

# Grant project No. AP08052928 “Development of new antiparasitic agents based on natural sesquiterpene lactones and their derivatives”.

The operational reserves of *Achillea nobilis* L., *Artemisia glabella* Kar. et Kir., *Artemisia sieversiana* Willd., *Chartolepis intermedia* Boiss., *Inula helenium* L. on the territory of Central Kazakhstan were determined. At the same time, it was determined that in the identified growing areas, the annual harvesting volume is: for *Achillea nobilis* L. - 136.5 t, *Artemisia glabella* Kar. et Kir. - 27.7 t, *Chartolepis intermedia* Boiss. - 8.5 t, *Inula helenium* L. - 13.7 t.

The quantitative content of sesquiterpene lactones in the raw material of *Achillea nobilis* L. was studied according to the phases of plant vegetation. When extracting raw material of *Achillea nobilis* L. with liquefied carbon dioxide, it was established that the quantitative yield of the sum of extractive substances from *Achillea nobilis* L. is provided at a pressure of 25 MPa, a temperature of 60°C, and process duration of 2 hours. From the aerial part of *Achillea nobilis* L., 10.0 g of estafiatin with the structure 3(4)- $\alpha$ -epoxy-guai-10(14), 11(13)-diene-6,12-olide and 3.3 g of hanfillin, the molecule of which has the structure 3 $\beta$ -hydroxy-3 $\alpha$ , 6 $\beta$ , 7 $\alpha$ (H)-germacra-4 (5), 1(10), 11(13)-triene-6,12-olide were isolated and developed.

For the quantitative extraction of biologically active compounds from the aerial part of *Artemisia sieversiana* Willd. the optimal parameters of supercritical fluid extraction were determined: pressure 25 MPa, temperature 60 °C and process duration 180 min. A technology was developed that allows the isolation of dimeric sesquiterpene lactone absintin.

The quantitative content of sesquiterpene lactones argolide and dihydroargolide in the carbon dioxide extract of the aerial part of *Artemisia glabella* Kar. et Kir., collected during the budding period was determined. The optimal parameter of supercritical carbon dioxide extraction for the isolation and production of sesquiterpene lactones argolide and dihydroargolide is a pressure of 16 MPa, a temperature of 60°C, and process duration of 180 min. From the aerial part of *Artemisia glabella* Kar. et Kir., 10.0 g of argolide, the molecule of which has the structure of 3-oxo-4,7 $\alpha$ ,6 $\beta$ (H)-germacr-1(10), 11(13)-diene-6,12-olide and 2.2 g of dihydroargolide having the structure 3-oxo-4,7 $\alpha$ ,6 $\beta$ (H)-germacr-1(10)-ene-6,12-olide were isolated and developed.

Ultrasonic extraction of *Chartolepis intermedia* Boiss. was carried out and the optimal parameters to ensure the quantitative extraction of grossheimin and cynaropicrin from raw materials were determined. It was established that the quantitative extraction of sesquiterpene lactone grossheimin from *Chartolepis intermedia* Boiss. is provided by fourfold extraction with ethyl acetate at a temperature of 80°C for 120 minutes.

From the aerial part of *Chartolepis intermedia* Boiss., 15 g of grossheimin and 29.4 g of the accompanying sesquiterpene lactone cynaropicrin were isolated and produced. According to data of IR-, PMR-, <sup>13</sup>C NMR-spectroscopy, the structure of 3-oxo-8 $\alpha$ -hydroxy-6 $\beta$ ,7 $\alpha$ (H)-guai-10(14),11(13)-diene-6,12-olide was proposed for grossheimin, and (3 $\beta$ -hydroxy-8-(4-hydroxymethacryloyl)-1,5,7 $\alpha$ ,8 $\beta$ (H)-guai-4(15),10(14),11(13)-triene-6,12-olide for cynaropicrin.

For the complete extraction of the sum of sesquiterpene lactones from the roots of *Inula helenium* L., the optimal parameters of supercritical fluid extraction were determined: pressure 30 MPa, temperature 60°C, process duration 210 min. At the same time, 78 g of the sum of the sesquiterpene lactones alantolactone (5,7,8 $\alpha$ (H)-eudesm-5(6),11(13)-diene-8,12-olide) and isoalantolactone (5,7,8 $\alpha$ (H)-eudesm-5(6),11(13)-diene-8,12-olide) were isolated and produced.

9 sesquiterpene lactones were isolated and produced for chemical modification and study for antiparasitic activity. The structure of the isolated compounds was established by IR-, UV-, <sup>1</sup>H and <sup>13</sup>C NMR, 2D <sup>1</sup>H-<sup>1</sup>H and <sup>13</sup>C-<sup>1</sup>H NMR-spectroscopy.

During the reporting period, according to the results of experiments, an article was published in the journal recommended by CCES:  
- Kishkentayeva A.S., Mantler S.N., Zhakanov M.M., Adekenov S.M. Biologically active substances from *Achillea nobilis* L. // Bulletin of the Karaganda University – Chemistry series. – 2020. – Vol.4, No. 100. – P.52-59. DOI 10/31489/2020Ch4/52-59.



## Grant project No. AP08052389 “Development of a new neurotropic drug: pharmacological and clinical studies”.

The extraction process of *Peganum harmala* L. roots, isolation and purification of alkaloid harmine were optimized. Pilot production of the substance of harmine hydrochloride and its dosage form for preclinical and clinical studies was organized.

Based on the experiments carried out, it was revealed that the mechanism of antiparkinsonian action of harmine hydrochloride is realized at the level of synaptic neurotransmission of monoamines (dopamine, serotonin, etc.).

During the reporting period, based on the results of the studies, 2 articles were published in the domestic edition recommended by CCES:

- Doskaliev A.Zh., Zhanymkhanova P.Zh., Epifantseva E.V., Abdrakhmanova M.G., Adekenov S.M. The influence of harmine hydrochloride on the motor and psycho-emotional state in experimental parkinsonism // Neurosurgery and Neurology of Kazakhstan. – 2020. - №3 (60). – P. 46-55. IF according to Kazakhstan citation base 0.036.

- Epifantseva E.V., Romanova M.A., Seidakhmetova R.B., Adekenov S.M., Pozdnyakova E.V., Kitova T.T. The effect of harmine hydrochloride on behavioral responses in rats with a model of stress-induced disorder // Medicine and Ecology. – 2020. - №1. – P. 77-87.

The specific antiparkinsonian activity and mechanism of action of harmine hydrochloride were studied. It was established that the effect of harmine hydrochloride at a dose of 2.5 mg/kg under conditions of haloperidol catalepsy is comparable in its effectiveness with the effectiveness of the drug Levodopa at a dose of 50 mg/kg.

The ability of harmine hydrochloride to reduce the severity of catalepsy caused by the dopamine D<sub>2</sub> receptor antagonist haloperidol indicates the dopamine-positive properties of harmine hydrochloride, which is confirmed by studying the mechanism of antiparkinsonian action of harmine hydrochloride.



## Grant project No. AP08052060 “Development of new medical-cosmetic and detergent agents based on plant substances”.

<p>By the methods of hydrodistillation and microwave extraction, essential oils were isolated from the raw materials of <i>Hypericum perforatum</i> L. The component composition of the isolated essential oils was studied by chromat-mass spectrometry. At the same time, trans-caryophyllene, trans-<math>\beta</math>-farnesene, valensene, <math>\Delta</math>-cadinene were identified as the main components.</p>	<p>Essential oils were isolated from raw materials of <i>Matricaria chamomilla</i> L. by the methods hydrodistillation and microwave extraction. The composition of the obtained essential oils was studied by chromat-mass spectrometry, the main components were bisabolol oxide A, chamazulene, trans-<math>\beta</math>-farnesene.</p>	<p>To develop the composition of new medical-cosmetic and detergent agents, 250 g of essential oil from <i>Matricaria chamomilla</i> L. raw materials were produced on the UEM-E industrial unit..</p>
<p>The sums of extractive substances were isolated by the methods of carbon dioxide and alcohol extraction from the raw materials of <i>Hypericum perforatum</i> L. under different modes. According to the results of HPLC analysis, the quantitative content of rutin in the alcoholic extract of <i>Hypericum perforatum</i> L. exceeds 10 times, and the content of quercetin is 2.5 times higher than in the CO<sub>2</sub> extract. Pilot batches of an alcoholic extract from raw materials of <i>Hypericum perforatum</i> L. in the amount of 250 g were prepared for the development of a composition of new medical-cosmetic and detergent agents. Laboratory regulations LR-40761819-09-20 were developed for the production of alcoholic extract from the raw materials of <i>Hypericum perforatum</i> L.</p>	<p>Carbon dioxide extraction of <i>Matricaria chamomilla</i> L. raw materials was carried out under different modes and samples of carbon dioxide extracts were obtained. The component composition of the obtained carbon dioxide extracts was studied by chromat-mass spectrometry, while the main components were identified as 2-(2,4-hexadiynylidene)-1,6-dioxospiro[4.4]non-3-ene, bisabolol oxide A, bisabolol oxide B. Laboratory regulations were developed for the isolation of essential oil from raw materials of <i>Matricaria chamomilla</i> L. (LR-40761819-08-20).</p>	<p>During the reporting period, according to the results of experiments, an article was published in the journal recommended by CCES: Makubayeva A., Adekenova Aigerim S., Rakhataeva A., Mamyrkhan Kh. Therapeutic and cosmetic agents based on biologically active substances of <i>Matricaria chamomilla</i> L. and <i>Hypericum perforatum</i> L. // Chemical Journal of Kazakhstan. – 2020. – № 4. – P. 105-112.</p>



## Grant project No. AP05130956 “Modeling and optimization of the technology of original drugs”.

<p>Mathematical models were developed - regression equations for the dependence of the yield of the sum of extractive substances from the raw materials of <i>Artemisia glabella</i> Kar. Et Kir. and buds of <i>Populus balsamifera</i> L.</p>	<p>The process of CO<sub>2</sub>-extraction of raw materials of <i>Populus balsamifera</i> L. buds was optimized, the extraction mode was determined, which ensures the quantitative extraction of essential oil and pinostrobin (pressure 30 MPa, temperature 70 °C, extraction duration 180 minutes) with a yield in terms of air-dry raw materials 8.2 and 2.99% respectively.</p>	<p>Pilot batches of CO<sub>2</sub>-extracts from <i>Artemisia glabella</i> Kar. Et Kir. and buds of <i>Populus balsamifera</i> L. were obtained.</p>
<p>On the basis of the calculated regression equations, the process of CO<sub>2</sub>-extraction of raw materials of <i>Artemisia glabella</i> Kar. et Kir. was optimized. An extraction mode has been determined that ensures the quantitative extraction of arglabin (pressure 22 MPa, temperature 65 °C, extraction duration 180 minutes) and argolide (pressure 30 MPa, temperature 65 °C, extraction duration 180 minutes) with a yield in terms of air-dry raw materials 1.35% and 0.013% respectively.</p>	<p>The regulations for processing buds of <i>Populus balsamifera</i> L. were developed, including the isolation of CO<sub>2</sub>-extract, treatment with nephras, extraction of essential oil components and the sum of flavonoids. The regulations provide for the complex extraction of a wide range of substances contained in this type of raw materials - essential oil with an antibacterial effect, pinostrobin is the basis of a new hepatoprotective agent.</p>	<p>During the reporting period, according to the results of experiments, an article was published in the journal recommended by CCES: Khabarov I.A., Zhurov V.V., Zhabayeva A.N., Adekenov S.M. Modeling the extraction process of medicinal raw materials // Bulletin of the Karaganda University. Chemistry series. – 2020. – №4. – P. 135-144. DOI 10/31489/2020Ch4/135-144.</p>

