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Research Article

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Safety assessment of different extracts of *Linaria vulgaris* Mill. in models of cytotoxicity and acute toxicity

The paper presents the results of a study on the acute toxicity and cytotoxic activity of extracts from the aboveground part of *Linaria vulgaris* Mill., collected during the flowering phase in the steppe areas of the Bukhar-Zhyrau district of the Karaganda region (Republic of Kazakhstan). The extracts were obtained by maceration, percolation, and ultrasonic extraction using various organic solvents (ethanol, ethyl acetate, and chloroform). Acute toxicity was studied in outbred white mice weighing 18–25 g after a single intragastric administration at doses of 500, 1500, and 2500 mg/kg. Cytotoxic activity was assessed using the *Artemia salina* larvae lethality assay. The data obtained showed that the 70 % ethanol extract of *Linaria vulgaris* Mill. belongs to the category of practically non-toxic substances and is classified as low-toxic (toxicity class III). The study of cytotoxic activity demonstrated that the *Linaria vulgaris* Mill. extracts, regardless of the method of preparation or the extractants used, do not exhibit toxic effects against *Artemia salina* larvae. Thus, the studied extracts of the aboveground part of *Linaria vulgaris* Mill. are characterized by low toxicity and lack of cytotoxic activity, which indicates their potential safety and prospects for further biological and pharmacological studies.

Keywords: *Linaria vulgaris* Mill., medicinal plant, extract, acute toxicity, cytotoxicity.

Introduction

Linaria vulgaris Mill. (*Scrophulariaceae* family) is a perennial herbaceous plant. The genus *Linaria* Mill. includes about 200 species, mainly distributed in the Northern Hemisphere, in East Asia, and the Mediterranean Basin [1]. In the flora of the Republic of Kazakhstan, 21 species are found, of which 8 are endemic [2].

It is known that in traditional medicine, *Linaria grandiflora* Desf., *Linaria genistifolia* subsp. *confertiflora* (Boiss.) Davis, and *Linaria aucheri* Boiss. have traditionally been used for treating wounds and vascular disorders, as well as for their laxative, tonic, antidiabetic, and diuretic properties [3]. In *in vitro* experiments, aqueous-methanol, ethyl acetate, and butanol extracts of *Linaria* Mill. species exhibited inhibitory activity against cholinesterase [4]. The use of certain species of the *Linaria* Mill. genus in folk medicine has attracted significant interest in chemical and biological research.

According to the literature [5, 6], studies addressing the phytochemical composition and biological activity of *Linaria vulgaris* Mill. are limited. Phytochemical investigations have identified benzyl alcohol glycosides, syringin, liriodendrin, and other phytoconstituents in *Linaria vulgaris* Mill. plants, supporting the presence of multiple compound classes such as glycosides and alkaloid-related substances. Available research also indicates that extracts of *Linaria vulgaris* Mill. contain phenolic acids and flavonoids with antimicrobial activity in vitro assays against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. Furthermore, chromatographic analyses have shown that *Linaria vulgaris* Mill. extracts contain other phenolic compounds that may contribute to additional biological effects [7].

For the first time, we performed microscopic and histochemical analyses of *Linaria vulgaris* Mill., collected from the Bukhar-Zhyrau district in the Karaganda region of Kazakhstan. The histochemical examination demonstrated that flavonoids, phenolic compounds, traces of essential oils, alkaloids, and sesquiterpene lactones are distributed within the tissues of the leaves and stems [8-9].

Previous studies have reported that cytotoxic activity in various plant extracts has been attributed to biologically active compounds such as alkaloids, flavonoids, and phenolics [10].

Studies on the acute toxicity of extracts help assess the risk and potential side effects associated with the use of plant extracts, which is crucial for ensuring their safe application in medicinal practice and pharmaceutical formulations [11].

No information is available in the accessible literature regarding the study of the acute toxicity of *Linaria vulgaris* Mill. extract, which served as the basis for determining its safety for further use as a medicinal product.

Thus, the aim of this study is to evaluate the acute toxicity and assess the cytotoxic potential of *Linaria vulgaris* Mill. extracts on the larvae of *Artemia salina* larvae.

Experimental

Acute toxicity was evaluated in white outbred mice weighing 18–25 g at the vivarium of the Institute of Life Sciences, Karaganda Medical University.

The animals were divided into four groups of six individuals each.

The studied samples were administered once via a gastric tube at doses of 500, 1500, and 2500 mg/kg.

A precise weight of 50 g of dried and crushed raw material (2 mm particle size) was placed in a round-bottom flask, followed by the addition of 500 mL of 70 % ethanol. The flask was connected to a reflux condenser and heated in a water bath for 3 hours. The obtained extract was filtered and evaporated under reduced pressure using a rotary evaporator. The extraction process was repeated three times, and the resulting fractions were combined and dried.

The administered dose was calculated individually based on body weight.

The acute toxicity study was conducted over a 14-day observation period, with continuous monitoring during the first 24 hours. Systematic evaluations were performed to assess the general condition of the animals, behavioral patterns, motor activity, the presence and type of convulsions, coat condition, mucous membrane coloration, food and water consumption, and changes in body weight [12].

No mortality was observed at any of the tested doses, including the highest dose of 2500 mg/kg. Therefore, the median lethal dose (LD_{50}) of the extract was considered to be greater than 2500 mg/kg after oral administration in mice.

Biochemical blood parameters of mice were analyzed on day 14 of the experiment. Blood samples were collected from the tail vein following the 14-day observation period. The analyses were performed at the veterinary clinic “Dobry Doctor” (Karaganda) using an automated biochemical analyzer [insert model and manufacturer] with standard commercial reagent kits [insert manufacturer]. The following parameters were measured: total protein, urea, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine.

Studies on the cytotoxicity of the samples were conducted at the Scientific Research Institute of New Chemical Technologies, L.N. Gumilyov Eurasian National University.

To assess cytotoxic activity, a series of extracts obtained by maceration (LV-96) and ultrasonic extraction (LV-U70) using various organic solvents, including ethanol, ethyl acetate (LV-EtAc), and chloroform (LV-Chl), were used.

Marine crustaceans *Artemia salina* larvae were used to determine cytotoxic activity. This method measures acute toxicity by comparing the mortality of *Artemia salina* larvae in the test samples with that in a control containing only water. A substance is considered acutely toxic if it causes 50 % or greater mortality of the larvae compared to the control.

Dilutions were prepared by dissolving 1 mg of the substance in 1 ml of solvent. Each sample was tested in triplicate. Experiments were conducted at 20 ± 2 °C under natural light conditions. The control artificial seawater was prepared in the laboratory and had a pH of 8.0–8.5. Newly hatched *Artemia salina* larvae, up to 1 day old, were used for the bioassays, with 20–40 larvae placed in each test tube [13].

All experimental procedures were approved by the Institutional Animal Care and Use Committee (IUCAC). There is a conclusion from the ethical committee of the NJSC “Karaganda Medical University” No. 45, Protocol No. 9 dated 19/06/24.

Results and Discussion

The overall condition of the animals was assessed daily based on appearance, behavior, physiological parameters, and food and water intake. Animals were classified as “normal” if they exhibited typical activity, intact fur and skin, regular food and water consumption, and no observable behavioral or physiological ab-

normalities. “Good condition” was assigned to animals showing all of the above characteristics along with strong responsiveness to stimuli and overall alertness.

Group 1 (Dose: 500 mg/kg): After administration, the mice remained active throughout the day. No observable changes in behavior or functional status were detected. Fur and skin remained intact, and the mice maintained regular food and water intake. No mortality was recorded. On the second day and throughout the entire observation period, no pathological changes in behavior or physiological parameters were observed. Food and water consumption remained normal, and no delays in growth or development were noted. All mice survived the 14-day observation period.

Group 2 (Dose: 1500 mg/kg): Following administration, the mice remained active throughout the day, showing no observable changes in behavior or physiological condition. Their fur and skin appeared intact, and they consumed food and water without any issues. No mortality was recorded. On the second day and throughout the 14-day observation period, no behavioral abnormalities or physiological disturbances were observed. Food and water intake remained consistent, and normal growth and development were maintained. No deaths occurred during the study.

Group 3 (Dose: 2500 mg/kg): Throughout the 14-day observation period following administration, no alterations in behavior or physiological parameters were noted. The mice maintained regular food and water intake and exhibited typical responses to light and sound stimuli. Fur and skin remained in good condition, and urination and defecation were normal. No delays in growth or weight gain were observed. No mortality occurred (Table 1).

After intragastric administration of the extract, all animals maintained normal overall condition, according to the defined criteria.

Over the following 14 days, no notable changes in appearance, behavior, or activity were observed in the mice.

Table 1 summarizes the results of the study assessing the effects of a single intragastric dose of the extract on mouse viability.

Table 1

Assessment of the toxic effects of the dry ethanol extract of *Linaria vulgaris* Mill. in mice following a single oral administration

Dose (mg/kg)	n (male)	n (female)	Deaths (male)	Deaths (female)	Mortality (%)
500	3	3	0	0	0
1500	3	3	0	0	0
2500	3	3	0	0	0
Control	3	3	0	0	0

Preclinical studies of sample LV-70 (*Linaria vulgaris* extract) demonstrated that it does not exhibit acute nonspecific toxicity. The maximum achievable dose for single intragastric administration in mice is 2500 mg/kg, which is considered safe.

Analysis of experimental mice over 7 and 14 days after acute administration of the ethanol extract of Linaria vulgaris Mill. at doses of 500, 1500, and 2500 mg/kg showed no adverse effects on appearance, general condition, body weight, or behavior. The results of the biochemical analyses are summarized in Table 2. No significant deviations from control values were observed for any parameter, confirming the low acute toxicity of the ethanol extract under the tested conditions.

Table 2

Biochemical parameters of mice after acute administration of *Linaria vulgaris* Mill. extract

Parameter	Sex	Control (n=3)	500 mg/kg (n=3)	1500 mg/kg (n=3)	2500 mg/kg (n=3)
Total protein, g/L	♂	63.6 ± 2.1	56.14 ± 0.3	45.6 ± 3.0	47.6 ± 0.7
	♀	61.5 ± 1.8	59.3 ± 0.8	56.72 ± 0.8	49.2 ± 0.5
Urea, mmol/L	♂	12.2 ± 0.9	13.7 ± 1.0	14.5 ± 0.7	15.6 ± 0.6
	♀	11.7 ± 0.2	16.3 ± 2.7	16.7 ± 0.6	14.5 ± 0.8

Continuation of Table 2

Parameter	Sex	Control (n=3)	500 mg/kg (n=3)	1500 mg/kg (n=3)	2500 mg/kg (n=3)
Glucose, mmol/L	♂	9.5 ± 0.24	10.6 ± 0.18	9.54 ± 0.5	10.2 ± 0.2
	♀	9.54 ± 0.41	8.43 ± 2.7	9.87 ± 0.63	9.34 ± 0.28
Total bilirubin, mmol/L	♂	5.46 ± 0.012	4.6 ± 0.61	5.94 ± 0.08	6.01 ± 0.02
	♀	5.68 ± 0.14	5.17 ± 0.25	6.13 ± 0.02	5.96 ± 0.02
AST, mmol/L·s	♂	43.74 ± 0.08	40.3 ± 0.06	42.1 ± 0.3	44.21 ± 0.3
	♀	42.5 ± 0.61	40.9 ± 1.7	43.2 ± 0.5	46.1 ± 0.7
ALT, mmol/L·s	♂	47.35 ± 0.02	42.0 ± 0.03	45.1 ± 0.05	49.2 ± 0.1
	♀	42.54 ± 0.06	43.8 ± 0.02	44.4 ± 0.03	47.3 ± 0.5
Creatinine, mmol/L	♂	170.24 ± 0.1	169.0 ± 0.8	167.2 ± 0.5	162.3 ± 0.2
	♀	167.43 ± 0.05	164.0 ± 0.3	168.3 ± 0.1	165.6 ± 0.5

Cytotoxic activity was studied using the survival method of the marine crustacean *Artemia salina* larvae. A flask was filled with artificial seawater, and *Artemia salina* eggs were added. They were kept for 3 days with gentle aeration until the crustaceans hatched.

Paclitaxel-Teva was used as a reference drug. The samples were tested at concentrations of 10, 5, and 1 mg/ml. The results of the cytotoxic activity study are presented in Table 3.

Table 3

Results of the cytotoxicity study

Sample	Concentration (mg/ml)	Number of larvae (Control: survived/dead)	Number of larvae (Sample: survived/dead)	Mortality (%)	Neurotoxicity (%)
Paclitaxel-Teva	10	22 / 1	0 / 22	96	0
	5	22 / 1	1 / 25	92	0
	1	22 / 1	9 / 18	63	0
LV-EtAc	10	22 / 1	26 / 1	0	0
	5	22 / 1	23 / 0	0	0
	1	22 / 1	21 / 1	0	0
LV-Chl	10	22 / 1	25 / 1	0	0
	5	22 / 1	22 / 0	0	0
	1	22 / 1	23 / 0	0	0
LV-U70	10	22 / 1	22 / 1	0	0
	5	22 / 1	22 / 0	0	0
	1	22 / 1	24 / 1	0	0
LV-96	10	22 / 1	26 / 1	0	0
	5	22 / 1	27 / 0	0	0
	1	22 / 1	22 / 1	0	0

Analysis of experimental mice over 7 and 14 days after acute administration of the ethanol extract of *Linaria vulgaris* Mill. at doses of 500, 1500, and 2500 mg/kg showed no adverse effects on appearance, general condition, body weight, or behavior.

Previous studies in our group demonstrated that the aerial parts of *Linaria vulgaris* Mill. contain up to 0.052 % flavonoids (expressed as quercetin equivalents), 20 amino acids (both essential and nonessential), and 62 components in the essential oil, of which hexahydrofarnesyl acetone accounts for 11.71 % [14-15]. The presence of these compounds likely contributes to the low acute toxicity and overall safety of the extracts.

Cytotoxicity assessment revealed that the samples LV-EtAc, LV-Chl, LV-U70, and LV-96 did not exhibit cytotoxic effects at any of the tested concentrations. In contrast, the reference drug Paclitaxel-Teva ex-

hibited cytotoxicity toward *Artemia salina* larvae across all tested concentrations, with mortality rates ranging from 63 % to 96 %.

Conclusion

Thus, for the first time, we have studied the acute toxicity and cytotoxicity of extracts of *Linaria vulgaris* Mill.

1. Following a single intragastric administration, the *Linaria vulgaris* Mill. extract caused no observable behavioral or physiological changes, and all mice survived the 14-day observation period, indicating low acute toxicity under the conditions and timeframe of this study.

2. The study of cytotoxic activity allows us to conclude that the samples LV-EtAc, LV-Chl, LV-U70, and LV-96 do not exhibit cytotoxicity at any of the tested concentrations.

These findings are limited to acute toxicity, and further studies are required to assess subchronic or chronic toxicity.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Nurkadirov D.K.** — plant material collection, investigation; **Itzhanova Kh.I.** — project administration; **Shaimerdenova Zh.R.** — writing original draft, writing review & editing; **Wirginia Kukula-Koch** — writing review & editing.

Conflict of Interest

The authors declare no conflict of interest.

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Linaria vulgaris Mill. өсімдігінің әртүрлі сығындыларының цитоуыттылық және жіті уыттылық модельдерінде қауіпсіздігін бағалау

Жұмыста Қарағанды облысы Бұқар жырау ауданының (Қазақстан Республикасы) дала учаскелерінде гүлдену кезеңінде жиналған *Linaria vulgaris* Mill. жерүсті бөлігі сығындыларының жіті уыттылығы мен цитоуыттылық белсенділігін зерттеу нәтижелері келтірілген. Жіті уыттылықты зерттеу үшін салмағы 18-25 г ақ тұқымсыз тышқандарға 500, 1500 және 2500 мг/кг дозада бір рет асқазан ішіне енгізілетін 70 % этанол сығындысы қолданылды. Цитоуыттылық белсенділікті бағалау үшін этанол, этилацетат және хлороформды қоса алғанда, әртүрлі органикалық еріткіштерді қолдана отырып, мацерация және ультрадыбыстық экстракция әдістерімен алынған сығындылар сериясы пайдаланылды. Цитоуыттылық *Artemia salina* дернәсілдерінің сынағы арқылы бағаланды. Нәтижесінде *Linaria vulgaris* Mill. сығындысы іс жүзінде улы емес заттар санатына жататынын және уыттылығы төмен (уыттылықтың III класы) ретінде жіктелетінін көрсетті. Цитотоксикалық белсенділікті зерттеу барысында *Linaria vulgaris* Mill. сығындылары өндіру әдісіне және қолданылған экстрагенттерге қарамастан *Artemia salina* дернәсілдеріне уытты әсер етпейтіні анықталды. Осылайша *Linaria vulgaris* Mill. жерүсті бөлігінің зерттелген сығындылары төмен уыттылықпен және цитоуыттылық белсенділіктің болмауымен сипатталады, бұл олардың әлеуетті қауіпсіздігін және одан әрі биологиялық және фармакологиялық зерттеулердің болашағын көрсетеді.

Кілт сөздер: *Linaria vulgaris* Mill., дәрілік өсімдік, сығынды, жіті уыттылық, цитоуыттылық.

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Оценка безопасности различных экстрактов *Linaria vulgaris* Mill. в моделях цитотоксичности и острой токсичности

В работе представлены результаты исследования острой токсичности и цитотоксической активности экстрактов надземной части *Linaria vulgaris* Mill., собранной в фазу цветения на степных участках Бухар-Жырауского района Карагандинской области (Республика Казахстан). Для исследования острой токсичности использовали 70 %-ный этанольный экстракт, который вводили белым беспородным мышам массой 18–25 г однократно внутрижелудочно в дозах 500, 1500 и 2500 мг/кг. Для оценки цитотоксической активности применяли серию экстрактов, полученных методами мацерации и ультразвуковой экстракции с использованием различных органических растворителей, включая этанол, этилацетат и хлороформ. Цитотоксическую активность оценивали с использованием теста на личинках *Artemia salina.* Полученные данные показали, что спиртовой экстракт *Linaria vulgaris* Mill. относится к категории практически нетоксичных веществ и классифицируется как малотоксичный (III класс токсичности). В ходе исследования цитотоксической активности установлено, что экстракты *Linaria vulgaris* Mill., независимо от метода получения и применённых экстрагентов, не проявляют токсического действия в отношении личинок *Artemia salina.* Таким образом, исследуемые экстракты надземной части *Linaria vulgaris* Mill. характеризуются низкой токсичностью и отсутствием цитотоксической активности, что указывает на их потенциальную безопасность и перспективность для дальнейших биологических и фармакологических исследований.

Ключевые слова: *Linaria vulgaris* Mill., лекарственное растение, экстракт, острая токсичность, цитотоксичность.

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