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REPRESENTATIVES OF MOTHERWORT GENUS (*LEONURUS* SPP.): ASPECTS OF PHARMACOGNOSTIC FEATURES AND RELEVANCE OF NEW SPECIES APPLICATION

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Abstract: The review deals with analysis and classification of literature data on pharmacognostic study (botanical characteristics, geographical distribution, chemical composition and use in medicine) of species of Motherwort genus (*Leonurus* L.*)*. The review unveils opportunities for comprehensive study and development of approaches to the standardization of raw materials of Turkistan motherwort (*L. turkestanicus* V.I. Krecz. & Kuprian). That will allow to expand the range of sources of herbal remedies raw materials in the framework of realization of the state program for import substitution.

Keywords: Turkistan motherwort, pharmacopoeia species, phytochemical analysis, standardization, herbal remedies, import substitution

Experience of many generations has proved that the plant world is an inexhaustible source of medicines. Today a revival of interest in phytotherapy and an increase in the use of herbal medicine in the complex treatment of different clinical groups are taking place. In our age of synthetic medicines there is a need for herbal remedies to which people evolutionarily got adapted, with good tolerability, a minimum of side effects, and a wide range of use of non-xenobiotics. Therefore, expanding of the range of plant raw materials sources for herbal remedies is one of the priorities of pharmaceutical study.

This problem is particularly relevant in the light of modern national trends of import substitution in major industries, a pharmaceutical one included, which is aimed at a fuller use of domestic raw materials. One of the ways of solving this problem can be a comprehensive study of medicinal plant species of native flora, which is widespread and secured with a resource base. Standardization and introduction to industrial processing of perspective species of Kazakhstani flora will allow, on the one hand, solving the problem of import substitution; on the other hand, making production much cheaper.

In this regard objects of interest are officinal (pharmacopoeia) species of medicinal plants, whose raw material reserves in Kazakhstan are limited (1-4). Taking into account the variety of Kazakhstani flora, which is characterized by a large number of endemic species, as well as the presence of a geographically confined populations of pharmacopoeia plants, their systematic study, standardization and development of monographs on domestic species, followed by an introduction to the pharmacopoeia is promising.

From this point of view attention is drawn to the motherwort genus *(Leonurus* L.*)* of the Lamiaceae family (*Lamiaceae* Lindl.), whose two species – motherwort cardiaca (*Leonurus cardiaca* L.). and five lobe motherwort *(Leonurus quinquelobatus* Gilib.*)* – are officinal, with rich experience of application in the scientific medicine, and are included in the majority of the world's pharmacopoeias (5-11).

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Historical aspects and ethnopharmacological features of the application of motherwort

Motherwort is a medicinal plant well-known since ancient times. In Tibet, motherwort herb was used for medical purposes about two thousand years ago (12). In the Middle Ages, it was used for lung and heart diseases, as a sedative preparation The herb was cultivated under windows, by university gardens and monasteries (13). In Russia, the first mention of the use of motherwort as a means of facilitating coughing and palpitations dates back to the year of 1485 (14). After studies done by V.V. Zverev and N.V. Vershinin (Tomsk Medical Institute) in 1931, motherwort was included in the USSR State pharmacopoeia VIII (15, 16) and became an officinal medicinal herb.

In Europe, motherwort has been known since Theophrastus and Dioscorides. Paracelsus and Fuchs recommended motherwort infusion for tachycardia and convulsions, broths – for epilepsy and as a diuretic preparation (12). In ancient Greece, this plant was given to pregnant women to relieve their anxiety (13). Drugs of motherwort are widely used as a means of regulating the functional state of the central nervous and cardiovascular systems. In Poland, it is recommended for nervousness, angina, heart diseases, myocarditis, hysteria, respiratory diseases (17). In Bulgarian medicine, motherwort cardiaca is used as an anticonvulsant and a sedative with nervousness, especially in menopause, painful menstruation, and anemia and as a diuretic (18); in Indian medicine – as a stomachic and sudorific. In Czech Republic, Slovakia, Hungary, Romania, motherwort is prescribed for heart rate and pain in the heart; in England, it is recommended for hysteria, neuralgia and heart weakness (19). In Chinese medicine, motherwort is used as a styptic, in case of uterine bleeding and endometritis, as hypotensive, improving blood circulation and stimulant remedy. A decoction of the plant reduces the effect of adrenaline on vessels. Externally herbs and seeds are applied for certain diseases of skin (20). In the late 50-ies of the last century, a Bulgarian team of pharmacologists studied pharmacological properties of motherwort cardiaca (*Leonurus cardiaca* L.), growing on the territory of Bulgaria and proved its anticonvulsant activity and efficacy in the treatment of epilepsy (21).

Phylogenetic and botanical characteristics of Motherwort genus

Motherwort genus includes 24 species, which are divided into 3 sections and 5 subsections (22). Some botanists systematize some species of motherwort as subspecies of the main species, which have a specific geographical confinement (23).

Scientific medicine uses motherwort herb as a medicinal plant raw material. It is represented by whole or chopped dried tops (40 cm) of motherwort cardiaca (*Leonurus cardiaca* L.*)*, collected at the beginning of flowering. Pharmacopoeias of the Commonwealth of Independent States (CIS) countries (in the national part) also allow procurement of raw materials of five lobe (shaggy) motherwort besides motherwort cardiaca (*Leonurus quinquelobatus* Gilib. ex Usteri, or L. *villosus* Desf. ex Spreng.) (7-9). Since the end of the XX century this species has been recognized by most of reputable sources on botanical taxonomy, but earlier this plant was often considered as a subspecies of motherwort cardiaca and its correct name was thought to be *Leonurus cardiaca* subsp. *villosus* Desf. ex Spreng. Hyl. The name *Leonurus quinquelobatus* Gilib. was regarded as synonymous with the name *Leonurus cardiaca* L. (23-26).

Officinal species of motherwort cardiac and five lobe motherwort are perennial more or less pubescent plants having height of 50-200 cm. Stems are mostly branched, four-sided. Leaves are opposite, petiolate, dark green, softly hairy, coarsely crenate-serrate. Five lobe motherwort has rounded or ovate cordate lower leaves, 6-12 cm long, quinquepartite almost to the middle-palmate, densely pubescent; in the middle part of the stem leaves are oblong elliptical or lanceolate with a tapered base, tripartite or three-lobed; terminal leaves are simple, solid and narrow. Motherwort cardiaca leaves are the same, only sparsely pubescent (15). Flowers are in false whorls, located in the axils of upper leaves and forming spike thyrse at the ends of the stems. The corolla is two-lipped, pink, with three-blade lower lip. The calyx is tubular-campanulate, with 5 awl-shaped teeth. The fruit is cenobia, remaining in the cup. It should be noted that motherwort's cardiac stem is pubescent only along the edges and the cup is almost naked, while five lobe motherwort's stem is densely and gently pubescent along the length and has a hairy calyx. Blooming is in June-July. The fruit are ripe in July and August (26, 27). Medicinal herbs are blooming tops up to 40 cm, collected at the beginning of flowering; thickness of the stems must not exceed 4 mm. The fruit cup of late collected herb becomes much barbed and tough due to lignification, which significantly degrades the quality of the medicinal herbs. The smell of the raw material is weak, peculiar, the taste is bitter (15, 26).

The area and phytocenotic peculiarities of growth

Motherwort cardiaca is widespread in the Mediterranean, Atlantic, Central and Eastern Europe, Scandinavia, Minor Asia, Mongolia, China, as an invasive plant - in North America. This is a European species, increasingly penetrating into Siberia as a weed (23). However, according to the literature data (28), the birthplace of the plant is Asia; and Europe is not native for motherwort cardiaca, since this species naturalized here during the last millennium. As healing properties of the plant has been known since ancient times, it was grown on purpose close to housing. In the Middle Ages motherwort plantings were common to each monastery and university botanical garden.

It is widely distributed almost throughout the whole European part of the CIS (except for the northern, semi-desert and desert areas), in the south of Western Siberia, western and eastern Transcaucasia. To the east its area is constantly narrowing, entering only as a narrow tongue the southern regions of Siberia and the north of Kazakhstan. Tomsk is the eastern limit of the spread of motherwort cardiaca, except for some of its adventitious locations in the south of Krasnoyarsk region and the Primorye. In the south the motherwort spread is limited to central Kazakhstan. It is ubiquitous in the Ukraine, the Crimea and Krasnodar region (26, 27). Five lobe motherwort is a Euro-Caucasian species; areas of its general distribution are Europe, the Caucasus, Western and Eastern Siberia, and Western Asia. In Central Russia it is found in all areas (25).

At the moment motherwort cardiaca is characteristic of eco-phytocenotic conditions of Baltics and Belarus, and five lobe motherwort is more common in the European part of Russia, in the Crimea, the Caucasus and Western Siberia (15)].

Biologically active substances of Motherwort genus

The chemical composition of the official species of motherwort has been studied well enough. The main group of biologically active substances (BAS) of the aerial parts - flavonoids: O-glycosides of quercetin (including rutin (Fig. 1), quercetrin (Fig. 2), isoquercetrin (Fig. 3), hyperoside (Fig. 4)), kempferol, as well apigenin (genkwanin (Fig. 5) and quinqueloside (Fig. 6)) (27, 29, 30). It is also established the presence of alkaloids ((-)-stachydrin (Fig. 7) and (Fig. 8)) in an amount of 0.5% (31, 32). N-9 iridoid glycosides (ayugol (leonuride) (Fig. 9), ayugoside (Fig. 10), galiridoside (Fig. 11), garpagide (Fig. 12), acetate of garpagide (Fig. 13) and others (33), cycloleonuripeptides (Fig. 14) (A, B, C and D) (34), diterpenes (furanolabdanetype, including clerodane derivatives such as marrubiin (Fig. 15)) (35, 36), triterpenes (ursolic (Fig. 18) and oleanolic (Fig. 19) acids) (17, 37), phenyl-carbonic acid (chlorogenic acid (Fig. 20) and others) and their derivatives – coffeoyl-pheniletanoids glycosides (verbascoside (Fig. 21), lavandulifolioside (Fig. 22)) (38) are present. In the literature (39, 40) it is reported about the identification of new diterpenes labdane type (leocardine (Fig. 16), leosibiricine (Fig. 17)) in the leaves of motherwort. There were found tannins (about 2%) and traces of essential oils (about 0.03%), where according to different authors (41, 42) from 41 to 62 compounds were identified, with the prevalence of epi-cedrol, α-humulene, dehydro-1,8-cineole, germakrenandspatulenol. Chinese scientists have extracted from herb Japanese motherwort coumarins: bergapten (Fig. 23), xanthotoxin (Fig. 24), isopimpinellin (Fig. 25) and others (43). Japanese scientists Tahmouzi and Ghodsi have extracted polysaccharides (9.5%) from the leaves of motherwort cardiaca (44).

Standardization of the herb motherwort in accordance with the requirements of the European Pharmacopoeia (and harmonized with it pharmacopoeias of the CIS) is recommended to be carried out basing on the total amount of flavonoids in recalculation on hyperoside (its content must be not less than 0.2%) (6-9). The State Pharmacopoeia of the Republic of Belarus also contains a monograph on the leaves of motherwort (*Leonuri folia*), whose standardization is recommended to be conducted on the total amount of iridoids in recalculation on of garpagid acetate (not less than 0.4%) (8).

Pharmacological properties of motherwort and fields of application in medicine

Through a series of clinical experiments a positive effect on the cardiovascular system was found, which manifests itself in the hypotensive, antispasmodic and vasoconstrictor effects (35, 45, 46) and is associated with the presence of lavandulifolioside. The mechanism of this effect is associated with a negative chronotropic effect of phenol carbonic acids derivatives and their influence on the extension of the PQ, QT and QRS intervals and reduction in blood pressure (38). Thus, in the experiment the aqueous extract largely ($p < 0.05$) inhibited the relaxation of aortic with stored endothelium caused by acetylcholine.

Traditionally motherwort herb has been used for some types of heart ailments, tachycardia syn-

FLAVONOIDS

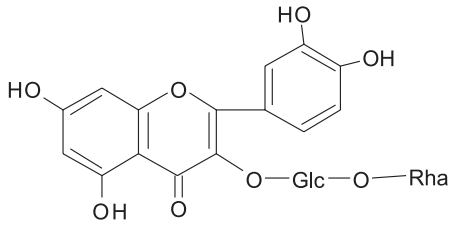


Figure 1

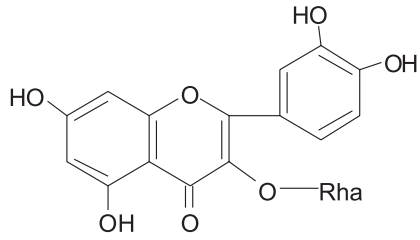
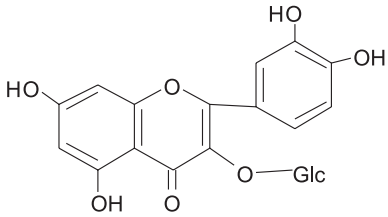


Figure 2



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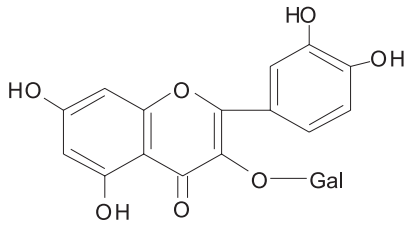

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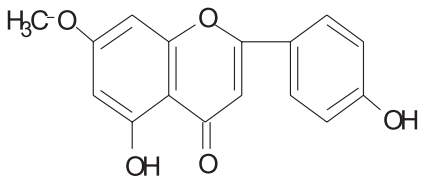

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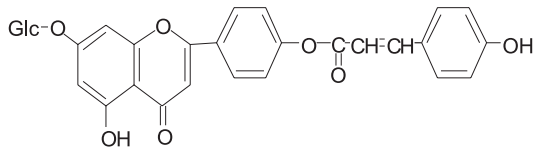
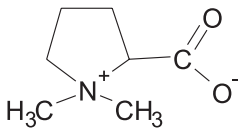


Figure 6

ALKALOIDS



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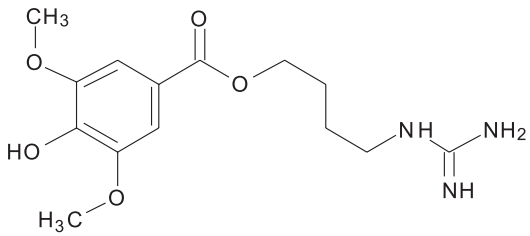
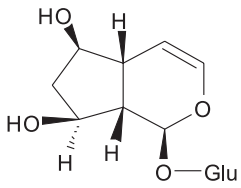


Figure 8

IRIDOID GLYCOSIDES



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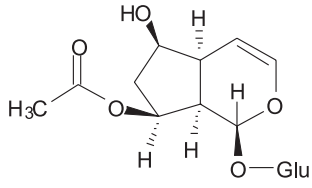

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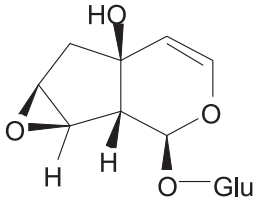

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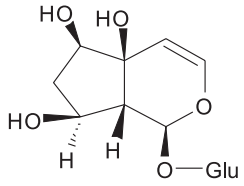

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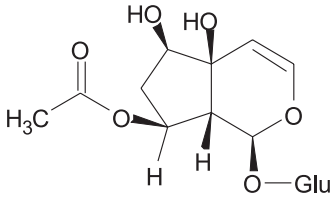


Figure 13

CYCLOLEONURIPEPTIDES (A, B, C and D)

[———X—CHR_1—CO—(X—CHR_1—CO)$_n$—X—CHR_1—CO———]
X = N or NH; n = 0, 3 – 10; R_1 = side chain of amino acids
Cyclo–(*L*-Pro^2-*L*-Pro^3-*L*-Tyr^1-*L*-Tyr^2-*L*-Thr^1-*L*-Pro^4–*L*-Ala-Gly-*L*-Pro^1-*L*-Thr^2-*L*-Gln-*L*-Tyr^3)
Figure 14

DITERPENE COMPOUNDS

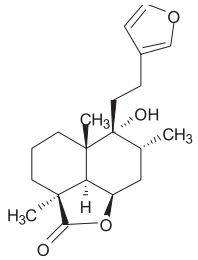
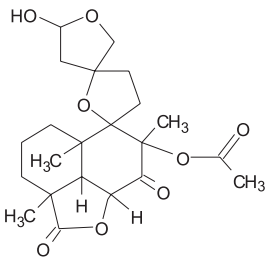


Figure 15



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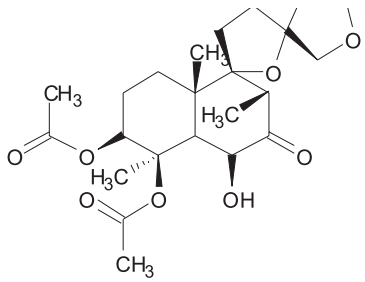
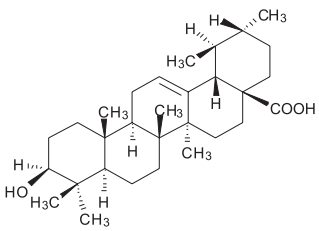


Figure 17

TRITERPENE COMPOUNDS



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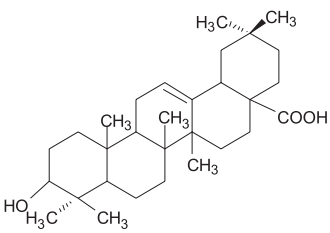


Figure 19

PHENOL CARBONIC ACIDS

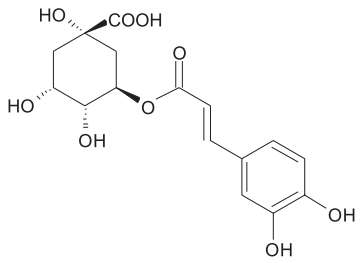


Figure 20

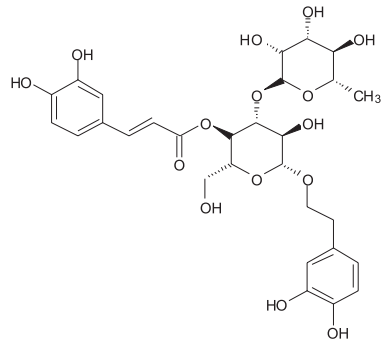


Figure 21

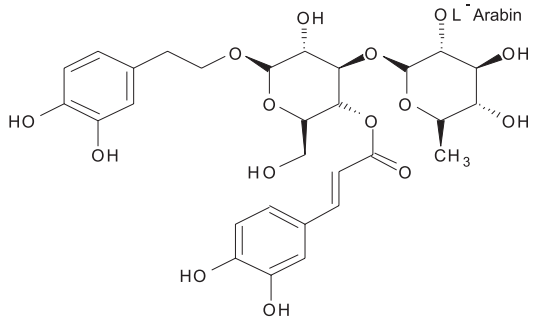
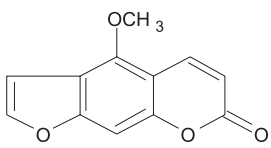


Figure 22

COUMARINS



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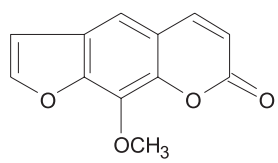

Figure 24

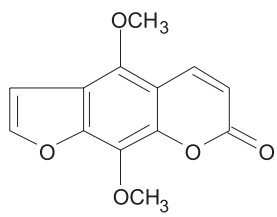

Figure 25

drome, physical stress, and also, in particular, in case of heart symptoms of neurotic character (47-49). Literature (50-52) gives evidences of antioxidant and cardioprotective effect of the extract of motherwort herb on the ischemic myocardium, which is associated with the ability of phenolic compounds (flavonoids in particular) to inhibit the mechanisms of free radical reactions. Thus, in the literature (29) it is stated that these compounds have an effect on mitochondrial respiration, selectively maintaining the activity of superoxide dismutase and glutathione peroxidase, and also reducing the formation of malondialdehyde and effectively inhibit the formation of free radicals in the mitochondria of the cardiac muscle, thereby providing antioxidant and cardioprotective effect. A special role in the cardioprotective

mechanism of action is played by diterpenes, marrubiin in particular, which is associated with the inhibition of platelet aggregation, hypercoagulability and inflammation in the ischemic area at an early stage of myocardial infarction (35, 36).

Motherwort herb exhibits *in vitro* cytotoxicity against lymphocytic leukemia, cell cultures of human lung carcinoma, colon tumor, and breast tumor (53). Photosensitizing and photoprotective effect of extracts of motherwort has been proved. It is associated with the presence of substances capable of absorbing light in UV- and visible spectral range, coumarin in particular (54).

In the literature (55) anti-inflammatory activity of the extract of motherwort and its positive effect on the course of mastitis are marked. Anti-inflammatory activity of motherwort is associated with the presence of ursolic acid and other terpenes, which in the experiment had an inhibitory effect on the production of superoxide in the free cell system by engagement of the xanthine/xanthine oxidase (56). Motherwort is also used for diseases of the female reproductive system (57-61), which is caused by the presence of leonurin, which in the experiment stimulates uterine contractions, and terpene compounds, that exhibit estrogenic activity. Motherwort herb in the experiment had a diuretic effect and is recommended for kidney stones (15).

Preparations based on motherwort occupy a significant assortment niche in the group of pharmacotherapeutic agents for the treatment and prevention of pathologies of the circulatory and the nervous systems (62-64). Formulations presented in tinctures and extracts are available in capsules and tablets. Dry motherwort extracts are a part of distinct complex preparations which are used in the combination therapy of cardiovascular diseases and disorders of the nervous system (65, 66).

Motherwort species of Kazakhstani flora

Flora of Kazakhstan has about 6,000 species of vascular plants, which belong to 1067 genera and 159 families (1, 2). Officinal medicine uses only 230 species of the varieties of Kazakhstani flora, 92 species are included in the State Register of Medicinal Products of the Republic of Kazakhstan (62). Representatives of the local flora have been very poorly studied in pharmacognostic aspect: for example, phytochemical studies have been conducted only for 20 species out of nearly 800 endemics of Kazakhstan, and only 0.02% of the species with a specific geographical confinement belong to medicines (3), while the medicinal flora is the fourth part (26%) of all vascular plants in Kazakhstan (67).

One of the largest families in the number of Kazakhstani endemic species is the family of *Lamiaceae* (30 genera, 77 endemic species), to which *Leonurus* genus belongs (67).

Leonurus L. genus in the flora of Kazakhstan is represented by 4 species: bluish grey motherwort (*Leonurus glaucescens* Bunge.), grey motherwort (*Leonurus incanus* V. Krecz. et Kuprian.), motherwort pancerioides (*Leonurus pancerioides* M. Pop.) and Turkestan motherwort (*Leonurus turkestanicus* V. Krecz. et Kuprian.), of which *L. incanus* is an endemic one (1, 68). According to the base of The International Plant Names Index (69) some taxonomists consider Turkestan motherwort to be a subspecies of motherwort cardiaca (*Leonurus caradiaca* L. subsp. *turkestanicus* (V. Krecz. et Kuprian.) Rech. f.).

Pharmacopeia medicinal plant raw materials of motherwort in Kazakhstan are *Leonurus cardiaca* and *Leonurus quinquelobatus* (national part) (7) grown in culture conditions in the territory of the Republic. Related wild species (*Leonurus glaucescens*, *Leonurus incanus, Leonurus pancerioides* and *Leonurus turkestanicus*) may be added to the list of pharmacopoeia species after complex phytochemical research and standardization. So, Kazakhstan lacks natural resources of pharmacopoeia *Leonurus species* and the need for their raw materials is provided by the cultivation of these species in the culture.

However, the Kazakhstani form of *Leonurus turkestanicus* used in folk medicine can be used today similarly to the officinal species of *Leonurus quinquelobatus* (4). Given that the demand for drugs on the basis of motherwort is stable (the State Register of medicines in Kazakhstan included 13 drugs), it is appropriate to extend the range of sources of raw materials of herbal remedies by adding native species of plants.

Annotated list of medicinal plants of Kazakhstan includes two species of motherwort: bluish grey motherwort (*Leonurus glaucescens* Bunge.) is a biennial, which is found everywhere, and Turkestan motherwort (*Leonurus turkestanicus* V. Krecz. et Kuprian.) (67). *Leonurus turkestanicus* was studied by V.I. Krechetovich and L.A. Komarova in Komarov Botanical Institute (1949). It is a perennial herb of 70-200 cm tall; its woody rootstock has erect or ascending from the base tetrahedral stems, bare or short-haired with compressed hairs; leaves are naked, on short petioles, rounded or ovoid in outline, with direct or little heart-shaped base, 6-10 cm long and 6 cm wide, 2/3 of the leaves surface is dissected into broad wedge-shaped blades,

incised in their turn in broadly wedge-shaped lobes, the most upper ones shallow incised in 3-lanceolate lobes. The inflorescence is long and sparse; bracts are subulate pointed, short-haired, equal to or longer than calyx tube; the calyx is 7-9 mm long, bent, short and pressed hairy, with subulate sharp teeth, triangular in the base. The corolla is pale pink, 1-1.2 cm long, the upper lip is white-tomentose pubescent, ovoid, tapering to the base, solid; the lower one is 3-lobed, shortly hairy inside, with a wider middle lobe. Stamens are with hairy filaments and bicameral divergent anthers; the upper threads are straight, parallel; the lower ones are, longer, slightly bent. Nuts are 2-2.5 mm long, 3 sided with oblique stub, pubescent tip. Flowering is in July, fruiting is in September (4, 68).

It grows in the forest belt of mountains, in shady places along the river banks, in bushes, on the cliffs. Turkestan motherwort is found in the mountains from the Jungar Alatau to the Western Tien Shan.

The main reserves are concentrated in the Jungar, Zailiyskiy, Kung, Ketmen, Terskey Alatau. In 80-s of the last century commodity stocks Turkestan motherwort in Semipalatinsk (hr. Tarbagatai West) and Zhambyl regions (Kyrgyz Alatau) were studied. They amounted to 1.02 tons and 4.52 tons of dry raw materials, respectively (70-72).

Analysis of available literature showed that phytochemicals comprehensive study materials Turkestan motherwort has not previously been carried out. Literature data, which are not systemic, tell about the presence of alkaloids (stahydrin), flavonoids, triterpenoids, steroids, organic and phenol carbonic acids, tannins, essential and fatty oils in *Leonurus turkestanicus*. A recent study of Turkestan motherwort extract has shown presence of such compounds as genkwanin and iridoid glycosides (67).

Traditionally, since ancient times folk medicine has used a decoction of the aerial part of Turkestan motherwort for the treatment of diseases of the heart, stomach and nervous system (73). Tea and infusion of Turkestan motherwort were used to treat disorders of the nervous system, hypertension, epilepsy, tachycardia, gastrointestinal diseases, as a sleep aid, diaphoretic, laxative and anti-inflammatory agent (74).

Clinical studies have shown that the infusion has sedative effect which exceeds 2 times that one of valerian tincture, and also lowers blood pressure, increases uterine contractions (73). It is considered to be a substitute for the pharmaceutical species of five lobe motherwort as a sedative, hypotensive and antibacterial agent (75). Alkaloid stahydrin, extracted from Turkestan motherwort herb, showed in the experiment a protective effect in the case of ischemic myocardial injury (76, 77).

DISCUSSION AND CONCLUSIONS

After a critical analysis and synthesis of the literature data on the pharmacognostic characteristics of Motherwort species and analyzing the need for raw materials plants of the genus, confinement of some species to certain ecological and geographical features of growth, we can draw the following conclusions and formulate a number of problems for further research:

Pharmacopoeia species of motherwort cardiaca (*Leonurus cardiacŕ* L.) and five lobe motherwort (*Leonurus quinquelobatus* Gilib.) do not grow in the flora of Kazakhstan, therefore they are cultivated. It should be noted that at the moment industrial plantations cannot meet the requirements in herbal remedies, so motherwort cardiaca is a raw material imported from Russia, Belarus, and Bulgaria.

Of 13 medicines on the basis of motherwort raw materials registered on the territory of Kazakhstan 6 items are imported means. That is a prerequisite for studying and standardization of raw materials of native flora species, expanding the range of raw material sources and addressing the issue of import substitution of medicines.

System comprehensive pharmacognostic research and development of approaches to standardization of raw materials of Turkestan motherwort (*L. turkestanicus* V. Krecz. et Kuprian), widespread in the flora of Kazakhstan and having a source of raw materials, opens up prospects for development of new herbal remedies based on it and allows to adjust the national part of the monograph "Motherwort herb" in the part of expanding the range of pharmacopoeia raw materials.

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