RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

PHARMACOLOGICAL ACTIVITY OF EXTRACTS FROM PLANTS OF *COSMOS BIPINNATUS CAV.* SPECIES

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Received 29 June 2020 After peer review 20 Dec 2021 Accepted 07 Feb 2022

The aim of the study is to determine antioxidant, anti-inflammatory and hypolipidemic activities of the extracts from *Cosmos bipinnatus Cav.* three varieties, obtained by the extraction with 70% ethyl alcohol.

Materials and methods. The antioxidant effect was studied *in vitro* using a model of iron-induced lipid peroxidation in the lecithin liposome system. The study of the anti-inflammatory activity was carried out on 30 male rats of the "Wistar" line. Diclofenac was used as a reference drug (p. o., the dose of 13 mg/kg in terms of the weight of an adult). The substances were administered to animals in the form of an aqueous suspension stabilized with Tween-80. To simulate the inflammatory process, a model of "cotton granuloma" was created. A hypolipidemic activity of the extracts was studied on 36 white male rats of the "Wistar" line. To study the hypolipidemic activity of the studied extracts, a tween model was used to create a hyperlipidemic state in rats, the concentrations of total cholesterol and triglycerides was determined in the serum of the experimental animals.

Results. The conducted model experiments made it possible to conclude that the alcohol extracts obtained from the dried inflorescences of the *"Dazzler", "Rosea"* and "*Purity"* varieties of *Cosmos bipinnatus Cav.* have antioxidant, anti-inflammatory and hypolipidemic kinds of activities. It has been established that the extracts from the *"Dazzler"* and *"Rosea"* varieties (*Cosmos bipinnatus Cav.)* contribute to a better reduction in the accumulation of peroxide compounds, compared to the extract obtained from the *"Purity"* variety. The data analysis on the anti-inflammatory activity shows that all the studied objects significantly (p = 0.05) reduce the stage of exudation compared with the control group animals by 50% (the «*Purity»* variety), by 52% (the «*Rosea»* variety) and by 40% (the *"Dazzler*" variety).

An experiment on the study of a hypolipidemic activity in the control group of the animals revealed a significant, in relation to the values of the intact group, increase in the cholesterol level of the blood serum by 78%, and in the level of triglycerides (TGCs) – by 64%.

The administration of the extracts obtained from *Cosmos bipinnatus Cav. "Purity"*, *"Rosea"*, *"Dazzler"* varieties to the animals, led to a decrease in cholesterol in blood serum by 44%, 47%, 50%, and triglycerides by 52%, 52% and 57%, respectively. Both indicators reached the normal level and did not differ significantly from the values in healthy (intact) animals.

Conclusion. According to the conducted studies, it can be concluded that alcohol extracts obtained from *Cosmos bipinnatus Cav*., have pronounced antioxidant, anti-inflammatory and hypolipidemic kinds of effect.

Keywords: *Cosmos bipinnatus Cav*.; hypolipidemic activity; cholesterol; triacylglycerides; anti-inflammatory activity; antioxidant activity, TBA-active products

Abbreviations: DNA – deoxyribonucleic acid; DMSO – dimethyl sulfoxide; TGCs – triglycerides; TBA – thiobarbituric acid; LPO – lipid peroxidation.

For citation: E.O. Kulichenko, O.A. Andreeva, E.O. Sergeeva, S.S. Sigareva, A.Yu. Terekhov, E.T. Oganesyan, S.Yu. Sidorskaya. Pharmacological activity of extracts from plants of *Cosmos bipinnatus Cav.* species. *Pharmacy & Pharmacology.* 2022;10(1):82-92. **DOI:** 10.19163/2307-9266-2022-10-1-82-92

Для цитирования: Е.О. Куличенко, О.А. Андреева, Е.О. Сергеева, С.С. Сигарева, А.Ю. Терехов, Э.Т. Оганесян, С.Ю. Сидорская. Фармакологическая активность извлечений растений вида *Cosmos bipinnatus Cav. Фармация и фармакология.* 2022;10(1):82-92. **DOI:** 10.19163/2307-9266-2022-10-1-82-92

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2022-10-1-82-92

ФАРМАКОЛОГИЧЕСКАЯ АКТИВНОСТЬ ИЗВЛЕЧЕНИЙ РАСТЕНИЙ ВИДА *COSMOS BIPINNATUS CAV.*

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Получена 29.06.2020 После рецензирования 20.12.2021 Принята к печати 07.02.2022

Цель. Определить антиоксидантную, противовоспалительную и гиполипидемическую активности извлечений, полученных экстракцией спиртом этиловым 70% трех видов Космеи дваждыперистой.

Материалы и методы. Антиоксидантное действие изучалось *in vitro* с применением модели железо-индуцированного перекисного окисления липидов в системе лецитиновых липосом. Исследование противовоспалительной активности проводилось на 30-ти крысах-самцах линии «Wistar». В качестве препарата сравнения использовали диклофенак (перорально, доза 13 мг/кг в пересчете на массу взрослого человека). Вещества животным вводили в виде водной суспензии, стабилизированной Твин-80. Для моделирования воспалительного процесса создавали модель «ватной гранулемы». Гиполипидемическую активность исследуемых экстрактов исследовали на 36-ти белых крысах-самцах линии «Wistar». Для изучения гиполипидемической активности исследуемых извлечений применяли твиновую модель для создания гиперлипидемического состояния у крыс, в сыворотке подопытных животных определяли концентрацию общего холестерина и триглицеридов.

Результаты. Проведенные модельные эксперименты позволили сделать вывод о том, что спиртовые извлечения, полученные из высушенных соцветий космеи дваждыперистой сортов *«Dazzler»*, *«Rosea»* и *«Purity»* обладают антиоксидантной, противовоспалительной и гиполипидемической видами активности. Установлено, что извлечения из космеи дваждыперистой сортов *«Dazzler»* и *«Rosea»* способствуют лучшему снижению накопления перекисных соединений по сравнению с извлечением, полученным из сорта *«Purity»*. Анализ данных по противовоспалительной активности показывает, что все исследуемые объекты достоверно (p=0,05) снижают стадию экссудации по сравнению с контрольной группой животных на 50% (сорт «*Purity*»), 52% (сорт «*Rosea*») и 40% (сорт «*Dazzler*»).

Эксперимент по изучению гиполипидемической активности у контрольной группы животных выявил достоверное, по отношению к значениям интактной группы, увеличение уровня холестерола в сыворотке крови на 78%, а уровня триглицеридов (ТРГ) на 64%. Введение животным извлечений, полученных из космеи дваждыперистой сортов *«Purity», «Rosea», «Dazzler»*, привел к снижению содержания холестерола в сыворотке крови на 44%, 47%, 50%, а триглицеридов на 52%, 52% и 57%, соответственно. Оба показателя достигли уровня нормы и достоверно не отличались от значений у здоровых (интактных) животных.

Заключение. Согласно проведенным исследованиям можно сделать вывод, что спиртовые извлечения, полученные из космеи дваждыперистой, обладают выраженным антиоксидантным, противовоспалительным и гиполипидемическим действиями.

Ключевые слова: *Cosmos bipinnatus Cav.*; Космея дваждыперистая; гиполипидемическая активность; холестерин; триацилглицериды; противовоспалительная активность; антиоксидантная активность; ТБК-активные продукты

Список сокращений: ДНК – дезоксирибонуклеиновая кислота; ДМСО – диметилсульфоксид; ТРГ – триглицериды; ТБК – тиобарбитуровая кислота; ПОЛ – перекисное окисление липидов.

INTRODUCTION

The search for natural biologically active compounds is an urgent and time-consuming task. Synthetic drugs are pharmacologically effective, but being broad-spectrum drugs, they often have many serious side effects. Preparations based on natural compounds exhibit fewer undesirable properties and are more effective when taken prophylactically. The use of plants as a source of drugs is very promising from the point of view of creating total substances characterized by a low toxicity and intended for a long-term use in the treatment of various diseases [1–5].

The native range of *Cosmos bipinnatus Cav.* is Mexico; in Russia it is used as an ornamental crop (a plant up to 1.5 meters high). Depending on the variety, it can have white (“*Purity*” variety), pink (“*Rosea*” variety) or purple (“*Dazzler*” variety) flowers, blooms from late May till late autumn and is very resistant to sudden chang-

es in temperature, not susceptible to various infections (Fig. 1) [6].

In the folk medicine of South America, the plants of the genus *Cosmos Cav.* are used as an antimalarial agent [7]. Africans use them to treat headaches and indigestion, as well as against bed bugs and lice, which indicates *Cosmos Cav.* insecticidal properties. In oriental traditional medicine (Japan, China), *Cosmos bipinnatus Cav.* has been used as a substitute for lotus, as a tonic and invigorating agent [8].

In China and Mexico, in traditional medicine, this plant is used as a hepatoprotector and a remedy for headaches, in the treatment of jaundice, intermittent malarial fever, splenomegaly, and flatulence [9]. The use of plants of the genus *Cosmos* as anti-inflammatory and antifungal agents has also been noted; its effectiveness in the treatment of arthritis, stomach ulcers and diabetes mellitus has been described [10]. There is evidence of the ability of *Cosmos bipinnatus Cav.* hydroalcoholic extracts to act as an antioxidant and protect DNA from damage and oxidation. Various extracts from inflorescences of the genus *Cosmos* plants have cytotoxic effects against cell lines of gastric and colorectal adenocarcinoma, and have an antidiabetic activity *in vitro* [9].

The chemical composition of all parts of the plant is mainly represented by polyphenols and essential oil components. Thus, the presence of chalcones (butein, ocanine, lanceoletin) [11], phenolic acids (chlorogenic and caffeic acids), anthocyanins (cosmocyanin), flavonoids (cosmosiin, luteolinglucuronide, trifolin, isoquercitrin, nelyumboside) [12], tannins [13], essential oils: monoterpenes and sesquiterpenes (E)-β-Ocimene, germacrene D, sabinine, α-cadinol, α-farnesin and terpinen-4-ol, β-elemen, β-caryophyllene, germacrene D and bicyclogermacrene [8, 11] has been established.

The following triterpene alcohols have been found out in the tubular flowers of *Cosmos bipinnatus Cav.*: helianol, taraxerol, β-amirin, cycloartenol, α-amirin, lupeol, 24-methylenecycloartanol. The triterpene composition of the reed flowers of the plant is slightly different: helianol, dammaradienol, β-amirin, tirucalla-7,24-dienol, α-amirin, lupeol, 24-methylenecycloartanol, ψ-taraxasterol, taraxasterol [15] (Fig. 2).

Unfortunately, there is very limited scientific information in the literature confirming the medicinal potential of *Cosmos bipinnatus Cav.* The present study is devoted to the study of the biological activity of extracts from three varieties of *Cosmos bipinnatus Cav*., obtained by the extraction with 70% ethanol.

THE AIM of this study was to determine the antioxidant, anti-inflammatory and hypolipidemic activity of alcoholic extracts of three varieties of *Cosmos bipinnatus Cav.*

MATERIALS AND METHODS

Objects of study

For the study of a biological activity, the extracts obtained from the inflorescences of three varieties *of Cosmos bipinnatus Cav. – "Purity", "Rosea", "Dazzler"* – were selected.

Obtaining active substances

Raw materials were collected in September 2018 in the Botanical Garden of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Federal State Budgetary Educational Institution of Higher Education "Volgograd State Medical University" of the Ministry of Health of the Russian Federation. The raw material was subjected to shade drying. The active substances were obtained by an exhaustive threefold extraction of 300 grams of raw material with 70% ethyl alcohol in a flask heated at reflux in a boiling water bath, each time for 30 minutes. The extracts were combined and filtered, and after short-term boiling, the filtrate was thickened in a vacuum rotary evaporator to the state of a thick extract, after that the residue was dried in an oven at 40–50°C to the constant weight (Fig. 3) [16, 17].

Experimental animals

Anti-inflammatory and hypolipidemic kinds of activity were determined on Wistar male rats obtained from the Rappolovo nursery (St. Petersburg) and kept in the PMFI vivarium, a branch of the Volgograd State Medical University. At the time of the experiment, the weight of the experimental animals was 250–280 g. All manipulations performed on the animals complied with the "Rules of the European Convention for the Protection of Vertebrate Animals" (Strasbourg, 1986).

During the experiment, optimal conditions were maintained in the vivarium: the air temperature of 22±2°C, a relative air humidity of 65±5%. The animals were housed in macrolon cages (T3) equipped with a food cavity and steel bars. For bedding, sawdust of any non-coniferous species was poured out into the cages. The animals were fed according to the standard diet and provided with a free access to food. The tap water was supplied in standard drinking bowls[1].

Reference drugs

When testing for an antioxidant activity, the reference drug was quercetin, a high antioxidant activity of which is known. Quercetin (Merck, Germany) was introduced into the reference sample at the concentration of 10 μg/ml, previously dissolved in dimethyl sulfoxide ("Vekton", Russia).

As a reference drug in the study of an anti-inflammatory activity, diclofenac was used (Enteric-coated tablets, 50 mg each, the manufacturer Hemofarm LLC, Obninsk, Russia, series 0291017). The reference drug was taken in the amount of 13 mg/kg in terms of the weight

[1] Directive 2010/63 / EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, September 22, 2010.

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DOI: 10.19163/2307-9266-2022-10-1-82-92

of an adult, the dose was calculated taking into account the interspecies dose conversion factor[2]. The substance was administered as an aqueous suspension stabilized with Tween-80 (Ferak Berlin, Germany).

In tests for a hypolipidemic activity, simvastatin was used as a reference drug, the drug was administered at the dose of 1.7 mg/kg (film-coated tablets, 20 mg each, the manufacturer – Ozon LLC, Zhigulevsk, Samara region, Russia, series 090618), and the dose was calculated taking into account the interspecies dose conversion factor[3].

Statistical processing

Student's t-test was used to assess the reliability of the study's results. The critical level of significance (p) when testing statistical hypotheses in this case was taken equal to 0.05. The sample size of the animals in each group was n=6[4].

When conducting the experiment on the study of the anti-inflammatory activity, the obtained data were statistically processed and presented as: *M±m,* where: *M* is the sample mean, *m* is the error of the mean.

Experiment design

The study design is shown in Figure 4.

Antioxidant activity

This type of activity was studied *in vitro* using the model of iron-induced lipid peroxidation (LPO) in the system of lecithin (phosphatidylcholine) liposomes (Fig. 4). Liposomes were obtained from lecithin (BAS MosLecithin, manufacturer of the Research Institute of Biomedical Chemistry, Russian Academy of Medical Sciences (Russia) at the lipid concentration of 40 mg/ml according to the methods described in the works by I.P. Kodonidi et al. [20]; M. Atas et al. [21]. To determine the effectiveness of the antioxidant action, the degree of inhibition of the lipid peroxidation intensity of lecithin liposomes in the test samples in relation to the control samples was studied. The absorption intensity of TBA-active products was measured 15 min before the incubation. The reaction was carried out in a water bath at 37°C with a continuous barbotage. The studied extracts were added to the test samples in the form of solutions in DMSO. Only the solvent was added to the control samples. The intensity of TBA-active products absorption was measured on SF-102 (SPA Akvilon, Russia) at 532 nm. The percentage of LPO inhibition was calculated in relation to the control sample using the formula:

$$AOA = \frac{\Delta D_k - \Delta D_{op.}}{\Delta D_k} \cdot 100\%,$$

$$\Delta D_k = D_k - D_k^0;$$

$$\Delta D_{op.} = D_{op.} - D_{op.}^0, \quad (1)$$

where: AOA – antioxidant activity, %; D_k^0 and $D_{op.}^0$ – are optical densities before incubation; D_k and $D_{op.}$ – optical density after 15 min of incubation.

Anti-inflammatory activity

To set up the experiment, aqueous suspensions of *Cosmos bipinnatus Cav.* alcoholic extracts of different varieties were used. To increase the stability of the suspension, the dried extracts were preliminarily triturated with a drop of Tween-80 (Fig. 4).

The study of the anti-inflammatory activity was carried out on 30 male rats of the Wistar line. It is known that the mechanism of the diclofenac action is associated with a decrease in the rate of prostaglandins synthesis, and prostaglandins play one of the leading roles in the development of inflammatory processes [22].

White rats were anesthetized with chloral hydrate at the dose of 350 mg/kg, then the hair was cut off in the back area and the supposed site of the subsequent incision was shaved. On a prepared site, in compliance with the rules of asepsis, the skin and subcutaneous tissue incision about 1 cm long was made with scissors. Then, a cavity was formed in the subcutaneous tissue through the incision with tweezers; there a pre-sterilized cotton ball weighing up to 15 mg was placed. After the manipulations, two or three sutures were applied to the wound. The animals were awakened and left under the standard conditions for a week. After 7 days, the balls were removed along with the granular tissue that had grown around them. The rats had been euthanized with chloral hydrate in advance. Then the balls were weighed and dried to constant weight at 60°C. The difference in the mass of the ball before and after drying indicated the size of the exudative phase of inflammation, the difference between the mass of the dried ball and its initial weight (up to 15 mg) was telling of the size of the proliferative phase.

The exudation was calculated by the formula:

$$m_3 = m_1 - m_2, \quad (2)$$

where: m_3 – exudation, g; m_1 – weight of the cotton ball immediately after the removal from the animal, g; m_2 – weight of the cotton ball after drying, g

Proliferation was calculated by the formula:

$$m_4 = m_2 - 0{,}015, \quad (3)$$

where: m_4 – proliferation, g; m_2 – weight of the cotton ball after drying, g; 0,015 – initial weight of the cotton ball, g.

The suspension of the studied extracts was administered at the dose of 300 mg/kg. Both test extracts and the reference drug were administered in equal volumes by gavage into the stomach for 7 days. The control group of the animals was injected with saline in the same way[5].

[2] Mironov AN. Guidelines for conducting preclinical studies of drugs. Part one. M.: Grif and K, 2013: 944 p. Russian
[3] Ibid.
[4] Glantz S. Medical and biological statistics. M.: Practice, 1998: 459 p. Russian
[5] Menshikov VV. Laboratory research methods in the clinic. M.: Medicine. 1987. – P. 365. Russian

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Variety "*Dazzler*" Variety "*Rosea*" Variety "*Purity*"

Figure 1 – Appearance of *Cosmos bipinnatus Cav.* different varieties
Note: these photos are subject to copyright.

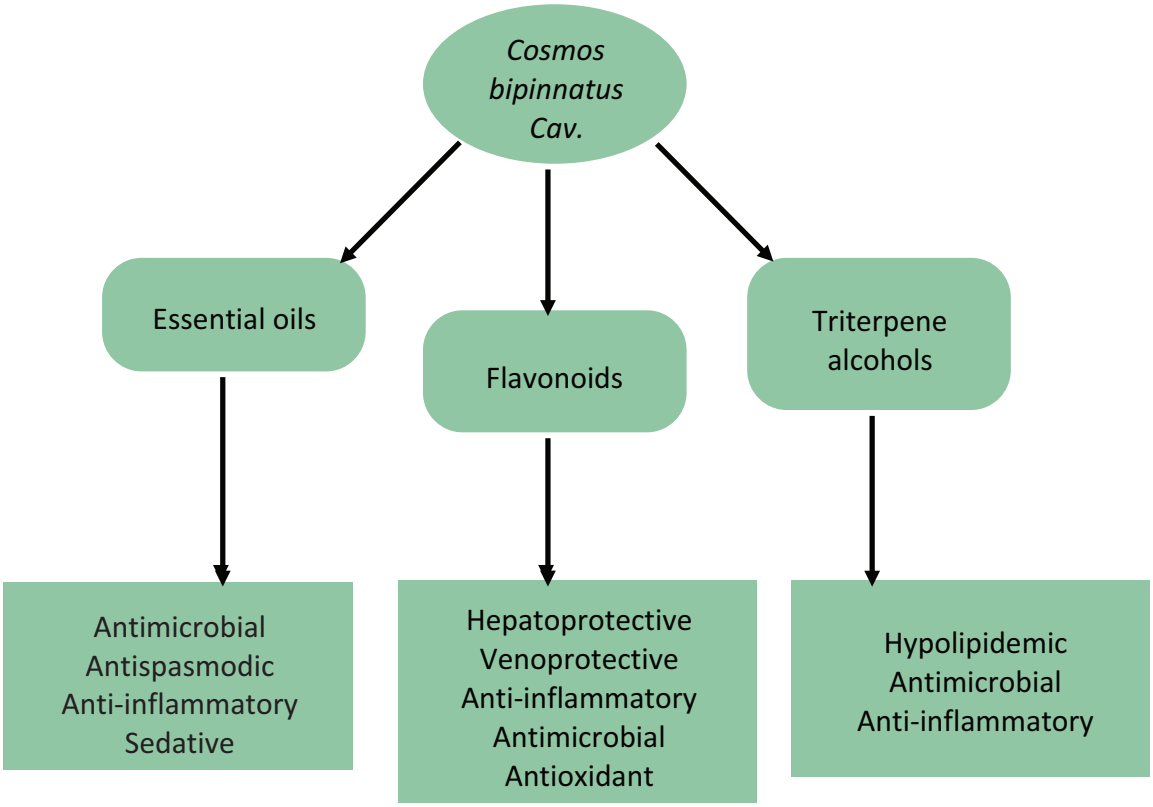

Figure 2 – Chemical composition of *Cosmos bipinnatus Cav.* and predicted pharmacological activity of the main classes chemicals

Table 1 – Effect of the sum of biologically active substances of alcoholic extracts from the *Cosmos bipinnatus Cav.* different varieties on the antioxidant activity

Final concentration of the studied extracts, mcg/ml	% in LPO decrease, n=3			
	Variety «*Purity*», n=3	Variety «*Rosea*», n=3	Variety «*Dazzler*», n=3	Quercetin, n=3 (concentration 10 µg/ml)
200	–24.3±1.29	–52.4 ±2.36	–54.3±3.23	–71 ±4.24

Note: n – is the number of the samples for each concentration

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DOI: 10.19163/2307-9266-2022-10-1-82-92

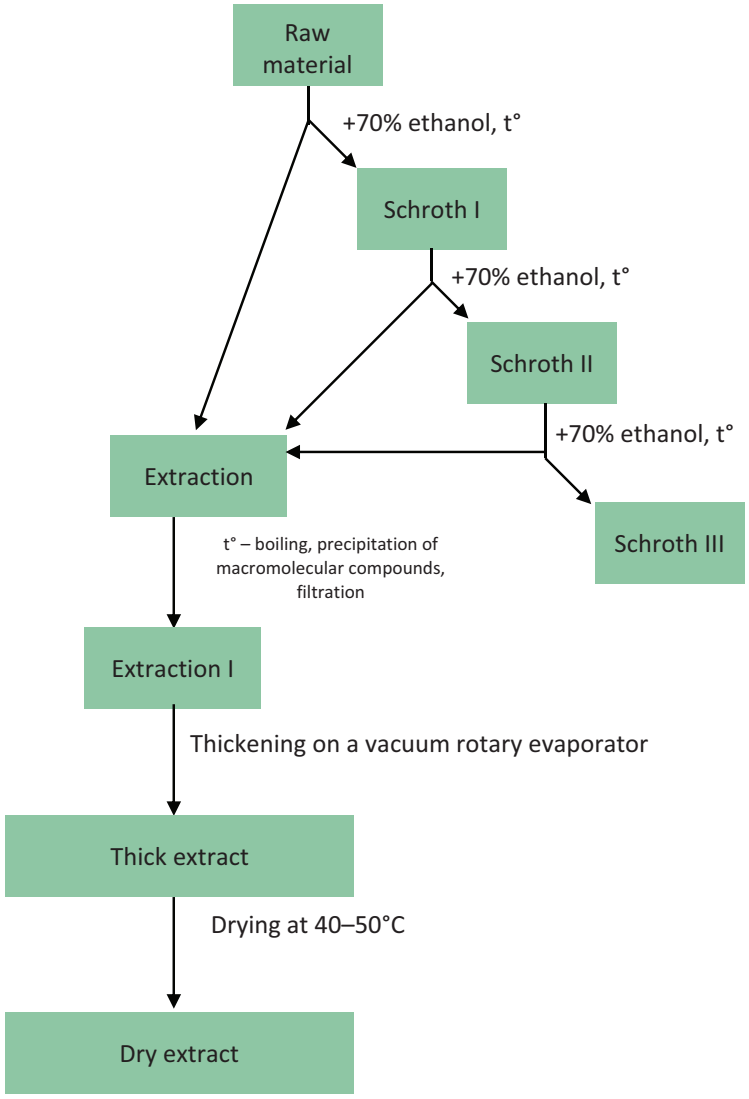

Figure 3 – Scheme for obtaining active substances from *Cosmos bipinnatus Cav.* raw materials

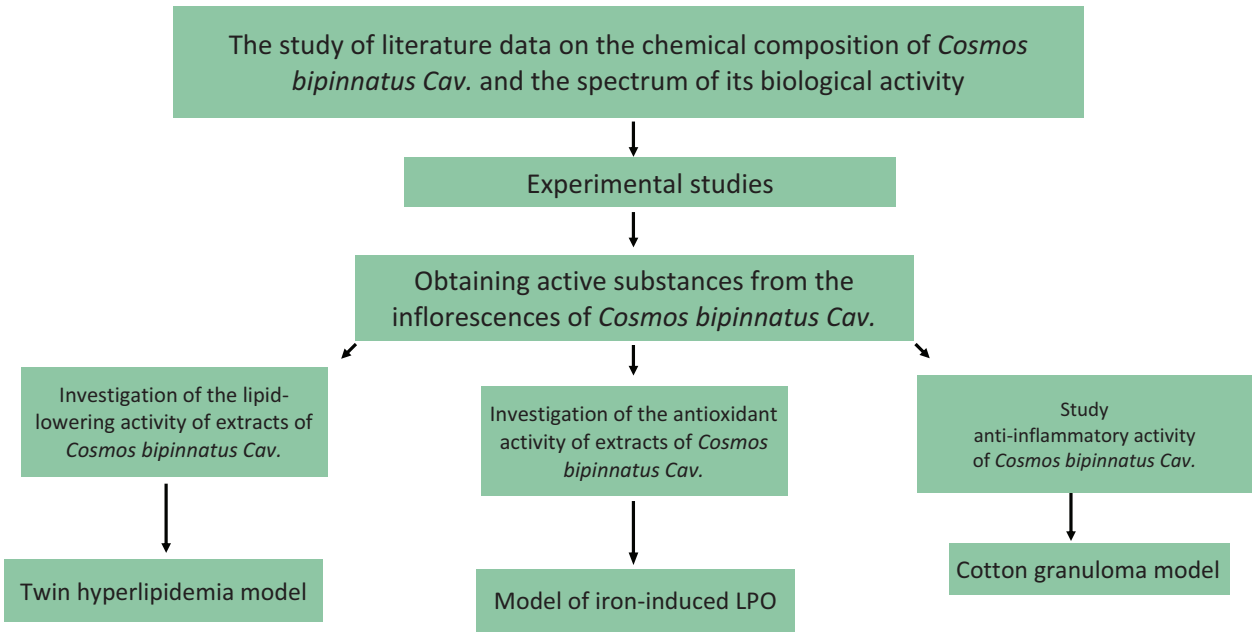

Figure 4 – Experiment design

Table 2 – Results of determining the anti-inflammatory activity of the studied *Cosmos bipinnatus Cav.* extracts in comparison with diclofenac

Object	Exudation, mg	Proliferation, mg
Control	210.0±7.1	33.0±2.9
Diclofenac, 13 mg/kg	117.7±8.9* P_C<0.005 – 44%	30.0 ± 1.7* P_C >0.1 P_D >0.1
70% alcohol extract from *Cosmos bipinnatus Cav.* of *"Purity»* variety", dose of 300 mg/kg	105.3±26.1* P_C <0.001 – 50% P_D >0.1	65.0±9.0*^ P_C <0.001 + 97% P_D <0.001 + 117%
70% alcohol extract from *Cosmos bipinnatus Cav.* of *«Rosea»* variety, dose of 300 mg/kg	101.8±28.3* P_C <0.001 – 52% P_D >0.1	59.0±4.1 *^ P_C <0.001 + 79% P_D <0.001 + 97%
70% alcohol extract from *Cosmos bipinnatus Cav.* of *«Dazzler»* variety, dose of 300 mg/kg	125.7±4.7* P_C <0.001 – 40% P_D >0.1	69.0±4.1 *^ P_C <0.001 + 109% P_D <0.001 + 130%

Note: P_C – the level of significant difference in relation to the control values; P_D – the level of significant difference in relation to the diclofenac values * – significant in relation to control; ^ – significant in relation to diclofenac.

Table 3 – Effect of alcohol extracts from *Cosmos bipinnatus Cav.* of different varieties on the parameters of lipid metabolism in blood against the background of Tween hyperlipidemia

Animal groups and their quantities	Indicators	
n=6	Serum cholesterol, mmol/l	Serum triglycerides, mmol/l
Intact group of animals	1.8±0.35	1.4±0.28
Control group of animals	3.2±0.28 P_I <0.001;+78%	2.3±0.06 P_I <0.001; +64%
Experimental group that received a 70% alcohol extract of *Cosmos bipinnatus Cav.* of *"Purity"* variety	1.8±0.25 P_C <0.001; –44% P_I >0.01	1.1±0.34 P_C <0.001; –52% P_I >0.01
Experimental group that received a 70% alcohol extract of *Cosmos bipinnatus Cav.* of *"Rosea"* variety	1.7±0.19 P_C <0.001; –47% P_I >0.01	1.1±0.30 P_C <0.001; –52% P_I >0.01
An experimental group that received a 70% alcohol extract of *Cosmos bipinnatus Cav.* of *"Dazzler"* variety	1.6±0.35 P_C <0.001; –50% P_I >0.01	1.0±0.36 P_C <0.001; –57% P_I >0.01
Comparison group treated with simvastatin	2.0±0.50 P_C <0.001; –38% P_I >0.01	1.2±0.22 P_C <0.001; –48% P_I >0.01

Note: P_I – the level of significant difference in relation to intact values; P_C – the level of significant difference in relation to the control values; n – number of animals in the group.

Hypolipidemic activity

The hypolipidemic activity of the extracts under investigation was studied on 36 white male rats of the Wistar line. The animals weighing 250–180 grams were taken. The experimental animals were in the same conditions as in the previous experiment. They were divided into 6 groups: 1 – intact; 2 – control; 3, 4, 5 – experimental; 6 – comparison groups. The intact animals were kept under the same conditions as the rest of the groups. The control group animals received distilled water in the equivalent volume of the studied suspensions. The animals from the experimental groups were injected with the extracts obtained from different varieties of *Cosmos bipinnatus Cav*. Group 3 received the extract from the inflorescences of *Cosmos bipinnatus Cav*. of the *"Purity"* variety; group 4 received the extract from the inflorescences of *Cosmos bipinnatus Cav.* of the *"Rosea"* variety; the 5th group received the extract from the inflorescences *of Cosmos bipinnatus Cav.* of the *"Dazzler"* variety. The sixth group of the animals was the control and received the reference drug (Fig. 4).

To study the hypolipidemic activity of the studied extracts, a Tween model was used to create a hyperlipidemic state in the rats: a single intraperitoneal injection of Tween-80 in the amount of 250 mg per 100 grams of the animal body weight [8]. The animals were administered with the dose of 300 mg/kg, p. o., daily (for a week) by means of probes into the stomach of the animals. The

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DOI: 10.19163/2307-9266-2022-10-1-82-92

purpose of the suspension administration during a week was to saturate the organs and tissues of the animals with biologically active compounds, which are associated with lipid metabolism. On the 7th day after the start of soldering, the animals were intraperitoneally injected with Tween-80, and 12 hours after the injection, the animals were slaughtered by decapitation. 12 hours before the slaughter, the animals had been deprived of food

The indicators of cholesterol and triacylglycerides were determined on an automatic biochemical analyzer BS-380 (Mindray, China).

RESULTS AND DISCUSSION

Antioxidant activity

The antioxidant activity investigation of the plant extracts in the models on integral multicellular microorganisms, makes it possible to evaluate only the intensity of the influence of the substances on free radical processes and the activity of the body antioxidant system, but it is not always possible to elucidate the mechanism of their antioxidant action. *In vitro* experiments often provide a clear understanding of the antioxidant effect of the studied substances or their combinations [10, 26].

The method of iron-induced peroxidation is based on the ability of oxidizing agents comprised by the studied extracts, to inhibit the formation of LPO products. Their content is determined by the ability to form colored complex compounds with thiobarbituric acid.

In this experiment, the degree of lipid peroxidation inhibition of liposomes by extracts introduced into the reaction was taken as the value of the antioxidant activity. The results obtained were compared with the results of the control samples. The following extracts were added to the test tubes – 70% extracts obtained from *Cosmos bipinnatus Cav.* three varieties: "*Purity", "Rosea",* and "*Dazzler"* in the concentration of 200 μg/ml. Only dimethyl sulfoxide as the solvent was added to the control samples. Based on the results obtained, the percentage of lipid peroxidation reduction in relation to the control sample was calculated.

Table 1 presents the data on the effect of biologically active compounds of the studied extracts on the accumulation of lipid peroxidation products complexes with thiobarbituric acid (TBA-active products) in the final concentration of 200 μg/ml. This concentration was chosen as the most effective.

It follows from Table 1 that alcohol extracts obtained from the *Cosmos bipinnatus Cav.* varieties *"Dazzler"* and *"Rosea*" contribute to a better reduction in the accumulation of peroxide compounds compared to those obtained from the *Cosmos bipinnatus Cav.* of the*"Purity"* variety. Thus, at the concentration of 200 μg/ml, the alcohol extracts obtained from the *Cosmos bipinnatus Cav.* varieties *"Dazzler"* and *"Rosea",* reduced the content of malondialdehyde by 54% and 52%, respectively, and the alcohol extract obtained from the *Cosmos bipinnatus Cav.* varieties *"Purity"* – only by 24%. When increasing the dose of the studied objects to 500 μg/ml, there was no significant decrease in lipid peroxidation. Quercetin at the concentration of 10 μg/ml contributed to the suppression of lipid peroxidation by 71% compared with the control – DMSO.

Therefore, the conducted model experiments showed that the studied extracts have an antioxidant effect. The mechanism of the antioxidants action directly depends on the environment in which the oxidation substrate and the antioxidant itself are located. In this experiment, the mechanism of the antioxidant action may be implemented by binding the resulting free lipid radicals with the antioxidants or the chelate complexes formation with ferrous ions [10, 26].

The results of the antioxidant activity study show that the extracts obtained from the three varieties of *Cosmos bipinnatus Cav.* – "*Purity", "Rosea", "Dazzler"* – show a clear antioxidant effect. The activity against free radicals and the ability to form chelate complexes with iron, underlies blocking of the inducing ability of iron against free radicals. Alcoholic extracts from the *Cosmos bipinnatus Cav.* varieties *"Rosea"* and *"Dazzler"* have the highest antiradical and antioxidant activities. Probably, this feature is due to the richer polyphenolic composition of the extracts. The corollas of these plants' varieties are colored in bright colors (pink and purple); this fact indicates a possible high content of anthocyanins, known for their high antioxidant activity.

Anti-inflammatory activity

From the experimental data obtained in the study of the anti-inflammatory activity it follows that alcohol extracts from the *Cosmos bipinnatus Cav.* varieties "*Purity", "Rosea", "Dazzler"* reduced the stage of exudation by 50%; 52% and 40%, respectively, significantly in relation to the control group of the animals. These indicators were compared with the experimental groups and the control group receiving diclofenac, no significant differences were found out between them. In terms of limiting exudation, the alcohol extract from the *Cosmos bipinnatus Cav.* "*Purity"* variety does not significantly differ in the effect of the alcohol extract from the *Cosmos bipinnatus Cav.* "*Rosea"* variety, the extraction from the *Cosmos bipinnatus Cav.* "*Dazzler"* variety is slightly inferior in the reduction of this indicator. The results of the experiment are presented in Table 2.

In the course of the results analysis, it was found out that all the studied substances significantly increased the proliferative phase of inflammation in comparison with the control group of the animals. The leader in terms of this indicator was the alcohol extract from *Cosmos bipinnatus Cav.* of the "*Dazzler"* variety.

It was established that against the background of chronic proliferative inflammation (a cotton granuloma model), the test substances in therapeutic and effective doses of 300 mg/kg have significant proliferative and anti-exudative activities, which can be compared with the reference drug.

In the experiment on the anti-inflammatory research of the extracts under study, it was found out that alcohol extracts at the dose of 200 μg/ml exhibit a distinct anti-inflammatory activity, cause a decrease in exudation in the inflammatory focus, which is caused by phlogogenic agents. The leader in terms of the anti-inflammatory activity is the alcohol extract from *Cosmos bipinnatus Cav.* of the *Dazzler* variety. It is possible that the anti-inflammatory effect of the studied extracts is due to their ability to reduce the degree of release of the body's natural inflammatory mediators from mast cells and basophils.

Hypolipidemic activity

According to the WHO, cardiovascular diseases are currently among the top three causes of death in the world. One of the causes and complications of cardiovascular diseases is a violation of lipid metabolism, accompanied by atherosclerosis. Worldwide, there is a trend towards the rejuvenation of cardiovascular diseases[6].

Current protocols for the treatment of lipid disorders are usually based on drug treatment and prevention of atherosclerosis. Usually, drugs for the correction of lipid metabolism are synthetic compounds. Currently, there are three main groups of hypolipidemic drugs: statins, fibrates, and fatty acid sequestrants. The use of these groups of drugs usually leads to a number of side effects: myopathy, asthenia, anorexia, etc. [26].

In the works of recent years, a hypolipidemic effect of plants and various herbal total preparations is often highlighted. A rather high efficiency of such drugs coupled with low toxicity, has been proved [24].

To characterize the influence degree of compounds on the blood lipid profile of animals, it is customary to determine the concentration of total cholesterol, triacylglycerides, low density lipoproteins and high density lipoproteins. In the described study, the content of total cholesterol and triglycerides (TGC) was determined in blood serum. The indicators of cholesterol and triacylglycerides were determined on an automatic biochemical analyzer BS-380 (TRG).

The administration of Tween-80 in experimental animals once intraperitoneally, is accompanied by severe hyperlipidemia. An increase in total serum cholesterol by 78%, and triglycerides by 64% was established. The concentration of total cholesterol and triglycerides in the blood serum of the intact animals corresponded to the norm (Table 3).

The suspension was administered to the animals at the dose of 300 mg/kg. The administration of a suspension in such a dose led to a decrease in cholesterol in the blood serum by 44%, 47%, 50%, when the animals received the extracts obtained from the *Cosmos bipinnatus Cav.* varieties *"Purity", "Rosea", "Dazzler"*, respectively. From the study, it can also be concluded that the concentration of cholesterol in the blood is completely normalized in comparison with the values in healthy (intact) animals. The level of blood triglycerides also decreased by 52%, 52% and 57% in the case of the use of the corresponding extracts obtained from the *Cosmos bipinnatus Cav.* varieties "*Purity", "Rosea", "Dazzler"*, respectively, and reached the normal level. The values of these indicators were comparable with the values of the reference drug.

When conducting the experiment to study the hypolipidemic activity of the extracts, it was found out that the oral administration of the extracts to the animals for a week led to a significant decrease in the concentration of free cholesterol in the blood and the level of triglycerides. The degree of reduction in the concentration of cholesterol and triglycerides in the blood serum of all extracts is approximately at the same level, and exceeds the hypolipidemic effect of the reference drug. The concentration of total cholesterol in the blood serum was most intensively reduced by a 70% alcohol extract of the *Cosmos bipinnatus Cav.* variety *"Dazzler"*, and triglycerides by a 70% alcohol extract of *Cosmos bipinnatus Cav.* varieties *"Purity"* and *"Rosea"*.

It is known that some triterpene alcohols (e.g., gelianol), comprised by the plants of the genus *Cosmos*, have an anti-inflammatory activity. [16].

Butein is chalcone, which is a part of plants of the genus *Cosmos*; it is a powerful antioxidant against lipids and low density lipoproteins (LDL), and also has an anti-inflammatory activity, is able to inhibit aromatase and cyclooxygenase [19, 20].

CONCLUSION

According to the conducted studies, it can be concluded that alcohol extracts obtained from *Cosmos bipinnatus Cav.* have pronounced antioxidant, anti-inflammatory and hypolipidemic effects.

The manifestation of the kinds of the biological activity described above, can be associated with the chemical composition of *Cosmos bipinnatus Cav.* The literature sources and the authors' previous studies have shown that the chemical composition of *Cosmos bipinnatus Cav* includes polyphenols (catechins, anthocyanins, flavonoids), organic acids, amino acids and polysaccharides. The manifestation of antioxidant, anti-inflammatory and hypolipidemic properties of 70% alcohol extracts from *Cosmos bipinnatus Cav.,* can be associated with the presence of the described classes of biologically active compounds in them.

The study and the data obtained in the course of it makes it possible to recommend three varieties of *Cosmos bipinnatus Cav*.: "*Purity", "Rosea", "Dazzler"* as of biologically active compounds with a wide range of a biological activity.

[6] World Health Organization (WHO). The top 10 causes of death. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

DOI: 10.19163/2307-9266-2022-10-1-82-92

FUNDING

This study did not receive any financial support from outside organizations.

CONFLICT OF INTERESTS

The authors declare no conflict of interest. All illustrations, drawings and photographs are made by the team of the authors, are original and do not violate anyone's copyrights.

AUTHORS' CONTRIBUTION

Evgenia O. Kulichenko – collection of plant materials for the experiment, conducting the experiment and collecting the data, analyzing and interpreting the data obtained, statistical processing of the results obtained, analyzing the literature, writing the manuscript; Olga A. Andreeva – collection of plant materials for the experiment; Elena O. Sergeeva – participation in the experiment and data collection, participation in writing the manuscript; Svetlana S. Sigareva – participation in the experiment; Alexander Yu. Terekhov – participation in the planning of the study and the development of the concept and design of the study; Eduard T. Oganesyan – study planning, participation in the development of the concept and design of the study, verification of critical intellectual content, final approval for publication of the manuscript; Svetlana Yu. Sidorskaya – statistical processing of the obtained results.

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