-23 min 20A/80B – 50A/50B. The compounds of interest were detected at 275 nm and were identified by their retention times, as well as by comparing their absorption spectra with those of standard substances. They were quantified using a calibration curve. For the analysis we used Star Chromatography Workstation Version 6.30 (build 5).

Preparation of substances

Carvacrol and rosmarinic acid were bought from Sigma-Aldrich. All used substances were prepared as solutions that were administered orally to the experimental animals. The volume of the solutions of dry extract of *Satureja montana*, the rosmarinic acid and carvacrol, was 1 ml/kg bw for each animal. The applied volume of olive oil and distillated water was 1 ml/100 g bw. Carvacrol was prepared as oil solution via dissolving in olive oil. The dry extract of *Satureja montana* and the rosmarinic acid were prepared as aqueous solutions with distillated water as a solvent.

Animals

All experiments were performed in accordance with protocol No. 01-2/10.04.2020 of the Ethics Committee of the Medical University of Plovdiv.

To investigate the chronic toxicity of dry extract of *Satureja montana*, we used 40 8-week-old male Wistar rats randomly divided in 5 groups (n=8). All animals were housed under standard conditions of 12-hour light/dark cycle with free access to food and water.

Chronic toxicity

The animals were treated orally for 3 months with saline and olive oil at a dose of 1 ml/100 g bw (control groups), dry extract of *Satureja montana* 500 mg/kg bw, carvacrol 500 mg/kg bw, and rosmarinic acid 15 mg/kg bw (test groups). On day 91 from the beginning of the experiment, the rats were sacrificed. Blood samples were obtained to analyze the complete blood count and the following biochemical indicators: AST, ALT, glucose, cholesterol, Ca ASX, triglycerides, and uric acid. Liver and kidney samples were taken for histological examination.

Blood samples

The blood samples were processed in the Department of Pharmacology and Clinical Pharmacology. Complete blood count was analyzed with RT-7600Vet hematological

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apparatus immediately after taking the blood samples. Biochemical indicators were analyzed using Chemray 120vet apparatus and Biomaxima kits.

Histological samples

The histological preparations from liver and kidney were processed in the Department of Human Anatomy, Histology and Embryology, Faculty of Medicine, Medical University of Plovdiv. Each organ was fixed in 10% neutral buffered formalin and then embedded in paraffin. The paraffin blocks were cut with microtome into 5-μm thick sections and stained with hematoxylin-eosin. This staining gives a general idea of the organs' structure and possible pathological abnormalities. The histological specimens were examined using an Olympus light microscope. Microphotographs were taken with the camera of the microscope.

Statistical analysis

Statistical analysis was performed with one-way analysis of variance (ANOVA) using IBM SPSS 19.0. Results were expressed as arithmetic mean and standard error of the mean (mean ±SEM). A p value ≤0.05 was considered statistically significant.

RESULTS

Composition

An HPLC method was developed to determine the rosmarinic acid, carvacrol, and thymol characteristic of *Satureja montana*. The parameters of the HPLC method are shown in **Table 1**.

The accuracy of the method is determined by the values of correlation coefficient (r^2) in the range from 0.9990 to 0.9998 and the coefficient of variation (RSD) in the range from 1.20% to 6.56%. The developed method was applied for quantitative determination of rosmarinic acid, thymol, and carvacrol in dry extract of *Satureja montana*. The presence of these compounds determines the biological activity of *Satureja montana*. Rosmarinic acid (44.730±3.500 mg/g) and carvacrol (0.020±0.001 mg/g) were detected in the studied dry extract. The presence of a small amount of carvacrol and the lack of thymol can be accounted for by our

Table 1. Parameters related to precision for HPLC method

Analyte	λ nm	Concentrations μg/ml					RT min	Regression equations	r^2	RSD %	LOD μg/ml	LOQ μg/ml
		S_1	S_2	S_3	S_4	S_5						
Rosmarinic acid	275	5	10	20	30	40	6.30	y=2.0692e+005x	0.9990	4.67	0.075	0.248
Thymol	275	2	5	10	15	20	18.31	y=1.3755e+005x	0.9998	1.20	0.093	0.279
Carvacrol	275	2	5	10	15	20	18.57	y=1.5361e+005x	0.9998	6.56	0.170	0.510

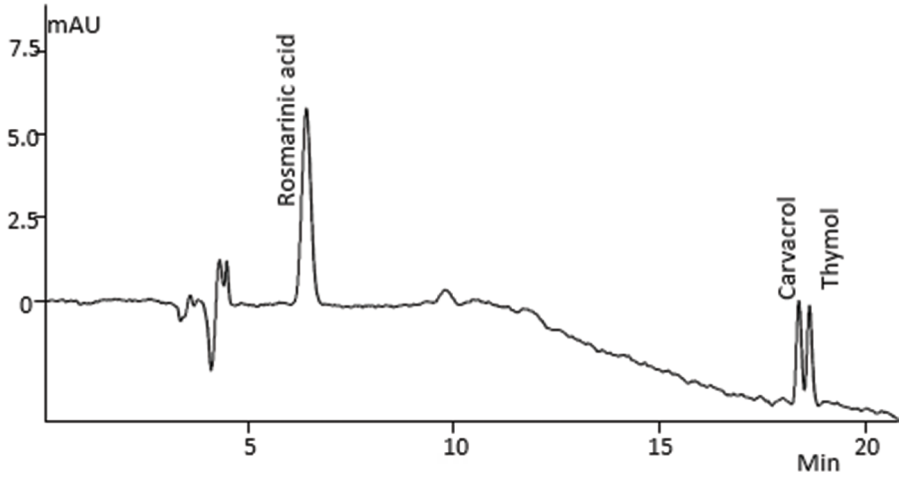


Figure 1. Chromatogram of standard solutions of rosmarinic acid, carvacrol, and thymol.

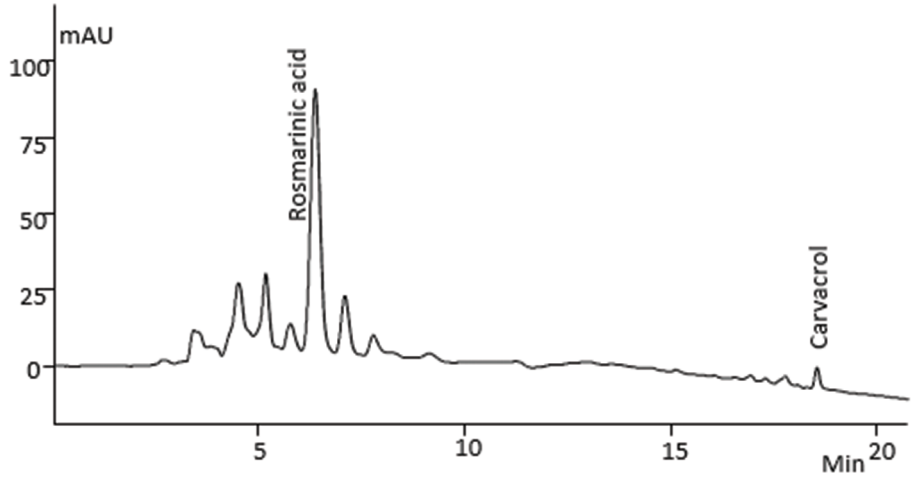


Figure 2. Chromatogram of dry extract from *Satureja montana*.

using dry methanol extract, while other authors determine carvacrol (from 15.19 to 57%) and thymol (up to 24.69%) in essential oil. [13,14]

Blood samples

The complete blood count (CBC) didn't show any markers for hematological toxicity. No significant differences were found between the number of white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), mean hemoglobin concentration (MCH), and hematocrit (HCT). The CBC showed a significant difference in the number of platelets between groups. However, all values were within the reference ranges. The results are presented in **Table 2**.

The investigation of biochemical parameters of AST, ALT, glucose, cholesterol, Ca ASX, triglycerides, and uric acid also showed no chronic toxicity signs similarly to the CBC. Significant variations were established for AST, ALT, and Ca levels, but all of them were within the reference ranges. No significant differences were found in the levels of glucose, cholesterol, triglycerides, and uric acid. The results are shown in **Table 3**.

Histological analyses

Examination of the histological samples from the liver and kidney of the animals of all examined groups demonstrated normal morphology of the organs. No pathological changes were observed. The hepatic lobes had preserved borders and structure of v. centralis, triads, and cells. No changes in the microscopic structure of the cortex and medulla (the glomeruli and all tubular systems) of the kidneys were found. The results are shown in **Table 4**.

DISCUSSION

The available literature contains a wealth of information about *Satureja Montana*'s chemical make-up. The plant is well known as a rich source of phenolic compounds.[5] Many phenolic acids, such as rosmarinic acid, caffeic p-coumaric acid, ferulic acid, and others, are found in the alcoholic extracts of *Satureja montana*, which is in accordance with our results.[6] It has also been found that the composition of the herb varies in a huge range depending on many factors, such as the climate of the growth region as well as the solvent, type of extract, and extraction technique.[9,11] This explains the differences in the composition between the findings in the available literature and our results.

Carvacrol is found to be one of the main ingredients in the essential oil from *Satureja montana*, responsible for its pharmacological activities.[15] This ingredient is non-polar, extracted usually with hydrodistillation.[5] Although we used extraction with 70% methanol and 30% water, which are usually used for extraction of polar substances such as phenolic acids, we found small quantities of the non-polar carvacrol in our sample.

Even though there are studies on the cytotoxicity of both ingredients found in our extract, there is not enough research regarding the systemic toxicity of rosmarinic acid and carvacrol. Both active ingredients are described to have organoprotective activities as well as to reduce increased blood glucose or cholesterol.[1,16]

Regardless of the statistically significant differences between the values of some of the studied blood (PLT) and biochemical parameters (AST, ALT, Ca), these parameters remain within the reference range for 17+ week-old male Wistar rats.[18] We therefore assume that these differences are due to individual variations between animals from different groups and do not consider them to be chemotoxic. In addition, other research teams reported similar platelet counts in their studies.[19]

In the animal models of diabetes, where blood glucose and cholesterol are increased, rosmarinic acid has been found to lower these two biochemical markers.[16,17] The lack of hypoglycaemic and hypocholesterolaemic effects in our study is due to the fact that we use healthy native rats whose glucose and lipid metabolism are not impaired.

Table 2. Complete blood count after 90-day application of the compounds

Group	WBC 109/L		RBC 1012/L		HGB g/L		MCH g/L		HCT %		PLT 109/L	
	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*
Saline 1 ml/100 g bw	6.58±0.52		5.21±0.28		136.67±3.38		26.53±0.99		29.75±1.28		437.17±38.89	
Olive oil 1 ml/100 g bw	5.98±0.58		5.51±0.25		135.33±6.61		24.82±1.54		32.13±1.34		590.50±48.78	
S. montana 500 mg/kg bw	5.78±1.07	0.77	5.34±0.30	0.22	125.50±8.02	0.60	23.73±1.42	0.20	30.58±1.88	0.12	488.17±60.62	0.00*
Carvacrol 500 mg/kg bw	5.25±0.82		5.70±0.37		132.83±3.53		23.78±1.63		31.07±2.29		525.17±41.25	
Rosmarinic acid 15 mg/kg bw	6.17±0.50		6.17±0.29		132.17±1.28		21.70±1.28		36.20±1.87		808.83±68.45	

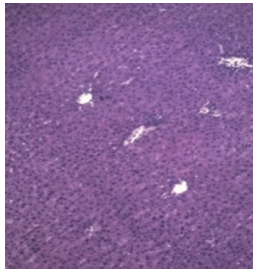
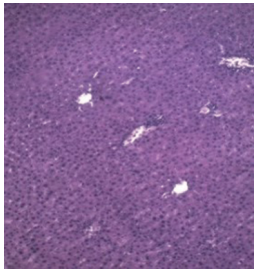
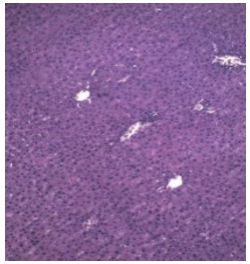
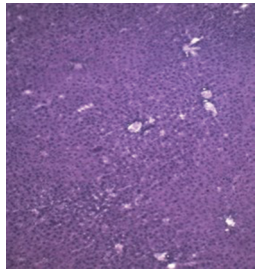
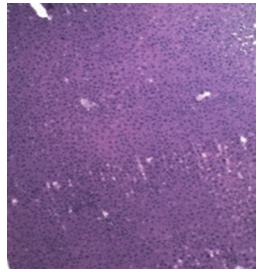
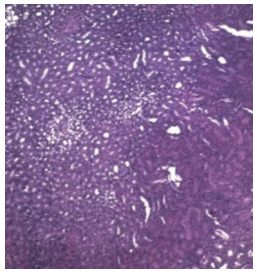
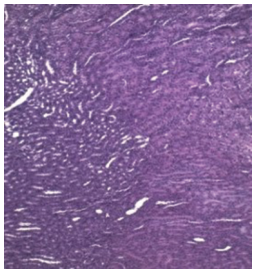
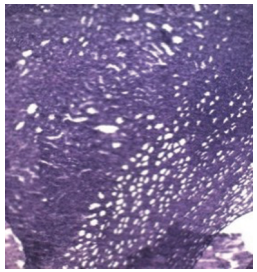
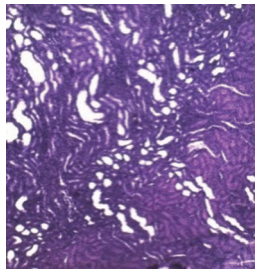
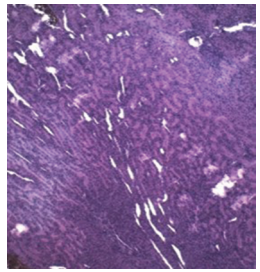
* significant difference was found between the groups treated with rosmarinic acid and saline, *Satureja montana* and carvacrol groups using Tukey HSD post hoc test with p values $p<0.001$, $p<0.002$, and $p<0.007$, respectively

Table 3. Biochemistry results after 90-day application of the compounds

Group	Glu mg/dL		AST U/L		Cho mg/dL		ALT U/L		Uric acid mg/dL		Trig mg/dL		Ca ASX mg/dL	
	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*	Mean±SEM	*P*
Saline 1 ml/100 g bw	127.5±7.09		130.83±13.46		56.51±4.46		7.67±0.67		1.12±0.09		35.17±2.44		5.63±0.34	
Olive oil 1 ml/100 g bw	140.83±15.95		88.17±7.81		68.88±4.84		5.50±0.67		1.08±0.06		37.67±3.55		6.62±0.39	
S. montana 500 mg/kg bw	133.00±7.00	0.821	130.33±5.31	0.000*	72.14±5.47	0.173	4.67±0.80	0.002	0.95±0.06	0.189	26.00±2.16	0.382	5.50±0.19	0.000** 0.000#
Carvacrol 500 mg/kg bw	137.17±2.50		153.67±10.02		68.96±7.62		11.83±2.06		0.95±0.04		73.00±10.75		8.95±0.19	
Rosmarinic acid 15 mg/kg bw	139.00±3.86		146.67±6.54		59.29±1.64		6.83±1.01		1.17±0.11		246.33±19.80		9.10±0.10	

* significant difference was found between groups treated with olive oil (control group) and carvacrol with $p<0.001$ with Tukey post hoc test; ** significant difference was found between groups treated with olive oil (control group) and carvacrol with $p<0.001$ with Tukey post hoc test; # significant difference was found between groups treated with saline (control group) and rosmarinic acid with $p<0.001$ with Tukey post hoc test

Table 4. Liver and kidney of animals from the tested groups. HE staining. ×200

Organ \ Group	Saline 1 ml/100 g bw	Olive oil 1 ml/100 g bw	Satureja montana 500 mg/kg bw	Carvacrol 500 mg/kg bw	Rosmarinic acid 15 mg/kg bw
Hepar					
Kidney					

Treatment with carvacrol for 60 days in another study didn't show significant differences in the values of AST, ALT, and uric acid compared with the control group.[20] This indicates that the observed statistically significant differences are due to individual variations between animals, which in rodents exist to a great extent and cannot be considered as hepatotoxic.[18]

The research team of Ana R Madureira has investigated the organ toxicity of rosmarinic acid, applied together with solid lipid nanoparticles as a carrier for 14 days. In this study, no evidence of hepatotoxicity or nephrotoxicity was found.[19] Similarly, we also didn't find any changes in the normal histological structure of the liver and kidneys, even though in our research we used pure rosmarinic acid for 90 days.

In another research, the liver and kidney organ samples taken from experimental animals treated with carvacrol for 60 days showed no changes in the histological structures.[20] This is in accordance with our results. In our study, we proved that even prolonged treatment (90 days) does not lead to histological markers for hepatotoxicity or nephrotoxicity.

In all mentioned studies, rosmarinic acid or carvacrol are used on their own. In the available literature, we found no research on the toxicity of alcoholic or water extract of *Satureja montana*. Our findings show that the administration of the dry extract of *Satureja montana* for an extended period of time is also not toxic for the organism similarly to the single administration of rosmarinic acid and carvacrol.

CONCLUSIONS

The dry extract of *Satureja montana* prepared from wild growing *Satureja montana* in Bulgaria is a rich source of rosmarinic acid and small quantities of carvacrol. The presence of a concentration of 44.73 mg/g rosmarinic acid could be used in the standardization of future medicines and food supplements based on an alcoholic-aqueous extract of wild growing *Satureja montana*.

The results from the histological examination and blood samples show that oral administration of the extract and of both active ingredients for 90 days does not cause any pathological, histological, and hematological changes in the experimental animals.

Funding

This study was supported by the Medical University of Plovdiv, Project No. DPDP-15/2020

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Состав и хроническая токсичность сухого метанольно-водного экстракта дикорастущей *Satureja Montana*

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Дата получения: 14 марта 2022 ♦ **Дата приемки:** 28 апреля 2022 ♦ **Дата публикации:** 30 июня 2023

Образец цитирования: Vilmosh N, Georgieva-Kotetarova M, Dimitrova S, Zgureva M, Atanassova PK, Hrischev PI, Kostadinova I. Composition and chronic toxicity of dry methanol-aqueous extract of wild-growing *Satureja Montana*. Folia Med (Plovdiv) 2023;65(3):482-489. doi: 10.3897/folmed.65.e83722.

Резюме

Введение: *Satureja montana* – дикорастущее лекарственное растение, относящееся к семейству губоцветных. Эта трава хорошо известна как источник фенольных соединений, которые могут варьироваться в широком диапазоне в зависимости от различных факторов и проявлять множество фармакологических действий.

Цель: Целью исследования было изучение состава и хронической токсичности сухого экстракта Satureja montana.

Материалы и методы: Состав исследовали на высокоэффективной жидкостной хроматографической установке с диодно-матричным детектором. Для установления хронической токсичности сухого экстракта *Satureja montana* использовали 40 восьминедельных крыс-самцов линии Wistar, получавших перорально физиологический раствор, оливковое масло (контрольные группы), *Satureja montana* в дозе 500 mg/kg массы тела, карвакрол – 500 mg/kg массы тела, а розмариновую кислоту в дозе 15 mg/kg массы тела. В конце эксперимента животных умерщвляли и брали образцы крови и органов для гистологического исследования. Статистический анализ проводили с помощью однофакторного дисперсионного анализа (ANOVA) с использованием IBM SPSS 19.0.

Результаты: Розмариновая кислота и небольшие количества карвакрола были обнаружены в сухом экстракте *Satureja montana*. Общий анализ крови и биохимические показатели ASAT, ALAT, мочевая кислота, холестерин, триглицериды, глюкоза и ионизированный Ca находились в референсных значениях для крыс-самцов Wistar в возрасте 17+ недель. Гистологические образцы не показали признаков органной токсичности.

Заключение: Основным ингредиентом сухого экстракта *Satureja montana* является розмариновая кислота. Экстракт не токсичен после 90-дневного перорального приёма.

Ключевые слова

биохимия, карвакрол, гистология, *Satureja montana*, розмариновая кислота, токсичность