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MEMBERS OF THE FAMILY *LAMIACEAE* LINDL. AS SOURCES OF MEDICINAL PLANT RAW MATERIALS TO OBTAIN NEUROTROPIC DRUGS

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The aim of this work is to review and analyze the data published in the modern scientific literature obtained in pharmacological, pharmacognostic and pharmacotechnological studies of various types of raw materials obtained from members of the family *Lamiaceae* L., which were sources of biologically active substances, pharmaceutical substances, total extracts and the drugs – with a neurotropic activity.

Materials and methods. For the review, we used the information of scientific literature from open and accessible sources of the last twenty years, located in the scientific and technical libraries of institutions, as well as in electronic databases: Elibrary, PubMed, Scopus, Cyberleninka, GoogleAcademy, J-Stage. The search inquiries were: the species of the family *Lamiaceae* (Russian and Latin), the samples of medicinal plant materials based on them as well as the names of the drugs and biologically active substances obtained from these raw materials.

Results. When working with the sources of scientific information, the main attention was paid to pharmacologic tests performed during the studies on laboratory animals and proving the presence of neurotropic activity in the studied objects – essential oils and extracts from plant raw materials: aqueous, aqueous alcoholic, and methanol ones. It has been established that the potential of the therapeutic and preventive application of pharmaceutical substances and drugs based on the medicinal plant materials obtained from 30 genera members of the Lamiaceae family, remains unrealized despite the close attention of various researchers.

Conclusion. This review comprised 71 species from 30 genera. Despite the significant level of the previous study presented in the analysis of this publication, an enormous potential of this family's species remains unexplored. In the future, they can be of both – pharmacognostic and practical interest, in particular, in creation of new medicinal preparations of the neurotropic action based on them.

Keywords: Literature review, Lamiaceae L., herbal medicine, medicinal plant materials, extract, herbal formulation фитопрепарат, medicinal preparation, pharmacognosy, pharmacology, stress, neurotropic activity, anxiolytic effect, sedative action, antidepressant action, GABA-α-receptors, benzodiazepine receptors

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ПРЕДСТАВИТЕЛИ СЕМЕЙСТВА *LAMIACEAE* LINDL. КАК ИСТОЧНИКИ ЛЕКАРСТВЕННОГО РАСТИТЕЛЬНОГО СЫРЬЯ ДЛЯ ПОЛУЧЕНИЯ НЕЙРОТРОПНЫХ СРЕДСТВ (ОБЗОР)

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Цель работы – обзор и анализ опубликованных в современной научной литературе данных, полученных в ходе фармакологических, фармакогностических и фармако-технологических исследований образцов лекарственного растительного сырья (ЛРС), заготавливаемого от различных представителей сем. *Lamiaceae* Lindl. (яснотковые), из которых получены биологически активные вещества (БАВ), фармацевтические субстанции, суммарные извлечения и лекарственные препараты, обладающие нейротропной активностью.

Материалы и методы. Для обзора использовали сведения научной литературы из открытых и доступных источников последних двадцати лет, размещенных в научно-технических библиотеках учреждений, а также в электронных базах данных: *Elibrary*, *PubMed*, *Scopus*, Киберленинка, *Google*-академия, *J-stage*. Поисковые запросы – названия видов растений сем. *Lamiaceae* (русские и латинские), заготавливаемых от них образцов ЛРС, а также наименования фармацевтических субстанций, лекарственных препаратов и БАВ.

Результаты. При работе с источниками научной информации основное внимание уделено фармакологическим тестам, проведенным в ходе специализированных исследований на лабораторных животных, подтверждающим наличие нейротропной активности у исследуемых объектов – эфирных масел и извлечений из ЛРС (водных, водно-спиртовых, метанольных). Установлено, что потенциал лечебного и лечебно-профилактического применения фармацевтических субстанций и лекарственных препаратов, получаемых из ЛРС представителей 30 родов семейства *Lamiaceae*, остается нереализованным, несмотря на пристальное внимание исследователей.

Заключение. Данный обзор охватил 71 вид из 30 родов. При значительном уровне изученности, который можно отметить при анализе данной публикации, остается не затронутым огромный пласт ресурсных видов данного семейства. В дальнейшем они могут представлять фармакогностический интерес и иметь практическое использование, в частности, для создания на их основе новых лекарственных препаратов нейротропного действия.

Ключевые слова: обзор литературы, яснотковые, *Lamiaceae,* фитотерапия, лекарственное растительное сырье (ЛРС), экстракт, фитопрепарат, лекарственный препарат, фармакогнозия, фармакология, стресс, нейротропная активность, анксиолитический эффект, седативное действие, антидепрессивное действие, ГАМК-α-рецепторы, бензодиазепиновые рецепторы

INTRODUCTION

In the modern world, in conditions of excessive intense and inadequately prolonged stressful effects of various external factors, a human body needs therapeutic and preventive agents that have a protective neurotropic, or neuroprotective, effect. Stress, especially chronic, is justifiably considered one of the main factors causing the development of a lot of pathologies [1–3]. Psychoemotional stress and constant overwork lead to the appearance of various symptoms, urging a human being to seek treatment. In the stressful situation, adaptive changes are observed on the physiological, mental and behavioral levels. In particular, a Canadian scientist Hans Selye described a triad of changes characteristic for ~~of~~ any severe stress: adrenal cortical hypertrophy, thymus involution, ulceration in the gastrointestinal tract [4]. Stress is characterized by an extreme complexity associated, interalia, with the individual char-

acteristics of a person, and can only be corrected by combining etiotropic treatment with prolonged pharmacotherapy with herbal formulations. All types of stress, which is considered a combination of exogenous and endogenous negative factors that create tension in the human body, are characterized by unspecific reactions of the hypothalamic-pituitary-adrenocortical system гипоталамо-гипофизарно-адренокортикальной системы and disorders of vegetal functions нарушения вегетативных функций of the cardiovascular and hematopoietic systems. In the modern world, an increase in the level of the emotional tension combined with сопутствующими negative factors (strokes, myocardial infarction, atherosclerotic cardiosclerosis, and others), has brought cardiovascular diseases to the first place among the causes of mortality. According to the World Health Organization, every year 17.5 million people die of diseases of the cardiovascular system [5]. Medicines correcting a person's perception of exogenous factors, as well as having a regulatory effect on endogenous stress mechanisms, can help overcome the devastating consequences. The advantage of herbal drugs created on the basis of modern scientific achievements, is the presence of a wide range of biologically active substances with multi-directional therapeutic and preventive agents in their composition. In most cases, these properties are combined with safety and the possibility of a long-term use. Extractive (total) drugs, biologically active food additives, separate fractions of biologically active substances and standardized medicinal preparations obtained from the medicinal plant materials of the members of the family *Valerianaceae* (rhizomes with valerian roots), *Paeoniaceae* (*Paeónia anómala* herb, rhizomes and roots), *Hypericaceae* (*Hypericum perforatum* herb), *Passifloraceae* (*Passiflora incarnata* herb), *Polemoniaceae* (*Polemonium coeruleum* rhizomes with roots), *Lamiaceae* (*Leonurum cardiaca* herb), which have pronounced neurotropic, mainly sedative, activities, are widely known [6]. Meanwhile, the analysis of the results of numerous scientific studies of medicinal plant materials carried out in order to expand the range of drugs with sedative and anxiolytic activites, shows that the greatest attention is paid to the members of the family Lamiaceae. The possibilities of creating new drugs and biologically active additives, therapeutic and prophylactic agents containing biologically active substances from raw materials of plant species of the family Lamiaceae, remain unrealized and need further comprehensive researches.

THE AIM of this work is to review and analyze the data published in the modern scientific literature obtained during pharmacological, pharmacognostic and pharmacotechnological studies of various types of raw materials obtained from members of the family *Lamiaceae*, which were sources of biologically active substances, pharmaceutical substances, total extracts and the drugs with a neurotropic activity.

MATERIALS AND METHODS

For the review, we used the information of the scientific literature from open and accessible sources of the last twenty years, located in the scientific and technical libraries of institutions, as well as in electronic databases: Elibrary, PubMed, Scopus, Cyberleninka, GoogleAcademy, J-Stage. The search inquiries were: the samples of medicinal plant materials based on them as well as the names of the drugs and biologically active substances obtained from these raw materials.

RESULTS AND DISCUSSION

The analysis of the publications on plant raw materials obtained from members of the family Lamiaceae, extracts or separate classes of biologically active substances, makes it possible to conclude that they comprise about 30 genera.

The data of pharmacological tests on the presence of the neurotropic effect of medicinal plant materials of the family Lamiaceae species obtained by researchers mainly in the process of the study of essential oils, their components, aqueous and aqueous-alcohol extracts using the following tests: "The open field", "Light-dark chamber", "Elevated plus maze", "Staircase», "The tail suspension test", "The forced swim test", "The hole-board test", "The *rotarod* test" [7–10].

In addition to conducting standard tests, the locomotor activity of the animals and the duration of the barbiturates' effect against the background of taking the investigated pharmaceutical substances, extracts, medicinal preparations, etc., have been studied. During these studies, neurotropic effects in varying degrees have been experimentally found out: anxiolytic, sedative, antidepressant, hypnotic, or the property of sleep prolongation. It has been established, that the drugs obtained from the medicinal plant materials from the members of the family Lamiaceae L. and having a neurotropic effect, enhance the affinity of gamma-aminobutyric acid (GABA) for GABA-receptors in the subcortical formations, primarily in the reticular formation, weakening its stimulating effect onto the cerebral cortex [11].

In the course of tests for the presence of the neutropic activity, the objects of the investigation were not only the crude total extracts, separate classes of biologically active substances, but also compounds isolated выделенные в чистом виде and obtained by synthetic and semi-synthetic methods. Flavonoids, triterpenic acids (ursolic and oleanolic), phenylpropanoids (rosmarinic and caffeic acids), terpenoids and aromatic compounds as components of the essential oil (linalool, linalyl acetate, thymol, carvacrol, etc.), alkaloids, alkaloid-like compounds and iridoids, are most often studied in this context.

Flavonoids, in most cases flavones, are able to interact with different zones of the GABA-α-receptors and, due to this, affect their functioning.

Neurotropic properties, expressed to a vary-

ОРИГИНАЛЬНАЯ СТАТЬЯ
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ing degree, were found out in the following flavones: hispidulin (5,7,4'-trihydroxy-6-methoxyflavone), apigenin (5,7,4'-trihydroxyflavone), chrysoeriol (5,7,4'-trihydroxy-3'-methoxyflavone), luteolin (5,7,3',4'-tetrahydroxyflavone), scutellarein (5,6,7,4'-tetrahydroxyflavone), baicalin (7-O-glucuronide 5,6,7-trihydroxyflavone), baicalein (5,6,7-trihydroxyflavone), etc.

Flavones interact with the GABA-α receptors, as well as benzodiazepines; these are ones of the most commonly used drugs. It is known that when interacting with allosteric sites of GABA-α, also so-called benzodiazepine sites, the influx of chloride ions into the cytoplasm increases, the inhibitory postsynaptic potential increases, and the excitability of neurons decreases. According to this mechanism, benzodiazepines and flavones act as anticonvulsants, providing sedative, hypnotic and anxiolytic effects [12].

In the experiments on Wistar rats, caffeic acid (3,4-dihydroxycinnamic acid) at the doses of 0.5 and 1.0 mg/kg, has an anxiolytic effect without changes in the locomotor activity in "The open field" and «Elevated plus maze» tests. It has also a protective effect in cases of the damage to the brain tissue by hydrogen peroxide [13].

Rosmarinic acid (caffeic acid dimer) at the doses of 2–4 mg/kg, has an anxiolytic effect, which, when the dose is increased to 8 mg/kg, is replaced by a stimulating effect. No effects on long-term and short-term kinds of memory, have been found out [14].

A neurochemical study showed that caffeic and rosmarinic acids did not affect the absorption of monoamines or the activity of monoamine oxidase; but none of the studies have revealed the possibility of these compounds to alter the transmission of monoamines on their receptor directly [15].

A neurotropic activity has also been established for essential oils components. When administered intraperitoneally, citral has a sedative (100 and 200 mg/kg) and muscle relaxant (200 mg/kg) effects at the doses of 100 and 200 mg/kg and increases the duration of barbiturate sleep [16]. In the experiment on mice, cineol has an anti-anxiety (400 mg/kg), antidepressant effect (200 and 400 mg/kg), does not affect the motor activity and reduces the latency of sleep caused by the administration of pentobarbital [17].

Overview of genera and species – sources of medicinal plant materials with neurotropic properties

Genus *Agastache* J.Clayton ex Gronov

The genus *Agastache* J. Clayton ex Gronov. comprises 22 species of perennial medicinal aromatic plants [18] that live mainly in the North America [19]. Some of these species are used as spicy aromatic, ornamental and nectareous plants, others are used as raw materials for obtaining essential oils and drugs [20].

In the aerial part of *Agastache mexicana* (Kunth. Link.et Epling), the fllowing substances were found out: malic acid, 7-O-β-D-glucoside, luteolin flavonoids, 7-O-β-D-luteolin (6"-O-malonyl)-glucoside, 7-O-β-D-glucoside diosmethine, 7-O-β-D-(6"-O-malonyl)-glucoside diosmetin, 7-O-β-D-glucoside acacetin, 7-O-β acacetin-D-(6"-O-malonyl)-glucoside, acacetin 7-O-β-glucoside-D-(2"-acetyl-6"-malonyl), acacetin, diosmetin, gardenin, 5,6,7,8,3-pentahydroxy-4-methoxyflavone, 8-hydroxy-salvigenin [21].

An aqueous extract from *A. mexicana* leaves of exhibits the antidepressant activity [22]. The results of three different tests ("Elevated plus maze", "The forced swim test", and "The open field") showed an anxiogen-like activity. In the "Elevated plus maze" test, the extract reduced the time spent by animals in the open sleeves. The results of "The forced swim test» did not show any antidepressant effect of the extraction (at the dose of 12.0 mg/kg) in comparison with the results obtained when using pentylenetetrazole (at the dose of 15 mg/kg) and desipramine (at the dose of 32 mg/kg) as reference substances. The extract enhanced the antidepressant effect of desipramine similarly to the effect of the sumaltenious administration of pentylenetetrazole and desipramine. "The open field test" did not reveal any sedative effect of the aqueous extraction from *A. mexicana* leaves in the used doses [23].

Genus *Ajuga* Benth L.

Genus *Ajuga* Benth. comprises ca. 80 species of annual and perennial herbaceous plants, common mainly in temperate zones [18].

Ajuga reptans L. and *A. remota* Benth. – syn. A. *integrifolia* Buch.-Ham, are also of great interest to researchers. In the aqueous-alcohol extract from *A. remota* aerial parts, the following substances were found out: iridoids (harpagide, 8-O-acetylgarpagide, 2,3-diacetylgarpagide, 6,8-acetylgarpagid-O-2,3-diacetylglycoside, 6-ramnosyl-garpagide, 6-halogen-7,8 dehydrogarpagide) and steroids (ciasterone, ergosterone-5.8-endoperoxide) [24].

The presence of the anxiolytic effect was established for cisteron steroids and ergosterone-5.8-endoperoxide from the roots of *A. remota* [25].

The oral administration of cisterone and ergosterone-5,8-endoperoxide (at the doses of 5 mg/kg) isolated from methanol extracts of the underground parts of *A. remota,* led to an increase in the duration of the study in the open sleeves by the animals in the «Elevated plus maze» test, and in the number of head dives in «The hole-board test» ($P<0.05$) compared with the control group. The same compounds (at the doses of 25 and 50 mg/kg, respectively) showed a dose-dependent increase ($P<0.01$) in the number and duration of immersion of the head in the holes, which is comparable to the anxiolytic effect of diazepam and indicates a potential use for relief of anxiety [24].

Genus *Anisomeles* L.

Anisomeles L. .is a genus of herbaceous plants that are outwardly similar to the members of the genus *Nepeta* L., growing mainly in the countries of Southeast Asia, in particular, China, India, New Guinea, Australia, etc.

Anisomeles indica (L.) Kuntze. (syn. Indian catnip, Indian catnip) is of the greatest interest for researches. Its chemical composition is represented by the following compounds: pedalitin, apigenin, methyl gallate, 3,4-dihydroxybenzoic acid, calceolarioside, betonioside A, campneoside II, acteoside, isoacteoside and terniflorin [25].

The methanol extract obtained from *A. indica* aerial part, was tested on Swiss albino mice for sedative properties in "The open field" and "The hole-board" tests, and anxiolytic properties - in the «Elevated plus maze» test. In "The open field" and "The hole-board" tests, a dose-dependent decrease in the locomotor activity was notified. In the «Elevated plus maze» test, the animals under the influence of the investigated extract showed an increase in the percentage of time spent in the open sleeves. The studied extract potentiated thiopental sleep to a lesser extent than diazepam [25].

Genus *Ballota* L.

The members of the genus Ballota L. (about 30 species) are perennial herbaceous plants found mainly in the Mediterranean region [26]. The most studied of them is *Ballota nigra* L., common in the European part of Russia. Flavonoids (rutin, dihydroquercetin), phenylpropanoids (verbascoside, forsitoside B, arenarioside, ballotetroside, isoferulic, ferulic, chicoric, cinnamic, caffeic, chlorogenic acids), coumarins and tannins (epicatechin, epigallocatechin gallate, catechin, gallic acid) were found in the composition of the aqueous-alcohol extracts from *B. nigra* herb. [27–30]. The herb *B. nigra* is officinal and is included in the pharmacopoeias of Britain, France, and Europe [31].

The antidepressant activity of the aqueous alcohol extract from *B. nigra* aerial parts is is associated with phenylpropanoids [29]. A mixture of phenylpropanoid glycosides significantly prolonged the sleep induced by pentobarbital; reduced the locomotor activity in mice and produced a slowing-down of the electroencephalographic trace [32]. The antidepressant activity of the extracts from *B. nigra* aerial parts has been proven by behavioral tests on albinos rats: «The forced swim» and «Elevated plus maze») [33]. Affinity tests with rat striates, the whole brain and the receptor-rich drugs, were used in order to study the ability of phenylpropanoids obtained from the aqueous-alcoholic extract of *B. nigra* aerial parts, to bind to связываться с benzodiazepine, dopaminergic and morphine receptors. The results showed that four out of five phenylpropanoids identified (verbascoside, forsitoside B, arenarioside, ballotetroside and caffeic acid) are able to bind to the studied receptors having a neurosedative effect at the doses from 0.4 to 4.7 mg/ml [29].

Phenylpropanoid derivatives isolated from *B. nigra subsp. Anatolica* aerial parts, are of a therapeutic interest as having also an antioxidant activity [34, 35].

Neurosedative properties of aqueous and aqueous-alcoholic extracts from aerial parts of *B. saxatilis* Sieber ex C. Presl. Species, are widely used in European medicine [36].

The aqueous extract from the aerial part of *B. larendana* Boiss. et Heldr., administered intraperitoneally to albino male rats, showed its anxiolytic activity, and its antidepressant activity was comparable to amitriptyline and *Passiflora incarnate L.* extract [33].

Genus *Clerodendrum* L.

The genus of plants is the subfamily *Ajugoide,* fam. Lamiaceae, comprising approx. 300 species – deciduous shrubs, small trees, sometimes vines, which grow in the tropics and subtropics, mainly in Africa, Central America, Southeast Asia. Some species are grown as ornamental plants [37].

The ethanol extract from *Clerodendrum serratum* L. leaves has an antidepressant effect, without reducing a motor activity, in an acute stress and an induced depressive behavior in mice.

The antidepressant and anxiolytic activity of the extract was investigated in "The forced swim" and «The tail suspension» test. The oxidative effects of the acute stress and biochemical changes in the brain tissue, were also evaluated. A preliminary use of the extract for 7 days, can reduce the damaging oxidative effect of the acute stress and quickly restore the level of norepinephrine and 5-hydroxytryptamine in the brain tissue. Flavonoids, apigenin and luteolin derivatives, were found out by HPLC in the butanol and ethyl acetate fractions of the extract from *C. serratum* leaves of [37].

Genus *Clinopodium* L.

Clinopodium L., the genus of herbaceous plants up to 100 cm high, has about 150 species. The scientific literature mentions *Clinopodium mexicanum* Benth Govaerts (Mexican fragrance). Its medicinal raw material is used as anesthetic and sedative remedies in the traditional medicine of Mexico [38].

Flavone glycoside 2S-neopincirin [(2S)-5-hydroxy-4'methoxyflavonone-7-O-{β-glucopyranosyl-(1→6)-β-ramnoside}] was found out in aqueous and methanol extracts from *C. mexicanum* leaves. In the experiments on mice, it had an anxiolytic effect associated with an effect on GABA receptors [38].

Genus *Dracocephalum* L.

The genus of herbaceous plants *Dracocephalum* L. has about 60 species occuring in the temperate climatic zone of the northern hemisphere [39]. The most studied one is *Dracocephalum moldavica* L., which is a promising

ОРИГИНАЛЬНАЯ СТАТЬЯ
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medicinal plant. The species grows everywhere in the Black Sea region, the European part of Russia, in Siberia, Central Asia, the Far East, China, Mongolia, etc. It was introduced into the culture as a spicy-aromatic, ornamental and medicinal plant. The aerial part of the plant accumulates up to 0.15% essential oil, which contains up to 70% citral, as well as geraniol, thymol, nerol [40].

The aqueous extract from *D. moldavica* aerial part, dose-dependently reduced a number of transitions in the avoidance test. This effect can be considered anxiolytic; however, the same doses also induced a significant reduction in the total activity of the mice in "The open field" test compared to the control group. This behavior cannot be considered an anxiogenic effect, since it is a consequence of a decrease in the activity of the animals due to the sedative effect of the drug. The obtained results are similar to those observed at a high dose of diazepam; in them, diazepam also induced a decrease in the number of transitions between the light and dark compartments in the avoidance test and overall activity in "The open field" test.

The aqueous extract from *D. moldavica* aerial part, has sedative and muscle relaxant activities, reduces a locomotor activity and leads to the general inhibition of the neuron activity in the central nervous system of the experimental animals. Most likely, flavone glycosides present in the extraction, contribute to the sedative effect [41].

Genus *Eremostachys* Bunge (*Phlomoides* Bunge)

The genus of *Eremostachys* Bunge herbaceous plants includes about 140 species, growing mainly in Central Asia. The most studied species is *Eremostachys laciniata* (L) Bunge –syn. *Phlomoides laciniata* (L.) Kamelin & Makhm. Pronounced sedative properties were found out in its aqueous-alcoholic extraction from the aerial part, in which flavonoids were identified (luteolin, apigenin, 5,8-dihydroxy-6,7-dimethoxyflavone, 5,7-dihydroxy-6,8-dimethoxyflavone, luteolin 7- O-β-glucoside) [42].

In «The forced swim test», the aqueous extract from *E. laciniata* aerial parts *in vivo* at the low doses showed an antidepressant effect, and at the higher doses - a depressive one.

The authors of the study consider that the antidepressant property is associated with the presence of apigenin derivatives in the extraction of flavonoids. And a depressive property, expressed in an increase in the duration of immobility and observed at higher doses of the extraction, is due to the sedative effect of luteolin. *E. laciniata* medicinal raw material can be a potential source for obtaining antidepressant medicinal preparations [42].

Genus *Hyptis* Jacq.

Members of the numerous genus *Hyptis* Jacq. (up to 300 species) are represented by annual and perennial herbs, shrubs and small trees prevalent mainly in the tropical and temperate zones of North and South America [43]

The aqueous extract from *Hyptis spisigera* Lam. leaves has a sedative effect, increases the duration of sleep induced by diazepam. The sedative activity can be associated with the presence of components that potentiate benzodiazepine and / or activate GABA receptors [43].

Genus *Hyssopus* L.

The genus *Hyssopus* L. has at least 7 species of perennial plants, among which there are herbs and shrubs growing in the Mediterranean, Asia Minor, Middle Asia, the Caucasus, southern Siberia [40]. Some members were introduced into the culture as sources of spicy aromatic raw materials and essential oils. The most studied is *Hyssopus officinalis* L. (Hyssop officinalis), shrub up to 80 cm tall, growing mainly in Africa, Western Asia. It is cultivated as an essential oil and spicy aromatic plant. The herb contains an essential oil (up to 2%), flavonoids (hesperidin, hyssopine, etc.), triterpene acids, bitter substances, etc. [40].

H. officinalis is official in several European countries. For a long time, the extracts and essential oil have been used in diseases of the upper respiratory tract and gastrointestinal tract, as well as an antiseptic. Currently, *H. officinalis* is the subject of numerous pharmacological studies. It was established, in particular, that the extract from the herb obtained by the extraction with 70% alcohol in the intragastric administration to white rats, leads to a significant increase in sleep duration – by 55% relative to the control (nembutal) and by 52% relative to the comparison object (alcohol + nembutal) [40].

Genus *Lagochilus* Bunge

A member of this genus is *Lagochilus inebrians* Bunge – a medicinal plant well-known in folk and official medicine. *L. inebrians* is a shrub growing in Central Asia, its areal is very limited. *L. inebrians* flowers and leaves contain a typical tetrahydric alcohol lagohillin, tannins (up to 14%), vitamins, organic acids, essential oil (about 0.03%), etc. *L. inebrians* aqueous extracts have adaptogenic, hypotensive and sedative activities, an anticonvulsant property, they reduce pain sensitivity, have an antispasmodic effect. Its infusion and tincture enhance blood coagulation [45].

The use of medicinal preparations from *L. inebrians* herbal raw materials gave positive results when obtained in the treatment of neuroses. It was determined that they normalize the balance between inhibition and excitation in the nervous system, inhibit the vestibular analyzer, which has been successfully used in the treatment of Meniere's disease. Thanks to the sedative effect of *L. inebrians,* reduce blood pressure [45]. Previously, *L. inebrians* medicinal preparations were used in medical practice; nowadays the State Register of the Russian

Federation does not include these drugs from *L. inebrians* medicinal plant materials [6].

Genus *Lallemantia* L.

The genus *Lallemantia* L. comprises several species; the most famous of them are: *Lallemantia iberica* F. et M., *L. royleana* (Benth. In Wall.) Benth. (l. Royle) and *L. canescens* L. (l. grayish) [46].

Asia Minor, Transcaucasia, Iran and the mountainous regions of Turkmenistan are considered the *habitats* of *Lallemantia* where it has long been widespread as a wild-growing and a weed-field plant, most often in flax crops. In the wildlife species, В диком виде *Lallemantia* is found in Syria, Mesopotamia, Afghanistan, as well as in the Crimea, in the south of Ukraine, along the eastern coast of the Caspian Sea and in the North Caucasus [46]. *Lallemantia* fruits contain fatty oil, therefore *l. Iberian's* oilseed is cultivated in the countries of the Middle East.

Sugars (mannitol 14.78%, saccharose сахароза 9.36%), fatty oil and fatty acids, essential oil, coumarins, flavonoids, alkaloids were found in the aqueous-methanol extract from *L. royleana* fruits [47]. Fatty oil contains the following acids: linoleic (up to 26%), palmitic (up to 10%), oleic (up to 60%), stearic (about 3%), etc. Aqueous and aqueous-alcohol extracts from fruits are used with insomnia, increased nervous excitement, as well as diseases of the gastrointestinal tract [47].

In the study by Hyder et al., the anxiolytic and sedative effects of the aqueous-methanol extract from *L. royleana* fruits were studied (after the removal of the extractant) in mice. To test the anxiolytic activity, the following tests were used: "The open field test», "The hole-board test", "Elevated plus maze", "Light-dark chamber" and "Stairscase", the reference drug was diazepam. The results showed that the test extract has an anxiolytic effect, maximally expressed at the dose of 250 mg/kg [47].

Genus *Lavandula* L.

The genus Lavandula L. is represented by perennials, mainly semi-shrubs, has about 50 species, distributed mainly in the Mediterranean [48].

The most common and actively studied species is *Lavandula angustifolia* Mill., syn. *L. officinalis* Chaix. This is a perennial, evergreen, highly branched shrub, 60–70 cm high, widely grown as an aromatic and medicinal crop. Shoots, leaves and inflorescences contain essential oil up to 2%, in the composition of which linalool (up to 80%) and its esters, linalyl acetate, terpinen-4-ol, lavenderulol acetate, octimene, cineole have been found out; anthocyanins, phytosterols, tannins have been detected in the aqueous-alcoholic extract [48]. *L. angustifolia* extracts from flowers and essential oil are used in the traditional medicine for migraines, neurasthenia, as an anticonvulsant and a sedative drug. In the study carried out on pigs, the anxiolytic activity has been confirmed. A significant decrease in the motion sickness and stress in the animals during transportation (measured by the concentration of cortisol in saliva) was observed in the animals when the floor of the vehicle was covered by lavender (*L. angustifolia)* [49].

Aqueous and aqueous-alcoholic extracts from *L. angustifolia* aerial parts (at the doses of 100–400 mg/kg), which were studied in comparison with fluoxetine, had an antidepressant effect. In the mice, the duration of immobility was significantly reduced in «The forced swim test» and «The tail suspension test». The inhalation of *L. angustifolia* flowers essential oil, induced an increase in the level of serotonin and its metabolites in pregnant women's plasma during childbirth [50].

Clinical trials on the study of the hypnotic properties of *L. angustifolia* flowers essential oil have shown an increase in sleep time with its use. A clinical study of a group of 245 people was conducted. 72% of patients inhaling lavender oil, experienced a healthy sleep, unlike 11% in the control group. About 80% of the study participants reported overall well-being, in contrast to 25% of those in the control group [49].

Besides *L. angustifolia, L. spica* L. (syn. *L. latifolia* Medik.) extracts from the aerial parts are also widely used in traditional medicine for the treatment of asthenia and depression. *L. spica* flowers contain essential oil with a higher content of camphor and cineole, in comparison to the content of *L. angustifolia* flowers essential oil. A liquid extract obtained from *L. spica* flowers (the extractant was 40% ethyl alcohol), has an established sedative activity. It was notifed that the activity of the extract is associated with the presence of lavenderoside phenylpropanoid (4-O-β-D-glucopyranoside 4-hydroxy-3-methoxy cinnamic acid) in its composition. In addition to these substances, flavonoids cinaroside and cosmosiin were also found in *L. spica* flowers [51–53].

Another species studied as a promising medicinal plant is *L. stoechas* L., which is common and cultivated in the Mediterranean countries. A sedative and hypnotic effect was established in water-methanol extraction (after removal of the extractant) from *L. stoechas* flowers – it contributed to an increase in the duration of pentabarbital sleep in mice by analogy with diazepam [54].

Genus *Leonotis* L.

This genus of perennial herbaceous plants amounts to 9 species, most of which grows in tropics, mainly in South Africa [55]. The most studied species *is Leonotis nepetifolia* L., which is common in tropical Africa and South India. Extracts from its stems are used in traditional medicine as a sedative drug. Methanol extract (after removal of the extractant) obtained from *L. nepetifolia* stems, in intraperitoneal administrationat to the mice at the doses of 37.5 mg/kg, 75 mg/kg and 150 mg/kg was studied. It was established that the mass content of LD_{50} is 3.8 g/kg. The results showed that in all the studied doses, the extract did not have a noticeable effect on the research activity and coordination of the animals' movements. However, at a dose of 150 mg/kg, it induced a

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-1-4-28

significant decrease in the number of collected grains in the "Staircase" test, which was also observed with the administrationat of an anxiolytic dose of diazepam, and also significantly increased the duration of sleep induced by diazepam. Preliminary phytochemical analysis showed the presence of alkaloids, saponins, glycosides and triterpenoids in the extract. The results obtained indicate that the crude methanol extract from *L. nepetifolia* stems has an anxiolytic activity, which explains the traditional use of the decoction of this plant as a sedative and tranquilizing agent [55].

Genus *Leonurus* L.

The Leonurus L. genus of perennial, or biennial plants, includes about 25 species growing around the world: in Europe, Asia, Africa and America; 13 species are found in Russia [56]. The most famous European members of the genus are *Leonurus cardiaca* L. and *L. quinquelobatus* Gilib., and in East Asia it is *L. japonicus* Houtt.

For a long time, the drugs obtained from the herbs of these species, have been widely used in traditional and official medicine for anxiety, neurosis, insomnia, as a sedative remedy, for epilepsy, and for the treatment and prevention of cardiovascular diseases [57]. In *Leonurus* L. aqueous-alcohol extracts, iridoids responsible for sedative and hypnotic properties were discovered: monoterpene compounds with partially hydrated cyclopenta / s / pyran system (ayugol, ayugozid, harpagide, harpagide acetate), phenylpropanoids (coffee, ferricoric acids), flavonoids (rutin, hyperoside, quercetrin), nitrogenous bases (leonurine and stachidrin or leonuricardin), tannins [58–60].

The State Register of Medicines of Russia includes *Leonurus* L. medicinal plant material for the preparation of the following infusions and medicines: *Leonurus* L. tincture, *Leonurus* L. extract, Lily of the valley- *Leonurus* L. t drops, Corvalol Neo (diphenhydramine + peppermint oil, oil + *Leonurus* L. tincture + ethyl bromisovalerianate), «Corvalol Fito» (peppermint leaf oil + *Leonurus* L. tincture + ethyl bromizovalerianate), «*Leonurus* L. Forte Evalar» (*Leonurus* L. + [magnesium asparaginate + pyridoxine]), «Calming collection No. 3» (Valerianae officinalis rhizomata cum radicibus+meliloti herba+Origani vulgaris herba+leonuri herba+Thymi serpyllum herba) [6]. Medicinal plant preparations obtained from *L. quinquelobatus,* have sedative properties, regulate the functional state of the central nervous system, lower blood pressure, slow down the rhythm and increase heart rate [61]. The mechanism of neurological action of *L. cardiaca* and *L. japonicus* extracts is based on the interaction with the GABA-α receptor [62]. Neuromodulating and neuroprotective effects of *L. japonicus* extract are associated with the presence of (leonurine, stachydrin) and triterpenoids (leonuruzoleanolide A) in their composition, and a sedative effect is associated with iridoids (stegioside). *L. japonicus* tincture also inhibits 5-HT3A receptors, the antagonist of which is Leonurin with an IC50 of 2.17 ± 0.15 mM. Since this receptor is involved in gastrointestinal motility disorder, *L. Japonicas* medications can be used to treat vomiting and nausea. [63].

Due to the ability to reduce mental stress, *L. Japonicas* drugs are used as sedative remedies for increased nervous excitability, in the early stages of hypertension and sleep disorders. Like other sedatives, they are able to facilitate the onset of natural sleep.

The neuroprotective effect of the synthesized alkaloid-like nitrogenous base of leonurin on nerve cells in the model of an ischemic stroke in rats, is mainly due to a decrease in the formation of the active oxygen forms, which supports a correct functioning of mitochondria and, therefore, apoptosis is inhibited. It is supposed that leonurin can be used to prevent and treat ischemic strokes due to its antioxidant properties and participation in the mechanism of apoptosis [64].

L. quinquelobatus drugs have not only a sedative but also antidepressant effect [61, 65]. In the experiments on rabbits and mice, the sedative effect of *L. Japonicas* tinctures was confirmed. Phenolpropanoid lavandulifolioside was isolated from *L. cardiaca* var. vulgaris Briquet butanol fraction. It has a pronounced negative chronotropic activity (reduces heart rate), the ability to change the parameters of the electrocardiogram (ECG), namely, to extend the intervals of the P-Q and Q-T QRS complex (ventricular complex) and reduce blood pressure. In his study, it was also established that it was not responsible for the sedative effect, since even at the doses of 800 and 1600 mg/kg only slightly reduced the mobility of mice [64]. Unlike the total butanol extract, lavandulifolioside does not reduce spontaneous locomotor activity, therefore its properties do not reflect all the pharmacological effects of *L. cardiaca* drugs [66]. Significant sedative effect was observed under the influence of *L. cardiaca* extract obtained with 30% ethanol. In the «Elevated plus maze» test, the extract increased the time spent by mice in open sleeves by 4 times, decreased a spontaneous activity twice, and increased the duration of sleep induced by barbiturates by 3 times. Similarly, the aqueous extraction of *L. cardiaca* was studied, which, when administered intraperitoneally, induced a decrease in motor activity in mice [64]. In the study [67], the authors compared the sedative activity of motherwort and valerian tinctures on rabbits with electrodes on their hind legs.

The values of the direct current intensity required to contract flexor muscles after the administration of tinctures were measured. It was found out that under the influence of the motherwort tincture there is an increase in the measured values to a greater extent than under the influence of the valerian tincture, which is associated with its strong inhibitory effect on the central nervous system [67].

The Iridol oil extract was worked out from *L. cardiaca*, *L. quinquelobatus,* then standardized by the content of iridoids in it and packaged in soft gelatin capsules.

In the experiments on the outbred male rats, the anxiolytic activity of Iridol was established, comparable with the effect of diazepam. During clinical observations it was found out that the studied drug increases the effectiveness of complex therapy in the treatment of arterial hypertension accompanied by psychoemotional disorders, reduces the dose of antihypertensive drugs, while the activity of the new drug exceeds that of *L. cardiaca*, *L. quinquelobatus* tincture [59].

L. cardiaca oleoresin was administered to 50 patients (300 mg 4 times a day for 28 days) with the first (22 patients) and second (28 patients) degrees of hypertension and symptoms such as anxiety and sleep disturbances.

In the patients with the first degree of hypertension, a reduction in symptoms of anxiety, emotional instability, headaches and sleep disturbances was achieved. After 21 days, there was a significant decrease in the level of blood pressure and its normalization (from 145/96 to 130/87), the patients' state of health and mood were improved, their activity increased and the fatigue decreased. A decrease in heart rate (from 81.7 to 75.4) was not statistically significant. A significant lowering of blood pressure (from 153/103 to 142/92) in patients with the second degree of hypertension, occurred a week later than in the first group. The psycho-emotional state of patients (anxiety, emotional pain, headaches and sleep disturbances) improved seven days before lowering blood pressure. Antihypertensive, anxiolytic and soothing effects could be induced by *Leonurus cardiaca* iridoid extracts [64].

Clinical researches. Arushanyan et al. studied the effect of *Leonurus* L. tincture and benzodiazepine anxiolytic grandaxin on anxiety and light perception in clinical trials in 26 volunteers with increased anxiety. The volunteers were divided into three groups, and a control group consisted of 12 patients without emotional disorders. It was established that in its activity, grandaxin slightly exceeded *Leonurus* L. tincture [68].

In randomized clinical trials, the sedative effect of *Leonurus* L. drugs was established. It was expressed in improving the quality of sleep, reducing the frequency of awakenings and nightmares, as well as in the general psycho-emotional state. Neurotropic effects were accompanied by a decrease in blood pressure [64].

In a double-blind randomised clinical trial, the sedative effects of tablets containing *Leonurus* L. (50 mg), valerian rhizomes with roots (170 mg), мелиссы balm lemon leaves (50 mg) and hop fruit systems (50 mg) were compared with a placebo. The study group consisted of 50 males (the average age was 45.6 years) suffering from alcohol withdrawal syndrome with sleep disorders (from mild to severe insomnia), anxiety and irritability. The patients, divided into two groups, received the preparation an hour before bedtime, once a day, and the next day they were given a placebo. Compared with the placebo, a significant improvement in sleep quality and a decrease in the frequency of awakenings and nightmares proved a mild sedative effect of the product used; however, it caused drowsiness the following day. Motherwort could, therefore, be helpful, to some extent, in disorders associated with alcohol abstinence.

A study to determine if the administration of sedatives, including *Leonurus* L. tincture, decreases the limitation of the retina ability to distinguish colours caused by the state of anxiety, was also carried out. The experiment involved 26 healthy volunteers with a diagnosed state of nervous anxiety. They were divided into three groups, and a control group consisting of 12 patients without emotional disorders. A decrease in anxiety and an improved ability to distinguish colours, both after the application of tofizopam (benzodiazepine derivative) (for 10 days) and *Leonurus* L. tincture, were registered, yet the anxiolytic effect of tofizopam persisted longer (up to one month after cessation) in comparison with the tincture. The positive effect of the treatment on vision, may have resulted from an impact on the GABAergic system in the retina and the brain structures connected with it.

In another experiment, 21 young patients (divided into three groups) with mild symptoms of anxiety and depression, were given melatonin, *Leonurus* L. tincture or placebo for 10 days (the control group was made up of 10 healthy volunteers). The quality of sleep and the emotional state of the patients, as well as the function of their retina, i. e., the threshold of excitability of light stimuli and the time of the sensorimotor reaction of the vision process, were evaluated before and after the use of the drugs. The administration of melatonin led to the increased sensitivity of the retina to light and an accelerated sensorimotor reaction. The effect of *Leonurus* L. tincture on the vision process after the administration of *Leonurus* L., was statistically insignificant, and the sleep quality improved only in some patients. The anxiolytic activity of *Leonurus* L. tincture was confirmed, but it was weaker compared to melatonin.

Genus *Leucas* L.

The genus *Leucas* L. has more than 130 species of herbaceous plants that are widely distributed in Africa, South and East Asia, India, China, Japan, and the islands of the Indian Ocean. In the scientific literature, studies of *Leucas lavandulifolia* Sm. methanol extract in mice and rats using models of psychopharmacological profiles, are referred to. The extract contains alkaloids, flavonoids, phenols, tannins, carbohydrates, proteins and amino acids, and in the experiments it showed a decrease in the animals' spontaneous motor, search and muscle kinds of activity, as well as potentiation of pentabarbital sleep in the mice [69].

Genus *Lycopus* L.

The genus *Lycopus* L. has 21 species of perennial herbaceous plants. The most famous and studied of them is *Lycopus europaeus* L., which is found throughout Europe, the European part of Russia and Siberia [70].

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-1-4-28

In "The hole-board test" the methanol extract from *L. europaeus* aerial parts (after the removal of the extractant) containing flavonoids, terpenes, saponins, has a pronounced sedative effect at the doses of 200, 400 and 600 mg/kg (p.o.). In that extract, diazepam was used as a reference drug. At the doses of 800 and 1000 mg/kg, the extract increases the duration of thiopental sleep. Thus, it was found out that methanol extract has pronounced sedative and hypnotic effects, which confirms the possibility of its therapeutic use for insomnia [70].

Genus *Melissa* L.

The genus *Melissa* L. includes, according to various authors, from 2 to 10 species [71, 72]. The greatest application as a spicy aromatic, food and medicinal culture is *Melissa officinalis* L. The place of *M. officinalis* origin is the eastern Mediterranean region, where it is found in wild nature [73–76]. It is also cultivated in many countries of the world, where it is included in the registers of pharmacopoeial and aromatic plants [73, 77–80]. In Russia, it is officially included in the State Pharmacopoeia (14-th ed.) [81].

In medicine, *M. officinalis* aqueous extracts have been used for thousands of years as they have sedative, anxiolytic, antidepressant, antispasmodic, immunomodulating, antiviral, antimicrobial, antioxidant and antiallergic properties [82, 83].

M. officinalis aerial part contains essential oil (0.02–0.20%). Its main components are: citral, geranial, citronellal, neral, geraniol [85]. In addition to the essential oil, the aerial part of the plant contains phenylpropanoids (rosmarinic and caffeic acids, etc.), flavonoids (apigenin, cosmociin, luteolin, cinaroside, etc.), tannins and coumarins [72, 75, 86–92].

In the experiments on mice, the sedative effect of *M. officinalis* extract of the aerial parts, was discovered by French scientists in 1889 [92]. The total crude extract obtained from *M. officinalis* extract induced sleep when a prehypnotic dose of pentobarbital was administered, and lengthened sleep after a hypnotic dose of pentobarbital [78, 79, 93]. In Lin et al [94], the antidepressant activity of *M. officinalis* aqueous extract was established by its effect on the behavior of rats under the conditions of «The forced swim test».

The behavioral effects, activ and subactive, p.o. administration of *M. officinalis* ethanol extract (after the removal of the extractant), were evaluated in Wistar male rats in the «Elevated plus maze», «The forced swim « and «The open field» tests. Diazepam and fluoxetine were used as reference preparations. As a result, it was established that the psychoactive properties of *M. officinalis* extracts can provide a unique pharmacological alternative for the treatment of certain mental disorders; however, the efficacy appears to depend on both gender and duration of the administration [95].

In a double-blind, randomized, placebo-controlled clinical trial, the efficacy and safety of lyophilized dried aqueous extract from *M. officinalis* leaves in adults suffering from mild tachycardia, were evaluated. The results showed that a 14-day course of treatment with the study drug, reduces heart rate and significantly reduces anxiety in patients, compared with placebo. It has been established that a continuous use of such an extract relieves stress. In addition, it does not have any pronounced side effects [96].

In another study, the effect of a continuous administration of the same extract was studied. Hereby, with moderate stress factors, the presence of an anxiolytic effect not changing the level of activity, was established [97].

In a double-blind, placebo-controlled, randomized study, the ability of *M. officinalis* total extract in a single dose of 600 mg to alleviate symptoms of laboratory-induced stress in healthy individuals, was found out. The most likely mechanism of *M. officinalis* drug action, is inhibition of the acetylcholinesterase in the central nervous system and a decrease in the activity of nicotinic and muscarinic receptors in the cerebral cortex [98].

Genus *Mentha* L.

The genus *Mentha L.* includes 25 species of perennial herbaceous plants [19]. The aerial part of the members of the genus is characterized by a high essential oil content, in the composition of which menthol, its esters and related compounds, as well as α-pinene, limonene, cineole, dipentene, pulegon, β-fellandren, etc. were found out [99, 100].

Flavonoids (naringenin, hesperidin), tannins, organic acids, carotenoids, and other biologically active substances were found out in the aerial parts and in *Mentha* L. aqueous extracts [101, 102]. The plants of this genus are widespread throughout the world, they are used in cooking and food industry as a spicy aromatic culture. The most studied and widely cultivated is *Mentha piperita* L. (peppermint) – a pharmacopeia species obtained by hybridization and consisting of many varieties.

M. piperita leaves serve a source of the essential oil and menthol. *M. piperita* infusion of leaves and collections containing leaves, has sedative, antispasmodic, choleretic, antiseptic and anti-inflammatory properties. The administration of *M. piperita* leaves extract to laboratory animals for 5 weeks, eliminates the effect of stress on plasma corticosterone and the metabolism of serotonin and dopamine in the brain, and the reduction in the animals' anxiety was also registered. The results are consistent with the anti-stress effect of *M. piperita* and suggest the role of cerebral serotonin and dopamine [104].

Mentha arvensis L., characterized by polymorphism, is of the greatest interest of the wild species of mint. It is very widespread in Russia and neighboring states in the temperate climate zone. *M. arvensis* infusion is used in traditional medicine as a sedative and appetite enhancer.

M. arvensis chemical composition is represented by essential oil (monoterpenoids and sesquiterpenoids: menthol, isomenthol, pinene, myrcene, linalool, geranial, camphene, sabinene, limonene), flavonoids (linarin), higher fatty acids (linolenic, linoleic, oleinic) [60].

It was notified that *M. arvensis* methanol extract from the leaves, potentiates pentabarbital-induced sleep [104].

Another member of this genus, investigated for the presence of neurotropic activity, is *M. aquatica* L., which grows in moist soil or along streams, and is widespread in Europe, Northwest Africa, central Russia and Asia.

Naringenin (5,7,4'-trihydroxyflavanone), isolated from *M. aquatica* aerial parts, has a pronounced anxiolytic effect. Intraperitoneally administered at the dose of 100 mg/kg, naringenin led to a significant decrease in basic and fine motor skills ($P<0.05$). The combination of naringenin (100 mg/kg) with midazolam (1.5 mg/kg) led to more significant anxiolysis compared to naringenin (100 mg/kg) with flumazenil at the dose of 3 mg/kg ($P<0.05$) [105].

Genus *Nepeta* L.

The genus of annual and perennial *Nepeta* L herbs, has about 250 species found in the temperate climatic zone of Europe, in Asia, North Africa, in the mountains of tropical Africa, etc. [72]. The main attention of researchers is drawn to *Nepeta cataria* L. (catnip), a perennial herbaceous plant found in the wild and also introduced into the culture. The aerial part of *N. cataria* contains up to 3.0% of essential oil containing more than 70% of nepetalactone, as well as terpineol, borneol, menthol, isomenolit, pinene, citral, linalool, geranial, camphene, sabinen, limonene. Tannins, flavonoids, phenylpropanoids, iridoids (nepetalactone, epinepeta-lactone, methylnepetonate), terpenoids, saponins were found in *N. cataria* aqueous-alcohol extract [60, 106]. Grown as a spicy aromatic culture, the infusion of *Nepeta* L herbs is used in folk medicine.

In addition to *N. cataria*, *N. grandiflora* Bieb and *N. persica* Boiss are of interest, too. Aqueous-alcohol extracts with an anxiolytic activity were obtained from their aerial parts [107]. *N. persica* also contains essential oil in which ne-petalactones and linalool were found out [108, 109]. Nepetalactones contained in essential oil from herb of representatives of the genus *Nepeta* L. possess anxiolytic, sedative and hypnotic activity [108, 109].

In Rabbani et al. (107), the effect of the aqueous–alcohol extract from *N. persica* aerial parts on the behavior of the laboratory animals in the «Elevated Plus Maze» test was investigated. When intraperitoneally administered to male NMRI mice, the studied extract at the dose of 50 mg/kg significantly increased the number of entries and the time spent in the open sleeve. This dose did not affect the locomotor activity of the animals and the duration of their sleep induced by ketamine. At the dose of 100 mg/kg, the extract increased the locomotor activity. Thus, it was established that the extract from *N. persica* aerial parts at the dose of 50 mg/kg, has an anxiolytic effect with less pronounced sedative and hypnotic effects than diazepam, and induces non-specific stimulation at the dose of 100 mg/kg [107].

N. cataria essential oil and nepetalic acid, significantly increased sleep induced by hexobarbital [110].

N. cataria aqueous–alcohol extracts showed two-phase effects on chick behavior: low and moderate dose levels (25–1800 mg/kg) led to an increase in the number of chicks falling asleep, while high dose levels caused a decrease in their number [111].

In Formisano et al. [112], the object of the research was *N. sibthorpii* Benth, a perennial herbaceous plant distributed in Greece, southern Albania and in south-eastern part of former Yugoslavia (now Northern Macedonia). In the experiments on rodents for the presence of a neuropharmacological activity, the preparations obtained from the herb were studied – the methanol extract (after the removal of the extractant), essential oil and the essential oil fraction containing epinepetalactone. All the drugs made changes in the general picture of behavior and potentiation of sleep induced by sodium pentobarbital. CNS depression is most likely associated with GABA-mediated effects of epinepetalactone. A sedative activity of ursolic acid isolated from *N. sibthorpii* herb, was also evaluated in mice. When administered orally at the dose of 2.3 mg/kg, ursolic acid had a significant depressant effect on the central nervous system. It was manifested in a decrease in the spontaneous motor activity [113].

N. sibthorpii ursolic acid isolated from the herb, has sedative and anticonvulsant effects [113]. The ursolic acid activity can be mediated through the GABA-energy system because it increases the waiting time for attacks induced by pentylenetetrazole (PTZ), a GABA-α receptor antagonist. In addition, ursolic acid exhibits a moderate affinity for the GABA-α receptor benzodiazepine site [112].

The paper presents data from a study of extracts from herb *N. glomerulosa* Boiss. – the total extract and its fractions – water, ethyl acetate and butanol. Studies were conducted in mice, it was found that all studied extracts at a dose of 50–200 mg/kg increased the duration of sleep induced by diazepam [113].

In Hosseini et al. [113], the data on the study of *N. glomerulosa* Boiss. (K. glomerular) extracts – the total extraction and its fractions (aqueous, ethyl acetate and butanol) are given. The studies were conducted on mice. It was found out that all the studied extracts at the dose of 50–200 mg/kg increased the duration of sleep induced by diazepam.

Clinical study. N. menthoides lyophilized aqueous extract was used in the treatment of depression. Twenty-two patients participated in a double-blind, randomized, controlled trial between April and September 2015. The patients were from two psychiatric clinics at Shiraz Medical University (Republic of Iran). Based on

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-1-4-28

the structured clinical survey, as defined in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.), the patients met the basic criteria for depression. They were randomly grouped to take *N. menthoides* extract or sertraline for 4 weeks. Compared to the control group, in the group receiving *N. menthoides* extract, the average values of the Beck questionnaire for detecting depression were significantly higher. In this group, which was examined within 2 weeks after the intervention, a lower relapse rate was detected. As a herbal formulation**,** the extract can be successfully used to normalize mood in patients with severe depression, since it was established that *N. menthoides* lyophilized aqueous extract has an antidepressant effect and prevents the relapse of depression [114].

Genus *Ocimum* L.

The members of the genus *Ocimum* L. are annual, less frequently short-living perennial herbaceous plants, sometimes sub-shrubs that grow wild in South America, Iran, China, the south of European Russia, the Caucasus, Central Asia and the Far East. *Ocimum* L. is cultivated in Western Europe, Asia, Africa, America. The genus has about 70 species. The greatest attention of researchers is drawn to *Ocimum basilicum* L., *O. sanctum* L. – syn. *O. tenuiflorum* L. (Tulsi) and *O. gratissimum* L. [115].

O. basilicum flowering aerial part (herb) contains 1.0–1.5% of essential oil, the main components of which are monoterpenes of a phenolic nature, anthocyanins, as well as phenolic glycosides, organic acids, vitamins, etc. [115]. The neurotropic properties of O. basilicum aerial part are associated with phenolic compounds and the essential oil containing methylchavicol (42.8%), geranial (13.0%), neral (12.2%) and β-caryophyllene (7.2%) [117]. O. basilicum is widely grown to obtain spices, its aqueous extract is used in folk medicine.

In the experiments on animals, anxiolytic, sedative, antidepressant, antistress effects of *Ocimum* L. essential oil and extracts from herbal raw materials of the species of the genus were established.

In experiments on the anxiolytic and sedative activities, the male Syrian mice were injected intraperitoneally with *O. basilicum* aqueous-alcohol extract at the doses of 100, 150 and 200 mg/kg and essential oil at the dose of 200 mg/kg 30 minutes before the test. It was found out that anxiolytic and sedative effects of the essential oil are higher than those of the aqueous-alcohol extract with the same doses. The extraction at the doses of 150 and 200 mg/kg and the essential oil at the dose of 200 mg/kg significantly increased the time spent by the mice in the open sleeves compared to the control group. None of the doses had a significant effect on the number of entries in the open sleeves. The aqueous-alcohol extracts, like the essential oil, reduced a locomotion of the mice compared to the control group [116].

An aqueous-alcohol extraction from *O. basilicum* leaves (in the author's designation "Sent-Ocim") prevents a depressive behavior in the rats sensitized with ovalbumin [117]. The animals were divided into three groups: the first was control, its animals were injected with saline, the second one was sensitized with ovalbumin, hereby, the extract was not used. The third group was divided into three subgroups, which were injected with hydroalcoholic extracts at the doses of 50, 100 and 200 mg/kg (Sent-Ocim 50, Sent-Ocim 100 and Sent-Ocim 200) against the background of sensitization with ovalbumin. In the «The open field» test, the number of intersections of the central zone was observed, the avoidance of which was directly associated with depression. The number of intersections of the central zone by the sensitized group animals was lower, and the number of intersections in the peripheral zone was higher than in the control group ($P<0.05$–$P<0.01$). The influence of Sent-Ocim 200 extraction significantly increased the number of intersections of the central zone ($P<0,05$), and in the subgroups with Sent-Ocim 50, Sent-Ocim 100 and Sent-Ocim 200, the number of intersections in the peripheral zone was lower than in the sensitized group ($P<0.01$–$P<0.001$). In the «The forced swim test», the immobility time in sensitized rats was higher, and the swimming and climbing times were lower than in the control group ($P<0.05$–$P<0.001$). In the animals of Sent-Ocim 200 group, the mobility was higher, just as the duration of swimming and climbing compared to the sensitized animals ($P<0.01$–$P<0.001$) [117].

O. gratissimum is an aromatic medicinal plant found in wild nature or cultivated throughout the tropics and subtropics. Hybrid *O. gratissimum* and *O. menthifolium* Hochst is known as *b. eugenolic*, which is a medicinal and spicy aromatic culture. It is used in official and traditional kinds of medicine. *B. eugenol* fresh leaves and inflorescences contains up to 0,6% of the essential oil. Its main component is eugenol and its esters [118].

A study on male albino mice showed that the methanol fraction of the extract obtained from *O. gratissimum* fresh leaves, has anxiolytic properties [118]. In order to detect sedative, anxiolytic, antidepressant and motility-coordinating effects of the influence of *O. gratissimum* essential oil on mice, the tests were performed using the "The open field», "Light-dark chamber", "The rotarod" and "The tail suspension" tests. The essential oil demonstrated calming, anxiolytic and antidepressant effects in mice and did not cause harmful effects on their motor coordination, which attributed by the authors to the synergistic effect of the components of *O. gratissimum* essential oil [119].

A spontaneous sedative effect was found in *O. gratissimum* essential oil of the thymol chemotype, which was rich in thymol and p-cymone and did not contain eugenol or 1,8-cineole. The authors also associate the observed effect with the synergistic interaction of the essential oil components [120].

O. sanctum is widely-spread in India as a spicy aromatic culture. In Ayurvedic medicine, drugs are obtained

from its aerial part. Flavonoids (circilineol, cirsimaritin, isotimusin, apigenin), phenylpropanoids (rosmarinic acid) were found out in the aqueous-alcohol extraction from the aerial part. Eugenol was found out in the composition of the essential oil [117].

O. sanctum extract from the leaves, induced a decrease in the duration of the state of immobility in rodents. This effect was enhanced under the influence of bromocriptine, an agonist of the dopamine D2 receptor, and was blocked by haloperidol and sulpiride, antagonists of the dopamine D2 receptor, which indicates that the antidepressant activity of the studied extract is associated with the involvement of the dopamine system and weakening of stress-induced changes associated with stress reduction serotonin in the brain in rodents [121].

O. sanctum extract obtained with 70% ethyl alcohol, showed the anti-stress activity in rats exposed to noise. In this study, Wistar albino rats were exposed to 100 dB broadband white noise 4 hours a day for 15 days. The analysis of norepinephrine, adrenaline, dopamine and serotonin contents in discrete regions of the rats' brain, performed by high-performance liquid chromatography (HPLC), indicates that a 15-day exposure to the noise stress can change the concentration of biogenic brain amines. The administration of *O. sanctum* extract had a normalizing effect on the discrete areas of the brain, controlled the change in neurotransmitter levels resulting from noise stress, thereby confirming the presence of the antistress activity in the extract [122].

The methanol extract from *O. sanctum* roots (after the removal of the extractant), was studied using «The forced swim» model. The intraperitoneal administration of the extract at the dose of 400 mg / kg increased the duration of swimming, which is associated with the antistress activity of the extract, while the effect was comparable to that of deschipramine, an antidepressant [123].

In the *in vitro* experiment it was established that the antistress activity of *O. sanctum* herbal raw material extracts is associated with inhibition of cortisol release, blocking of the CRHR1 receptor, and inhibition of the activity of type 11β-hydroxysteroid dehydrogenase and catechol-O-methyl transferase [124].

Genus *Origanum* L.

The genus Origanum L. has about 40 species and 18 hybrids, most of which are perennial herbaceous plants and shrubs, common in the eastern Mediterranean region [125].

Medicinal preparations *based on Origanum vulgare* L., are most widely used in folk and official medicine. In the aerial part, collected in the blossom period, the essential oil was found. It contained aromatic compounds (thymol, carvacrol, thymyl acetate, eugenol, trans-anethole thymol and carvacrol), monoterpenoids and sesquiterpenoids (terpineol, borneol, menthol, isomentol, pinene, citral, linalool, geranial, camphene, sabinene, limonene), triterpenoids (squalene, ursolic and oleanolic acids), steroids (sitosterol, daukasterin), carbohydrates (stachyose, raffinose), lignans (origalignanol), phenolpropanoids (rosmarinic ferulic, caffeic, protocatechuic), flavonoids (luteolin, apigenin, quercetin, naringenin, galangin, taxifolin), higher fatty acids [60]. The medicinal preparations obtained from *O. vulgare* herb, have a calming effect on the central nervous system, and are used for neurosis, insomnia, and hypertension.

The intraperitoneal administration *of O. vulgare* aqueous extract to the mice at the dose of 200 mg/kg had anxiolytic as well as sedative effects. In the «The open field test», it increased the number of exits to the open fields ($p<0.05$) and the duration of the time spent on them ($p<0.001$) compared with the animals that were administrated with saline. In addition, the extract reduced the locomotor activity of the mice ($p<0.05$), but, unlike diazepam, did not cause the muscle relaxant action [126].

Rezaie et al. provide an assessment of the anxiolytic effect of *O. majorana* extract on male rats, compared to diazepam. The extract was administered to the rats intraperitoneally 30 minutes before the experiment under the conditions of the «Elevated plus maze» test. The results showed a significant increase in the time spent by the animals in the open sleeves when the extract was administered at the doses of 200 mg/kg and 400 mg/kg. In addition, it was found out that the extract increases the duration of sleep induced by ketamine. It was found out that *O. majorana* extract at the dose of 200 mg/kg exhibits sedative and anxiolytic effects in the excess of those of diazepam at the dose of 1,2 mg/kg [127].

Genus *Perilla* L.

Perilla L. is a monotypic genus, the only member of which is *Perilla frutescens* (L.) Britton. It has two varieties: *P. frutescens* var. *crispa* (Thunb.) H. Deane and *Perilla frutescens* var. *hirtella* (Nakai) Makino [18].

Perilla is an annual herbaceous plant grown as an oilseed and food crop, initially in China and the countries of the Far East, then around the world, for a long time. *Perilla* L. is used in folk medicine. Rosmarinic and caffeic acids were found out in its aqueus-alcohol extract [128].

P. frutescens leaves are commonly found in traditional eastern collections, aqueous extracts which are mainly used to treat depression and anxiety disorders. Behavioral studies and chemical analyses showed that *P. frutescens* extracts, which exerted an antidepressant effect in «The forced swim test» contained rosmarinic acid. It was established that isolated rosmarinic and caffeic acids cause an antidepressant effect and exhibit an anxiolytic activity in a stress test. Neurochemical studies have shown that neither rosmarinic nor caffeic acids affect the absorption of monoamines or the activity of monoamine oxidase, which underlies the therapeutic value of existing clinically effective antidepressants.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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It was previously discovered that caffeic acid produces antidepressant and anxiolytic effects by modulating signals mediated by alpha-1-adrenergic receptors, and also weakens the downregulation of BDNF protein transcription (Brain-Derived Neurotrophyc Factor), which occurs as a result of forced swimming. These results indicate that rosmarinic and caffeic acids can have antidepressant and anxiolytic effects by a mechanism different from the mechanism of the action of the drugs currently used in clinical practice [128].

Genus *Rosmarinus* L.

The genus *Rosmarinus* L. has five species of evergreen shrubs. The most famous of them is *Rosmarinus officinalis* L. (medicinal (ordinary) rosemary) – a shrub or sub-shrub, with petiolate, evergreen leaves, the shape of the leaf blade is linear, the leaf is induplicate. *R. officinalis* place of origine is the western part of the Mediterranean. It is cultivated widely around the world: in Italy, France, Spain, Asia Minor, it is also grown on the southern coast of Crimea, the Black Sea coast of the Caucasus, in Azerbaijan and Central Asia. *R. officinalis* is one of the oldest medicinal plants, the leaves of which are used for food, as well as for obtaining drugs and performing rituals [129, 130].

In *R. officinalis* aerial part, there is up to 1.2% of the essential oil, in which α-pinene, 1,8-cineole, camphor, borneol, bornyl acetate are found, aqueous -alcohol extracts from the leaves contains diterpen carnosol, carnosolic and rosmarinic acids, salvigenin, rosmanol and cirsimaritin, flavonoids (apigenin), triterpenes and tannins [131].

For a long time, infusions from *R. officinalis* leaves, have been used in medicine as a means of improving digestion, choleretic, tonic, relieving stress, as well as in the post-stroke period, due to the ability to improve cerebral circulation.

R. officinalis aqueous-alcoholic leaves extract increases dose-dependently the number of entries and the time spent by the mice in the open sleeves. At the high doses its effect is similar to the effect of diazepam. In this case, the extract does not significantly affect the locomotor activity. The complex of flavonoids from *R. officinalis* leaves, especially apigenin, is able to penetrate the blood-brain barrier and, as a positive and allosteric regulator, enhance the effect of GABA on GABA receptors. Luteolin has sedative and anxiolytic effects, interacting directly with GABA receptors [132].

The substances isolated from *R. officinalis* leaves (diterpen rosmanol, flavonoids salvigenin and cirsimaritin), were examined in mice for acute toxicity, antinociceptive and antidepressant effects (in “The tail suspension” and “The forced swim” tests), effects on anxiety (“Elevated plus maze” and “Light-dark chamber” tests).

The studies revealed antinociceptive, antidepressant and anxiolytic properties of the compounds under study, realized by two-phase modulation of GABAA receptors. The anxiolytic activity of all three compounds did not increase under the influence of the antagonist of the benzodiazepine receptors of flumazenil, but was inhibited under the influence of the analeptic of petylenetetrazole (corazole), which indicates a mechanism of action through the GABAA receptors at the binding site, which is different from the site possessing affinity for benzodiazepine. It was also established that the isolated compounds do not cause signs of acute toxicity at the doses of 50 to 200 mg/kg [132].

Other studies have shown that total extract from *R. officinalis* leaves, favorably affects memory, eliminates anxiety, depression, and insomnia. The improvement in memory, is explained by inhibition of acetylcholinesterase in the brain, the remaining properties of the extract are associated with its effect on GABA receptors [130, 134].

Genus *Salvia* L.

One of the largest genera of the *Lamiaceae* family, including about 900 species, which are mainly represented by perennial herbaceous plants, shrubs and sub-shrubs [134]. All members of the genus are essential-oil-bearing. The most studied medicinal plant is *Salvia officinalis* L. Aqueous and aqueous-alcohol extracts from leaves, as well as essential oil, have been used in medicine for a long time. This is a perennial herb or subshrub, well-spread in wild nature in the countries of the Mediterranean and the Balkan Peninsula. This ubiquitous species is grown as a medicinal and spicy aromatic culture. *S. officinalis* leaves contain essential oil (up to 2.5%), as well as di- and triterpenes, phenylpropanoids, and derivatives of caffeic acid, including rosmarinic and lithospermic acids, flavonoids, tannins, etc. [135] The drugs based on *S. officinalis* leaves, have a disinfectant, anti-inflammatory, astringent, hemostatic, emollient and diuretic effect, and reduce perspiration. Leaves decoction has a stress-protective activity.

Carnosole and carnosolic acid isolated from *S. officinalis* leaves, inhibit binding of tert-butylbicyclofluoro [35S] thionate to the chloride channel of the GABA-benzodiazepine receptor complex in the brain tissue (at IC_{50} values of 57±4 μM and 33± 3μM, respectively), but have no effect on binding of [3H]-muscimol, [3H]-diazepam or [3H]-flunitrazepam. Therefore, the site of action of these compounds, apparently, is located directly on the chloride channel and differs from miltiron [136]. In another study, three flavones and two abitan diterpenes, functioning as active benzodiazepine receptors, were identified by fractionating a methanol extract from *S. officinalis* leaves. Some flavones, such as apigenin [137], luteolin [93], linarin [138] and hispidulin, exhibit anxiolytic effects through the GABAergic mechanism similar to benzodiazepines [139].

Apigenin, Hispidulin, and cirsimaritin competitively inhibit binding of 3H-flumazenil to the benzodiazepine receptor with IC_{50} values of 30, 1.3, and 350 mM, respec-

tively. The IC_{50} values of abietane diterpenes, 7-methoxysmanol and haldosol consist of 7.2 and 0.8 mM, respectively [140]. In addition to the official form, *S. aethiopis* L., *S. sclarea* L., *S. pleberia* R. Brown, *S. daghestanica* Sosn., *S. elegans* Vahl. and etc are also of scientific interest [60, 141].

In the aqueous-alcohol extract from *S. elegans* leaves, ursolic acid and flavonoid 5-O-(6-rhamnosylglucoside)-7-hydroxy-4'-methoxyflavonone were detected and isolated [142]. They showed antidepressant activity in mice [143]. Herrera-Ruiz et al. estimated the anxiolytic and antidepressant activities of the aqueous-alcohol extracts (the extractant was 60% ethyl alcohol) obtained from *S. elegans* flowers and leaves, in mice. The extract, administered orally, increased the time the mice spent on the light side in the "Light-dark chamber" test and the time of the animals' immobility subjected to forced swim. The administration of the extract also increased the animals' time, spent in the open sleeve, and the entrances to the open sleeves in the "Elevated plus maze" test. The same extract could not modify the spontaneous locomotor activity measured in "The open field test" [144].

The aqueous-alcoholic extract from *S. reuterana* leaves (100 mg/kg) had an anxiolytic effect in mice in the "Elevated plus maze" test [145].

According to Javdan et al [146], neuropharmacological effects of *S. hypoleuca* leaves extract administrated to Wistar line rats at the dose of 150 mg/kg/day for 10 days, potentiated pentobarbital-induced sleep, reduced the number of animals in the open sleeves outputs. *S. leriifolia* aqueous leaf extract increased the sleep induced by pentobarbital, at the doses of 1.15 and 1.57 g/kg, but the effects were weaker than that of diazepam [147].

S. sclarea essential oil significantly increased the hexobarbital anesthetic effects (drug "Evipan") at the doses less than 20% LD_{50} (520 mg/kg in male mice), but had no significant effect on the spontaneous locomotor activity and statokinetic reflexes [148].

The biologically active substances of *S. triloba* essential oil, prolong sleep induced by hexobarbital in rats. *S. triloba* ethanol extract showed moderate affinity for the benzodiazepine $GABA_A$ receptor site [149].

S. guaranitica is an officinal medicinal plant in Latin America. Its herbal raw materials are used to produce sedative drugs. It was proved that circyliol (5,3',4'-trihydroxy-6,7-dimethoxyflavone) and caffeic ethyl ester, which are part of the plant's ethanol extract, are ligands with a competitively low affinity for benzodiazepine receptors [150]. In another study, circiliol exhibited a dose-dependent hypnotic effect in a sleep induced by pentobarbital. Circiliol was found to be stronger in binding 3H-zolpidem (Ki = 20 μM) than in binding 3H-flunitrazepam (Ki = 200 μM) to rats' benzodiazepine receptors. Consequently, circiliol has sedative and hypnotic properties, probably acting on the so-called benzodiazepine receptor type I [151].

*S. haematodes (*syn.*S. pratensissubsp. haematodes* (L.) Arcang.) ethanol extract from the aerial part, has an antidepressant activity in mice. It significantly increased pentobarbital-induced sleep and decreased the rats' excitation induced by amphetamine. Sedation is also apparent from the results that indicated an increase in hypoxic survival time in mice [152, 153].

S. miltiorrhiza root is widely used in China to produce drugs for the treatment of neurasthenic insomnia [154]. From the extract obtained by diethyl ether from the roots of this plant, ten diterpenic quinones were isolated. In the carried out radioligant studies, they inhibit binding of [3H] -flunitrazepam to central benzodiazepine receptors with an IC_{50} of 0.3 to 36.2 μM. Among the isolated compounds, the highest activity (IC50 = 0.3 μM) was demonstrated by miltiron, which showed an increase in the affinity in the presence of 100 μM GABA. Miltiron induced muscle relaxation, sedation, dependence, and withdrawal symptoms in mice at the doses of 10–60 mg/kg, which were effective in a behavioral test. Consequently, miltironderivatives may represent a new class of plant-derived tranquilizers [155].

The aqueous-alcohol extract from *S. pleberia* aerial part, contains flavonoids (Hispidulin, homoplantoginin, nepetin, nepetrin, 6-hydroxyluteolin, apigenin, luteolin) and rosmarinic acid [155].

Johnston et al. [156] conducted animal experiments using compounds isolated from *S. pleberia*. Ethyl acetate fractions obtained from *S. pleberia* aerial part, are more active than methanol ones due to the content of rosmarinic acid, which is active at 10 mg/kg in the model of pentobarbital-induced sleep in mice.

Flavone Hispidulin (5,7,4'-trihydroxy-3'-methoxyflavone) isolated from *S. pleberia*, has agonistic GABA receptor activity.

Genus *Satureja* L.

The genus *Satureja* L. has up to 50 species represented by annual plants, shrubs and sub-shrubs, which are distributed mainly in the countries of Asia, the Middle East and the Mediterranean [157].

Medicinal preparations based on *Satureja hortensis* L., are widespread in folk and official medicine. *Satureja hortensis* L. is an annual herb that grows and is cultivated in southern Europe, Central Asia, Turkey, and the Caucasus. Aqueous extracts and essential oil from *Satureja hortensis* L. aerial part, have insecticidal, antibacterial and anthelmintic activity, and used for diseases of the gastrointestinal tract, headaches, dizziness, tachycardia, etc. The chemical composition of the essential oil is represented mainly by terpenes and aromatic compounds (carvacrol, thymol, p-tsimen, g-terpinene, α- and β-pinene, sabinene, limonene, carvone, caryophyllene oxide). Aqueous-alcohol extracts contain phenylpropanoids (rosmarinic, caffeic, isoferulic, chlorogenic acids), flavonoids (naringenin, quercetin, apigenin, kaempferol, luteolin and their glycosides) [157].

ОРИГИНАЛЬНАЯ СТАТЬЯ
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S. hortensis aqueous-alcohol extract was examined for the antidepressant activity in the "Elevated plus maze", "Force swim" and "Forced immobilization" tests on Wistar rats. It was found out that the studied extract reduces depression in the test animals at the dose of 400 mg/kg [158].

Carvacrol, which is present in *S. hortensis* essential oil, was administered to the mice p.o. at the doses of 12.5, 25 and 50 mg/kg. It exhibited an anxiolytic effect in the «Elevated plus maze» test, which was leveled out under the influence of flumazenil, the antagonist of the benzodiazepine receptors. However, carvacrol did not show sedative or muscle relaxant properties and did not affect the motor activity [159].

Genus *Schizonepeta* (L.) Briq.

Genus Schizonepeta (L.) Briq. consists of 3 species of annual or perennial herbaceous plants, growing mainly in Siberia, Primorye and Northern China [160].

The most studied species is *Schizonepeta multifida* (L.) Briq., a perennial herbaceous plant growing in the herbage of meadow steppes, stepped and forested upland meadows in southern Siberia, Yakutia, the Far East, Central Asia and Mongolia. The aerial part of the plant contains up to 1.6 *S. multifida* dry extract in the dose range of 50–300 mg/kg, increases the number of water intakes in the conflict methodology according to Vogel. Thereby, the effectiveness of the extract (in the dose range of 100–300 mg/kg), in a number of parameters, exceeded that of the drugs of rhizomes with valerian roots [161].

S. multifida dry extract in the dose range of 50–200 mg/kg, has pronounced anxiolytic, antidepressant, nootropic and anticonvulsant activities, and at the dose of 300 mg/kg – moderate sedative properties. The anxiolytic effect is realized to a greater extent due to the essential oil and luteolin-7-O-glucoside included in its composition, to a lesser extent - due to ursolic acid. In an experimental therapeutic dose, *S. multifida* extract provides pronounced pharmacotherapeutic efficacy in chronic stressful situations, reduces the feeling of fear and anxiety, restores emotional status, helps maintain a memorable trace, limits the severity of stress changes in the internal organs of animals, as well as the formation of regressive forms of neurons in brain structures. The main pharmacological mechanisms that determine anxiolytic, antidepressant and neuroprotective effects of *S. multifida* dry extract are: restriction of hyperactivation of the sympatho-adrenal and hypothalamic-pituitary-adrenal systems, inhibition of free radical processes, activation of the antioxidant system of the body and GABA-energy metabolic normalization with its ability to provide antioxidant, membrane-stabilizing, stress-protective and antihypoxic drugs action [160].

Genus *Scutellaria* L.

Scutellaria L. is one of the largest genera, uniting about 350 species, widely-spread in temperate subtropical and tropical zones including Europe, North America and East Asia [162]. Most of them are perennial, rarely annual, herbaceous plants, less commonly shrubs and sub-shrubs. Unlike most members of the genus *Lamiaceae*, which are essential-oil-bearing and belong to the subfamily *Nepetoideae*. The members of the genus *Scutellaria* form the subfamily *Scutellarioideae* and are among the dyeing plants. The most famous member of the genus is *Scutellaria baicalensis* Georgi, a perennial herbaceous plant. Its areal comprises the Russian Baikal region, Amur region, PrimorskyTerritory, as well as Mongolia, China, and Korea.

The roots of *S. baicalensis* contain flavonoids (baikalin, scutellarin, baikalein, apigenin, luteolin, etc.), chalcones, isoflavones, biflavones, lignoflavonoids, phenylpropanoids, phytosterols, saponins, etc. This species is among the most popular medicinal plants in China, Mongolia and the Far East. Drugs from its roots have a pronounced sedative and antiepileptic effects [163].

Baikalin and vogonin are commonly considered the main active components of *S. baicalensis* flavonoids.

In the experiments on rats and mice (7.5–30 mg/kg), Baikalin (5,6,7-trihydroxyflavone 7-O-glucuronide) had an anxiolytic effect, but did not affect the motor activity of the mice [169]. Baikalin interacts preferably with subtypes of GABA-α receptors containing subunits of α-2 and α-3, in contrast to benzoadepins that do not have such a specificity [12].

Vogonin is the main *S. baicalensis* component, inducing anxiolysis in male mice at the dose of 7.5–30 mg/kg in the "Elevated plus maze" test [164]. Vogonin exhibits neuroprotective and anxiolytic effects. Having a pronounced affinity for the active benzodiazepine centers of GABAergic ergic receptors, it inhibits the activation of microglia [165, 166].

In European medicine, the aerial part of *S. lateriflora* has been widely used for more than 200 years to obtain drugs – a mild relaxant and agent for treating anxiety, nervous tension and seizures [167]. Flavonoids baikalin and baikalein, are considered the main active compounds in *S. lateriflora* herb. Baikalein is defined as a ligand of the benzodiazepine receptor (with a weak affinity) and has shown sedative and anxiolytic effects that occurs through the GABA-α-nonbenzodiazepine sites [168].

S. lateriflora aqueous-alcoholic extract was studied in rats *in vivo* behavioral tests. The extract (after the removal of ethanol) a mixture with milk was introduced: in the test group, 100 mg of the amount of extractives in 1 ml of milk was administered; in the control group it was only 1 ml of milk. It was found out that the rats receiving the extract, showed a more risky and less anxious behavior than the rats in the control group [169].

Genus *Stachys* L.

The genus *Stachys* L. consists of more than 270 species distributed throughout the world. These are: peren-

nial, rarely annual herbaceous plants or shrubs [170]. Among them there are: *Stachys officinalis* (L.) Trevis. – syn.: *Betonica officinalis* L., *S. palustris* L., *S. lavandulifolia* Vahl., *S. tibetica* Vatke., *S. betoniciflora* Rupr.– syn. *Betonica foliosa* Rupr., *S. sylvatica* L. et al.

Flavonoids (luteolin, apigenin, scutellarine, stachyflaside, vitexin), quinones, iridoids (harpagide, harpagoside, acetylgarparide, ajugol, and ajugoside), phenolic acids, diterpenoids (stachysic acid, abietatriene, annuanone, stachylone) were detected in aqueous-alcohol extracts from various *Stachys* species. In the composition of essential oil, D-germacrene, β-fellandren, α- and β-pinenes, myrcene were detected [60, 170, 171]. Flavonoid glycoside apigenin-7-glucoside is present in *S. tibetica* aqueous-alcohol extracts, acipylene (66.4%), fenchyl alcohol (8.9%), α-pinene (8.2%) caryophyllene oxide (4.7%), menthol (1.7%) and geraniol (1.3%) are in the essential oil [172]. *S. betoniciflora* aerial parts contain flavonoids, apigenin derivatives, stachidrin nitrogen base, iridoids, essential oil [173].

For a long time, *Stachys* extracts from herbs of various types have been used in folk medicine, in particular, in cases of gynecological bleeding. *S. sylvatica* hydroalcoholic extract has pronounced hypotensive and sedative effects, the latter being superior to Leonurus L. tincture [173, 174].

The fractions obtained from *S. lavandulifolia* aerial part extraction with petroleum ether, ethyl acetate, butanol and water, were tested for a spontaneous locomotor activity and the behavior of mice in the "Elevated plus maze" model. The test samples (after the removal of organic solvents) were administered intraperitoneally to the male mice in various doses for 30 minutes before assessing their behavior. The aqueous-alcohol extract (50 mg/kg), the fractions obtained with petroleum ether (25 and 50 mg/kg), ethyl acetate (25 and 50 mg/kg) and water (50 mg/kg) significantly increased the time and number of entrances in the open sleeves. The butanol fraction up to 50 mg/kg did not significantly affect any of the measured parameters. A spontaneous locomotor activity was significantly reduced in the animals injected with each fraction, compared to saline. The ethyl acetate and water fractions showed the smallest and maximum decreases in activity, respectively. The anxiolytic effects of ethyl acetate, petroleum ether and water fractions may be associated with the content of flavonoids, phenylpropanoids or terpenoids [174].

S. lavandulifolia aqueous-alcoholic extract and its essential oil were administered intraperitoneally to the male mice in various doses 30 minutes before the behavior assessment. *S. lavandulifolia* extract at the dose of 100 mg/kg increased the period of time spent, spent by the animals in the open sleeves; and it decreased the number of entries in the open sleeves. Besides, it decreased the period of time, spent by the animals in the closed sleeves. The extract at the doses below 100 mg/kg, did not significantly affect any of the parameters measured on the «Elevated plus maze» model. This dose of the extract prolonged ketamine-induced sleep time and decreased a locomotor activity in mice. *S. lavandulifolia* extract has an anxiolytic effect with a relatively lower sedative activity than diazepam. *S. lavandulifolia* essential oil in the doses up to 100 mg/kg did not significantly affect the behavior of the mice [175].

Methanol extracts obtained from *S. tibetica*at roots and herbs at the doses of 200 and 400 mg/kg significantly increased the time and number of entries into the open sleeves ($P<0.01$), but reduced the time and number of entries into closed sleeves. At the same time, the extracts reduced the time spent by the animals in the center of the maze (latency) [176].

Kumar et al. isolated flavonoids from *S. tibetica* and evaluated their anxiolytic activity in Wistar rats. The number of entries and the percentage of entries in the open sleeves increased, while the number of entries and the duration of time spent in the closed sleeves, decreased in the group receiving apigenin-7-glucoside. Apigenin-7-glucoside significantly reduced the number of head dives in the «Elevated plus maze» test. Apigenin-7-glucoside showed anxiolytic potential comparable to the reference drugs apigenin and diazepam [177].

In the test on the social interaction, apigenin-7-glucoside at the doses of 25 and 50 mg/kg, decreased the aggressive behavior of albino rats, while the time of social interaction significantly increased in bright light, in familiar and unfamiliar conditions. In «The hole-board test», *S. tibetica* essential oil significantly increased the number of head dives in the holes, the number of entrances and the time spent in the open sleeves of the "Elevated plus maze" test, while in the "Light-dark chamber" test it showed an increase in the number of transitions and the time spent on the bright side. The results indicate that *S. tibetica* essential oil has an anxiolytic effect [177].

The effect of methanol extracts from four Balkan endemic taxa – *Stachys*: *S. anisochila* Vis. et Pancic, *S. beckeana* Dorfl. et Hayek, *S. plumosa* Griseb. and *S. alpina (L.) subsp. dinarica* - administered intraperitoneally in the range of 100–400 mg/kg, on the behavioral activity, was studied on the adult male Wistar rats in the "Elevated plus maze test", during the observation of the spontaneous locomotor activity, in the tests on strength and compression, mainly predicting anxiolytic, sedative and muscle relaxant actions. As a result, it was established that the studied *Stachys* extracts do not have any anxiolytic or muscle relaxant activity, and *S. beckeana* at 400 mg/kg has an anxiogen-like effect. The study using β-carboline-3-carboxylate-tert-butyl ether, a selective antagonist of benzodiazepine receptors, showed that the sedative effect of the methanol extract of *S. alpina subsp. dinarica* was partially mediated by GABA-α receptors containing the α-1 subunit. The behavioral effects of *S. anisochila* and *S. plumosa* extracts did not differ. Chlorogenic acid and verbascoside were identified in all the extracts. *S. anisochila*, *S. beckeana* and *S. alpina sub-*

ОРИГИНАЛЬНАЯ СТАТЬЯ
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sp. dinarica flavonoid fraction consisted of isoscutellarin and hypoalectin glycosides, whereas in *S. plumosa* fraction had chrysoriol and apigenin glycosides. The results show a psychotropic potential of the flavonoids of four *Stachys* endemic taxa. *S. alpine subsp. dinarica* turned out to be the most promising for the preparation of a sedative drug [178].

Genus *Thymus* L.

The genus *Thymus* L. is one of the largest in the family *Lamiaceae*, it includes several hundred species, distributed mainly in Eurasia and North Africa. On the territory of Russia and neighboring countries, there are about 170 species [56]. The members of the genus are low-growing shrubs and sub-shrubs belonging to essential-oil-bearing plants.

In the composition of the essential oil from various plant raw material samples of species of the genus *Thymus*, the following substances were detected: thymol (12–61%), carvacrol (0.4–20.6%), 1,8-cineole (0.2–14.2%), p-cimen (9.1–22.0%), linalool (2.2–4.8%), borneol (0.6–7.5%), a-pinene (0.9–6.6%), camphor (up to 7.3%), etc. [180]. The most studied are *T. vulgaris* L. and *T. serpillum* L., the latter is more common in nature. The herb of both types is used to obtain drugs, which are widely used in medicine.

F. Komaki et al. showed an anxiolytic effect of the aqueous-alcoholic extract from *T. vulgaris* leaves when weekly administrated p.o. to the male rats of the Wistar strain in the “Elevated plus maze” model [180].

Thymol (monoterpene phenol – 2-isopropyl-5-methylphenol) is the dominant essential oil component of *T. vulgaris*, at the dose of 20 mg/kg, it significantly increases the time spent by Swiss albino mice in the open sleeves in the «Elevated plus maze» test [181].

Methanol extracts and *T. fallax* Fisch essential oil from the aerial parts of & C.A. Mey., *T. kotschyanus* Boiss. & Hohen., *T. pubescens* Boiss during “The forced swim” test significantly reduced the period of immobility of the animals, compared with the control, and showed a dose-dependent antidepressant activity. The test results showed that *T. fallax* extracts and essential oil have a greater antidepressant activity than those from *T. kotschyanus* and *T. pubescens* [182].

CONCLUSION

The review presents some of the results of the scientific research on the pharmacological activity of various fractions of biologically active substances, essential oils and individual compounds obtained mainly from the aerial parts of plants of *Lamiaceae* family members.

Most of the plant species considered play an important role in traditional medicine of different countries and have a therapeutic and prophylactic value in the stress-correction-therapy. Many of them, being pharmacopoeial, are sources of medicinal plant raw materials in modern pharmacy and medicine.

The members of the Lamiaceae family often become objects of the scientific invesigation, where a search for new sedative, anxiolytic and neuroprotective agents is carried on. A lot of attention is paid to both - relatively well-studied plant species (for example, from the genera Salvia, Stachys, Thymus) and insufficiently explored genera, including tropical and subtropical ones, which are not represented in the flora of Russia (Agastache, Clerodendrum, Clinopodium, Eremostachys, Leucas, ets.).

This review has comprised 71 species from 30 genera of the family. In spite of a fairly significant level of a previous study which can be notified in the analysis of this publication, a large number of potentially resource species remain unexplored. In the future, they may be of pharmacognostic interest and have a practical application, in particular, in the field of creating new drugs with neurotropic effects.

The carried out analytical review makes it possible to assess the current level of knowledge of the neurotropic activity of various substances obtained from the plant raw materials from the *Lamiaceae* Linddl. family and to establish promising areas of the scientific research for the creation of new drugs.

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All authors equally contributed to the research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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