PharmacologyOnLine

Archives • 2021 • vol.2 • 352-360

INVESTIGATION OF THE INFLUENCE OF THE THICK EXTRACT OF COMMON CENTAURY (*CENTAURIUM ERYTHRAEA* RAFN.) HERB ON THE SECRETORY FUNCTION OF THE STOMACH

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Abstract

Centaurium erythraea Rafn. known as common centaury, belongs to the family *Gentianaceae* and is well-known all over the world. Common centaury herb is used for different diseases such as the illness of the liver, kidneys, biliary tract, diabetes, as well as to increase bile secretion and enhance the contraction of uterine muscles. The aim of our study was to acute toxicity and the effect of the thick extract of common centaury herb on the secretion of gastric juice. The investigation on the study of acute toxicity allowed establishing an absence of toxic action of thick extract (LD50 500-5000 mg/kg). According to the classification of substances according to K. K. Sydorov, thick extract of common centaury herb is referred to the class IV of substances toxicity – low-toxic substances. As a result of the assessment of the secretory function of the stomach, it was found that the introduction of a thick extract of common centaury herb at a dose of 25 mg/kg stimulates the secretion of gastric juice and herewith does not change the acidity of gastric juice. Therefore, extract of common centaury herb may be used for the development of new drugs as an active pharmaceutical ingredient.

Keywords: *Centaurium erythraea Rafn., common centaury, herb, thick extract, secretory function of the stomach*

Introduction

There is a tendency to expand the range of finished drugs every year in the pharmaceutical market. Among them, there is a significant number of herbal medicines and medicinal plant raw materials. The use of medicinal plants in the prevention and treatment of various diseases is known since ancient times [1]. The methods of treatment using plants have become increasingly common too [2]. Combinations of different medicinal plants deserve special attention as such herbal mixtures have many biologically active substances [3, 4]. 25 % of remedies in the pharmacopeia are plant-derived [5]. The peculiarity of such drugs is a wide range of pharmacological properties, which are realized through many groups of phytochemicals, their environmental friendliness, polyvalence (versatile direction of action), mild action, achieved through biological affinity for the human body and, in turn, determines their use for regulation of metabolic disorders, the prevention, and pharmacotherapy of many diseases [6-8].

Experimental studies and clinical use of herbal medicines show their great value in the treatment of many, especially chronic diseases.

Development of new medicines from herbal raw materials, taking into account a rational approach to the use of a wide raw material base of plants is one of the important tasks of modern pharmacy and medicine.

Plants with a large raw material base include common centaury (*Centaurium erythraea* Rafn.). Medicinal properties of *Centaurium erythraea* Rafn. have been known since ancient times.

Centaurium erythraea Rafn. commonly known as common centaury, belongs to the family *Gentianaceae* is a well-known plant in many countres of the world [9].

The *Gentianaceae* family consists of 99 genera and about 1736 species [10]. Plants of this family have a long history of usage, minor side effects, and high tolerability, regardless of the age of patients, and are the objects of interest in our society [11- 13].

The herb *Centaurium erythraea* Rafn. is the official raw material in Croatia, Serbia, Ukraine, Poland, Turkey, Morocco, Canada, and other countries. Common centaury is included in the European Pharmacopoeia and 23 pharmacopeias of the world [14-16].

Centaurium erythraea Rafn. is a biennial herb that grows in humid and semi-arid areas throughout the northern hemisphere [17, 18].

Common centaury herb contains the following biologically active substances: phenolic acids, alkaloids, monoterpenoids, triterpenoids, secoiridoid glycosides, xanthones, flavonoids, and others [19-23]. Flowers and stem of *Centaurium erythraea* Rafn. are rich in iridoids, the leaves are less.

The plant is used in metabolic disorders caused by alcoholism, anemia, leukemia, and cancer [24].

Common centaury is also used in diseases of the liver, biliary tract, kidneys, hemorrhoids, and diabetes [25-27].

Biologically active substances of common centaury can affect the secretion of glands of the digestive tract, increase bile secretion, enhance the contraction of uterine muscles, have an anti-inflammatory, analgesic, weak laxative effect and antioxidant activity [24].

Svertsiamarin, which is converted in vivo to gentianin, has a calming effect on the central nervous system, that is why common centaury is used for hysteria, neurasthenia, and neurosis.

Common centaury herb has antimutagenic properties on *Salmonella typhimurium TA8 and TA100* strains due to the presence of gentiopicroside and svertsiamarin in the plant [28, 29].

The alkaloid gentianin has anthelmintic properties.

Secoiridoids, contained in common centaury, increase appetite and have a tonic effect. The mechanism of action is explained by reflex secretion of gastric juice as a result of irritation of taste receptors.

Various studies indicate the presence of a large number of iridoids affecting the secretory function of the stomach [30]. Therefore, the study aimed to establish the effect of a thick extract of *Centaurium*

erythraea Rafn. on the secretory function of the stomach and investigate its acute toxicity.

Methods

Plant Materials

The herb of *Centaurium erythraea* Rafn. was collected in Western Ukraine, on the outskirts of Zboriv (Ternopil region) during the flowering period in July 2017. The herb was authenticated by professor Dr Svitlana Marchyshyn (I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine) [31]. A voucher specimen no. 133 is kept at the Department of Pharmacognosy and Medical Botany, TNMU, Ukraine [32, 33]. The study plant material was dried using the conventional method and stored in paper bags in a dry, protected from direct sunlight place [34, 35].

Preparation of extract. About 5000 g of dried *Centaurium erythraea Rafn.* herb were powdered with the help of an appropriate grinder. It was taken in an extractor and extracted using 70% ethanol. Extraction was performed by the maceration method at a temperature of 20 ± 2° C. The obtained extract was concentrated under a rotary vacuum evaporator at a temperature of 60° C.

Study of acute toxicity: was performed on nonlinear mice-males weighing 18–24 g at the age of 2.5 months. Before intragastric administration of a thick extract of *Centaurium erythraea* Rafn., mice fasted overnight. Animals were administered the substance intragastrically at a dose of 5000 mg/kg once. The animals had free access to water, they were allowed to eat only 3 hours after the administration of a thick extract of *Centaurium erythraea* Rafn. The animals were observed for 14 days. The degree of the substance toxicity was assessed by mortality, changes in general condition, animal behavior, appetite, skin condition, visible mucous membranes, and body weight dynamics on days 3, 7, and 14. At the end of the observation on day 15, the animals were removed from the experiment by euthanasia under sodium thiopental anesthesia [36]. After that, an autopsy, macroscopic analysis of internal organs (lungs, thymus, heart, kidneys, liver, spleen), weighed and mass coefficient was calculated [37-39].

Investigation of the influence of thick extract of common centaury on the secretory function of the stomach.

The effect of the substance on the secretory function of the stomach was performed following the methodological recommendations of the State Expert Center of the Ministry of Health of Ukraine according to the method by N. I. Andreeva and S. D. Sharova [40].

The study was performed on 30 nonlinear white rat-males body weight, 140-160 g, which were kept for 48 years without food with free access to water.

Screening studies of a thick extract effect were performed in comparison with wormwood tincture. Experimental samples were administered once intragastrically at doses of 5, 10, and 25 mg/kg, wormwood tincture – at a dose of 0.15 ml/kg. One hour after administration of the test agents, the animals were anesthetized with sodium thiopental, and laparotomy was performed. A ligature was placed on the pyloric sphincter of the stomach.

After 4 hours, a ligature was placed on the cardiac sphincter, then the stomach was removed and the volume of gastric juice was measured. The intensity of gastric juice secretion was calculated per 100 g of animal body weight. Total acidity was determined by titration of gastric juice with 0.1 M sodium hydroxide solution in the presence of phenolphthalein and bromothymol blue indicators. The acidity of gastric juice is expressed by the amount of 0.1 M sodium hydroxide solution, in milliliters, necessary to neutralize 100 ml of gastric juice.

During the experiments, all experimental animals must be in standard sanitary conditions: at a temperature of 19–24°C, humidity not more than 50%, in plastic cages, natural light mode "day-night", on a standard diet and free access to food and water. All manipulations with animals were carried out by the sanitary and hygienic norms and principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986; Law of Ukraine, No. 3447-IV, 2006) [41].

Statistical analysis

Statistical processing of the results was performed using Statistica 8.0 program. The obtained values by using the Student's t-test were compared and the non-parametric Mann-Whitney U-test [42]. The nonparametric Mann-Whitney U-test was used to estimate the statistical difference in the two independent samples, and the Kruskal-Wallis method was used to compare the independent samples in different groups [39] The difference of significance was set at *p<0.05 for all statistical analyses [43, 44].

Results and Discussion

Study of acute toxicity of thick extract of common centaury herb by intragastric administration to mice.

A short-term decrease in locomotor activity of mice was observed in the assessment of acute toxicity 30 min after administration of extracts at a dose 1000 times higher than the conventionally effective (5000 mg/kg). This effect is probably due to the overload of phytoextract solutions. No other symptoms of poisoning, such as incoordination, blepharoptosis, hypersalivation, and lateral position, were observed.

Intragastric administration of thick extract of common centaury at a dose of 5000 mg/kg after 2 weeks did not cause the death of animals.

Determination of the body weight dynamics of male mice showed that the administration of excessive doses of the studied extract did not lead to a decrease in body weight of mice in relation to the basic data and in comparison with the data of intact animals. Positive dynamics of the body weight of mice were observed, indicating the absence of toxic effect of the studied herbal medicine on general trophic processes in the body of mice when the dose of the studied extract was exceeded (Table 1).

At the end of observation, on day 15, the animals were decontaminated by decapitation under inhalation anesthesia, macroscopic changes of internal organs were examined, weighed and mass coefficient was calculated.

Analyzing the obtained data, we can conclude that the administration of thick extract of common centaury herb in overdoses did not significantly affect the mass coefficient of the internal organs of animals, except for the spleen, the relative weight of which was statistically significantly higher than in the group of intact control. Fluctuations in the mass of the organs of mice in groups were within the physiological norm.

The results of the conducted research testify that thick extract of common centaury herb, according to the indicator of acute toxicity, belongs to the class IV of compounds toxicity according to the classification by K. K. Sydorov (low-toxic substances – LD_{50} 500–5000 mg/kg (Table 2) [45].

Study of the effect of thick extract of common centaury herb on the secretion of gastric juice.

The effect of thick extract of common centaury herb on the secretory function of the stomach was studied in accordance with the methodological recommendations of the State Expert Center of the Ministry of Health of Ukraine according to the method by N. I. Andreeva and S. D. Sharova in comparison with wormwood tincture. The results of the study are shown in Table 3.

The results of the study, shown in Table 4, indicate a stimulating effect of thick extract of common centaury herb on the secretion of gastric juice.

The most pronounced increase in the secretion of gastric juice occurred with the introduction of thick extract of *Centaurium erythraea* Rafn. herb at a dose of 25 mg/kg. The volume of gastric juice in this group of animals increased 2.4 times in comparison with intact control, without changing the acidity of gastric juice.

Conclusions

The complex of the conducted researches on studying of acute toxicity of thick extract of *Centaurium erythraea* Rafn. herb on mice-males allowed establishing an absence of toxic action of the drug at an intragastric way of administration (LD_{50} 500-5000 mg/kg). According to the classification of substances according to K. K. Sydorov, thick extract of *Centaurium erythraea* Rafn. herb is referred to the class IV of substances toxicity – low-toxic substances.

As a result of the assessment of the secretory function of the stomach, it was found that the introduction of a thick extract of *Centaurium erythraea* Rafn. herb at a dose of 25 mg/kg stimulates the secretion of gastric juice and does not change the acidity of gastric juice.

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Table 1. Dynamics of body weight of mice after intragastric administration of thick extract of common centaury herb at a dose of 5000 mg/kg (M ± SEM, n=6)

Group of animals	Dynamics of body weight, g			
	Initial mass	On day 3	On day 7	On day 14
Intact control	23.3±0.7	24.7±0.9	24.3±1.2	26.3±1.2*
Thick extract of common centaury	23.3±4.2	25.0±5.0	25.0±5.0	26.0±5.0*

Notes: * – differences are statistically significant with respect to baseline values, p <0.05 (Newman-Keuls test); n – number of animals in group.

Table 2. Parameters of acute toxicity of thick extract of common centaury herb when administered intragastrically to mice

Group of animals	Dose, mg/kg	Toxicity class	Toxicity degree	LD_{50}, ml/kg
Thick extract of common centaury herb	5000	Class IV	low-toxic substances	500-5000

Table 3. Investigation of the effect of thick extract of common centaury herb on the secretory function of the stomach in rats (n=6)

Experimental groups	Doses	Number of animals
Intact control	–	1-6
Common centaury extract	5 mg/kg	7-12
Common centaury extract	10 mg/kg	13-18
Common centaury extract	25 mg/kg	19-24
Wormwood tincture	0.15 ml/kg	25-30

Note: n – number of animals in group.

Table 4. Influence of thick extract of common centaury herb on the secretion of gastric juice in the stomach of rats (n = 6)

Group of animals	Dose	Volume of gastric juice, ml/100 g of animal's weight	Total acidity, ml of 0.1 M NaOH/100 ml of gastric juice
Intact control		0.29 ± 0.02	2.89 ± 0.21
Thick extract of common centaury	5 mg/kg	0.60 ± 0.05*α	3.38 ± 0.35
	10 mg/kg	0.65 ± 0.06*	3.07 ± 0.26
	25 mg/kg	0.69 ± 0.07*/#	2.96 ± 0.26
Wormwood tincture	0.15 ml/kg	0.66 ± 0.10*	6.14 ± 0.24

Notes: * – deviations of the indicator are reliable in comparison with the group of negative control (Mann-Whitney test);

– deviations of the indicator are reliable in comparison with the group of animals administered centaury extract at a dose of 5 mg/kg (Mann-Whitney test);

α – deviations of the indicator are reliable when compared with a group of animals injected with the comparison drug wormwood tincture (Mann-Whitney test);

n – number of animals in group.