Journal of Ethnopharmacology 154 (2014) 481–536

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Review

# Medicinal Plants of the Russian Pharmacopoeia; their history and applications

Alexander N. Shikov [a,*], Olga N. Pozharitskaya [a], Valery G. Makarov [a], Hildebert Wagner [b], Rob Verpoorte [c], Michael Heinrich [d]

[a] St-Petersburg Institute of Pharmacy, Kuz'molovskiy town, build 245, Vsevolozhskiy distr., Leningrad reg., 188663 Russia
[b] Institute of Pharmacy, Pharmaceutical Biology, Ludwig Maximilian University, D - 81377 Munich, Germany
[c] Natural Products Laboratory, IBL, Leiden University, Sylvius Laboratory, PO Box 9505, 2300 RA Leiden, Sylviusweg 72
[d] Research Cluster Biodiversity and Medicines. Centre for Pharmacognosy and Phytotherapy, UCL School of Pharmacy, University of London

ARTICLE INFO

*Article history:*
Received 22 January 2014
Received in revised form
31 March 2014
Accepted 4 April 2014
Available online 15 April 2014

*Keywords:*
Aralia elata
Bergenia crassifolia
Bidens tripartita
Gnaphalium uliginosum
Inonotus obliquus
Tussilago farfara

ABSTRACT

*Ethnopharmacological relevance:* Due to the location of Russia between West and East, Russian phytotherapy has accumulated and adopted approaches that originated in European and Asian traditional medicine. Phytotherapy is an official and separate branch of medicine in Russia; thus, herbal medicinal preparations are considered official medicaments. The aim of the present review is to summarize and critically appraise data concerning plants used in Russian medicine. This review describes the history of herbal medicine in Russia, the current situation and the pharmacological effects of specific plants in the Russian Pharmacopoeia that are not included in the European Pharmacopoeia.
*Materials and methods:* Based on the State Pharmacopoeia of the USSR (11th edition), we selected plant species that have not yet been adopted in Western and Central Europe (e.g., selected for inclusion in the European Pharmacopoeia) and systematically searched the scientific literature for data using library catalogs, the online service E-library.ru, and databases such as Medline/Pubmed, Scopus, and the Web of Science regarding species, effectiveness, pharmacological effects, and safety.
*Results:* The Russian Federation follows the State Pharmacopoeia of the USSR (11th edition), which contains 83 individual plant monographs. Fifty-one of these plants are also found in the European Pharmacopoeia and have been well studied, but 32 plants are found only in the Pharmacopoeia of the USSR. Many articles about these medicinal plants were never translated in English, and much of the information collected by Russian scientists has never been made available to the international community. Such knowledge can be applied in future studies aimed at a safe, evidence-based use of traditional Russian medicinal plants in European and global phytopharmacotherapy as well as for the discovery of novel leads for drug development.
*Conclusion:* The review highlights the therapeutic potential of these Russian phytopharmaceuticals but also highlights cases where concern has been raised about product safety and tolerability, which would aid in supporting their safe use.


**Contents**

1. Introduction . . . 482
2. The history of herbal medicine in Russia . . . 483
3. Current situation . . . 484
4. Classification of HMPs . . . 484
5. Information found in pharmacopoeia monographs . . . 484
5.1. Anti-inflammatory agents . . . 486
5.1.1. HERBA BIDENTIS . . . 486

* Correspondence author. Tel.: +7 812 3225605; fax +7 812 6032432.
*E-mail addresses:* spb.pharmacy@gmail.com, alexs79@mail.ru (A.N. Shikov), m.heinrich@ucl.ac.uk (M. Heinrich).

http://dx.doi.org/10.1016/j.jep.2014.04.007

5.2. Diaphoretic and anti-inflammatory agents. . . . 488
5.2.1. FRUCTUS VIBURNI . . . . 488
5.3. Hypotensive, anti-inflammatory, and choleretic agents. . . . 488
5.3.1. HERBA GNAPHALII ULIGINOSI . . . . 488
5.4. Bitterants (appetite stimulants) . . . . 488
5.4.1. HERBA CENTAURII . . . . 488
5.5. Astringents. . . . 492
5.5.1. FRUCTUS ALNI . . . . 492
5.5.2. HERBA HYPERICI . . . . 492
5.5.3. RHIZOMATA BERGENIAE . . . . 493
5.6. Choleretic agents . . . . 493
5.6.1. FLORES HELICHRYSI ARENARII . . . . 493
5.7. Antihelmintic and choleretic agents . . . . 493
5.7.1. FLORES TANACETI . . . . 493
5.8. Expectorants . . . . 495
5.8.1. CORMUS LEDI PALUSTRI . . . . 495
5.8.2. FOLIA FARFARAE . . . . 497
5.8.3. FOLIA PLANTAGINIS MAJORIS . . . . 500
5.8.4. GEMMAE PINI . . . . 500
5.8.5. RHIZOMATA ET RADICES INULAE . . . . 500
5.8.6. RHIZOMATA CUM RADICIBUS POLEMONII . . . . 500
5.9. Diuretic agents. . . . 503
5.9.1. CORTEX VIBURNI . . . . 503
5.9.2. FLORES CENTAUREAE CYANI . . . . 503
5.9.3. FOLIA VITIS-IDAEA . . . . 503
5.9.4. GEMMAE BETULAE . . . . 505
5.10. Cardiotonic agents . . . . 505
5.10.1. HERBA ADONIDIS VERNALIS . . . . 505
5.10.2. HERBA CONVALLARIAE et FOLIA CONVALLARIAE et FLORES CONVALLARIAE . . . . 508
5.11. Cardiovascular agents . . . . 509
5.11.1. FLORES CRATAEGI et FRUCTUS CRATAEGI . . . . 509
5.12. Haemostatic agents . . . . 509
5.12.1. HERBA POLYGONI HYDROPIPERIS . . . . 509
5.13. Spasmolytic agents . . . . 510
5.13.1. FRUCTUS ANETHI GRAVEOLENTIS . . . . 510
5.13.2. RHIZOMATA ET RADICES RUBIAE . . . . 512
5.14. Sedatives . . . . 516
5.14.1. HERBA LEONURI. . . . 516
5.15. Polyvitamins . . . . 516
5.15.1. FRUCTUS SORBI . . . . 516
5.16. Regulation of metabolism and anti-inflammatory agents . . . . 516
5.16.1. INONOTUS OBLIQUUS . . . . 516
5.17. Tonics . . . . 520
5.17.1. RADICES ARALIAE MANDSHURICAE . . . . 520
5.17.2. RHIZOMATA ET RADICES RHODIOLAE ROSEAE. . . . 522
5.18. No pharmacological group is stated in the Pharmacopoeia. . . . 525
5.18.1. HERBA POLYGONI PERSICARIAE . . . . 525
5.18.2. HERBA THERMOPSIDIS LANCEOLATAE . . . . 527
6. Conclusions . . . . 529
References . . . . 530

## 1. Introduction

Approximately 350,000 higher plants are estimated to exist (Heywood 2011). Relatively speaking, very few medicinal plants have been studied scientifically. Russia's large size and varied soils, topography and climate favor the growth of an extensive number of herbs, trees, and other plants. This had led to an active interest in locally grown plants, which has stimulated serious study by traditional healers and early official physicians alike. Herbal and natural remedies are the product of hundreds of years of careful observation of their therapeutic effects and risks; thus, their properties and side effects are quite well known. In one approach, scientists isolated one or more of the medicinal principles from individual herbs in the laboratory (and possibly enhanced them chemically) to create new medications that were often more powerful than the original plant. This approach eventually led to the development of a number of new herb-based medicines and the creation of synthetic pharmaceuticals that duplicate the active medicinal element of the original plant. Aspirin, codeine, digoxin, and other drugs have their origins in herbal medicine (Yarnell, 2000). However, not all of these efforts were successful. Scientists have often found that the herbs themselves, which possess unique combinations of chemical components, are more effective than the chemical derivatives (Li, 2002). As a result, medical science has also focused on the medicinal values of the herbs themselves and how they could best be incorporated into medical practice.

Although synthetic medicine continues to progress, the value of medicinal plants (especially those in the highly developed and unique Russian herbal medical tradition) remain largely unknown in the West.

Nevertheless, information about plants that are referenced in the Russian Pharmacopoeia and their applications remain

fragmentary. The aim of the present review is to fill this gap by summarizing the data concerning plants used in Russian officinal medicine. This review describes the history of herbal medicine in Russia, the current situation and the pharmacological effects of plants that appear in the Russian Pharmacopoeia but are not included in the European Pharmacopoeia. Such knowledge can be applied to expanding the use of these plants in the pharmacotherapy of European and other countries and in the development of new drugs.

## 2. The history of herbal medicine in Russia

In many regions of the world and in a very generic way, the use of herbal medicines can be classified into two main strands: popular orally transmitted traditions that are passed on from generation to generation and dogmatic or “official” traditions that today are often based more on scientific investigation (Zevin et al., 1997).

Until the tenth century, popular Russian healing traditions had a limited exchange of ideas between the various regions, at the time when the herbal and medical literature was first introduced. At this time, copies of several Greek herbals found their way into Russia through the monasteries and were eventually translated into Russian. Unlike the herbal practice in other countries, however, the Russian herbal tradition was strong and well-established. The first pharmacy (potion store) (Rus= зелейная лавка) was opened in Russia in the hospital of Kiev-Pechora Lavra in 1005–1010 by the monk Makoveit from Athos; this event is likely to have strengthened the Greek influence on Russian medicine. According to the chronicles of the old city of Novgorod, Russian herbalists (called "knowledgists") were able to cure infected wounds with "banya mold" (Solovieva, 2005). In the thirteenth century, these herbalists discovered the properties of the mold, which was used to poultice wounds. This predates the development of penicillin in England by seven centuries. Thus, these chronicles give a good indication of the level of Russian popular medicine during this period.

Starting in the mid-thirteenth century and for over three hundred years, Russia was occupied by Tartars and Mongolians. These people brought their own herbal traditions, which were incorporated into healing praxis by local herbalists.

Although practically no information is available regarding the following centuries, from the 15$^{th}$ to the 16$^{th}$ century, the Russian empire expanded. Among its neighbors, Russia counted countries in Western Europe and Asia, and herbalists began to accumulate and adapt the Asian-Arabic and West European herbal traditions. This led to the development of the unique features and advantages of the Russian herbal system, combining autochthonous and introduced knowledge and practice.

State-control over medicine in Russia can be traced back to the end of sixteenth century. The first enterprise to hold responsibility for medical affairs was the Apothecary's Chamber, which was opened in Moscow in 1581 by Tsar Ivan the Terrible (Ivan Grozny). In 1620, this enterprise was reformed as the Apothecary's Order (Blinova, Yakovlev, 1990). The first head of the Apothecary's Order was oprichnik (a member of an organization established by Tsar Ivan the Terrible to govern the division of Russia known as the Oprichnina), Knjaz Afanasy Vjazemsky. Apothecary James Frencham from Great Britain is generally regarded as the founder of the first Moscow Court Pharmacy - the progenitor of the Russian medico-apothecary system. The exact date of its foundation is uncertain but is likely to be in the years before 1581 (Appleby 1983). The Moscow Court Pharmacy in the Apothecary's Chamber served the exclusive needs of the Tsar and his family (Appleby, 1983).

The first public pharmacy was opened within a public hospital on March 20, 1672 in Moscow. One famous herbalist manuscript, "Cool vineyard" (rus= Прохладный вертоград) was published in 1672. The main part of manuscript was "about the overseas and Russian potions and about wood and herbs" (Sokolov, 2000).

In the eighteenth century, Tsar Peter the Great initiated major reforms to the system. One of those reforms was the Apothecary's Reform, which fixed European normative and European type of the pharmaceutical service. Under a decree by Peter the Great, Korpisaari Island in Saint-Petersburg was designated in 1714 as the location of the Apothecaries' Chancery and the principal Pharmacy. At the same time, the local Apothecary's Garden was founded.

Establishing of the State Academy of Science (1724) opened new horizons in the systematization of knowledge and in surveys of the rich Russian floral resources. New medicinal plants were documented in the four-volume work, "Flora of Siberia", the result of a Siberian expedition by I.I. Gmelin (1732-1743). After exploring Siberia and the Volga river regions, academician P.S. Pallas published the classical text, "Description of herbs of Russian State with pictures". Prof. I.I Lepehin (1740-1802) promoted the utilization of local flora and argued that the importation of medicinal plants should be decreased (Muraviova, 1991).

Russia was among the first countries to compile a pharmacopoeia. In 1778, the Pharmacopoeia Rossica was published in St. Petersburg by the Russian Academy of Science. This work contains 770 monographs, including 316 texts relating to herbal medicinal preparations, 147 relating to chemical substances, and 29 relating to the preparation of medicines from animal sources and complex mixtures. Each entry is written mostly in Latin, but the Russian name of the botanical simple or preparation is provided. Entries for medicinal plants include their name, geographical origin, odor, taste, therapeutic qualities, uses, doses, and preparation (Tshibilaev et al., 2006). However, Russia's first National Pharmacopoeia written in Russian was published nearly a century later, in 1866.

In the nineteenth century, European physicians had completely forgotten about the herbal traditions that had once predominated in their countries, whereas Chinese healers had almost no awareness of the medical developments in the West. Russian doctors were unique because they knew of both their own folk-herbal tradition and of modern Western medicine.

The nineteenth century was marked by the beginning of the study of the chemical composition of medicinal plants. Starting with the isolation of atropine (1833), it became apparent during the early 19th century that the pharmaceutical properties of plants result from specific compounds that can be isolated and characterized (Heinrich et al., 2012). For example, Prof. G.G. Dragendorff (1879) published a series of articles on the "Relationship between the chemical constituents and botanical features of plants" in the Pharmaceutical Journal.

By the early twentieth century, Russian scientists had generated much scientific data regarding medicinal plants. However, after the October revolution in 1917, the Soviet Union became closed off from the rest of the world, and this research progress was not shared for a long time. Luckily, the Soviet Union government did not discard Russian medicine and herbalism. Many institutes and academies for the study of medicinal plants were established in all regions of the Soviet Union.

A new era of the intensive study of medicinal plants was initiated in the middle of the twentieth century. On March 4, 1943, Joseph Stalin signed Order No 4654-p of the People’s Commissars Council of the Union of Soviet Socialist Republics "… to study limonnik (*Schisandra chinensis* (Turcz.) Baill. (*Schisandraceae*) with the purpose of finding tonic substances” for both soldiers and persons working in the USSR defense industry during

the Second World War. In 1945, the stimulant effects of *Schisandra* on nervous muscular excitability in humans were published (Panossian, Wikman, 2008). As a result of intensive work by scientists in all parts of the country, the concept of herbal substances that would increase "the state of non-specific resistance" under conditions of stress was developed, and the term "adaptogen" was formalized between 1947 and 1960. The term adaptogen was introduced in 1947 by N.V. Lazarev while working on a synthetic compound, dibazol, which was found to stimulate nonspecific resistance of organisms (Lazarev et al., 1959). Later, the term 'adaptogen' was defined more precisely by the famous herbalists I.I. Brekhman and I.V. Dardymov. An adaptogen must produce a nonspecific response, i.e., increase the power of resistance against multiple (physical, chemical or biological) stressors; have a normalizing effect, irrespective of the nature of the pathology; and be nontoxic, innocuous and not influence normal body functions more than required (Brekhman, Dardymov, 1969; Panossian et al., 1999).

## 3. Current situation

The results of recent survey show that 14% of the Russian population regularly uses phytopreparations for treatment and 44% uses them from time to time (Shikov et al., 2011). Phytotherapy is a separate branch of medicine in Russia, and herbal medicinal preparations (HMPs) are considered official medicaments. A herbal medicinal preparation is the finished product, and this terms refers to a medical preparation containing herbal materials and/or herbal preparations as its active ingredients. More than 600 HMPs have been registered for use as medications and are included in the Governmental Register of Medicinal Preparations (Register Russia, 2012).

All aspects relating to the development, preclinical, and clinical studies, evaluation, state registration, standardization and quality control, manufacturing, preparation, storing, transporting, importing and exporting, advertising, releasing, selling, using, and disposing of pharmaceutical preparations (including HMPs) are regulated by Federal Law No. 61 FZ (dated 12.04.2010) "Regarding the circulation of drugs".

## 4. Classification of HMPs

Depending on the processing method used, herbal pharmaceutical formulations can be classified into the following categories (Severtsev et al., 2003):

(1) Medicinal plant materials are usually dried; however, freshly gathered parts of medicinal plants (rarely, entire plants) are sometimes used for the production of medical drugs. Medical species are mixtures of several kinds of crushed or integral plant materials with salts and ethers as additives.
(2) Summarized non-refined or galenic formulations contain a number of related substances together with the biologically active substances. In the course of production, inactive ingredients are removed from galenic formulations. Galenic formulations include herb infusions and decoctions, tinctures, extracts, and elixirs.
   - Infusions and decoctions are liquid medicinal preparations representing aqueous extracts from medicinal plant raw materials, as well as aqueous solutions of dried material or liquid extractions (concentrates).
   - Tinctures are medicinal formulations in the form of alcoholic and aqueous/alcoholic extracts of medicinal plant materials (1:5 or 1:10) produced without heating or removal of the extractant.
   - Extracts are concentrated extractions from medicinal plant materials in liquid (1:1), semi-solid (moisture $< 25\%$), or dried (moisture $< 5\%$) forms.
   - Elixirs are liquid medicinal formulations in the form of a transparent mixture of alcoholic/aqueous extractions from medicinal plant materials to which medical drugs, sugars, and flavors are added.
(3) Novo-galenic formulations are phyto-preparations containing a mixture of biologically active substances that are free from inert and concomitant ingredients. These formulations contain a mixture of alkaloids, coumarins, etc. Novo-galenic preparations also include such substances as flamine (a dried extract of *Helichrysum arenarium* L flowers containing flavonoids), ergotal (a mixture of ergot alkaloid phosphates), adonisid (extract from *Coronaria* aerial parts), etc.
(4) Active pharmaceutical ingredients (APIs) are individual compounds isolated from plants (serotonin, morphine, rutin, lysergin, etc.). These compounds act directly, and most are used to prepare injection formulations.
(5) Combined phyto-preparations combine the substances extracted from plants with synthetic, endocrine and other types of ingredients such as "Allokhol" (based on dry extracts from garlic and nettle with coagulated active coal as an additive), "Cholagolum" (which contains an extract of *Curcuma longa*, emodin from the bark of *Frangulae alni*, magnesium salicylate, peppermint essential oil, eucalyptus essential oil, olive oil, menthol, and ethanol), and "Valocormyde" (which is based on a tincture of valerian, lily of the valley, and belladonna, and contains sodium bromide and menthol as additives).

## 5. Information found in pharmacopoeia monographs

The Russian Federation follows the State Pharmacopoeia of the USSR ($11^{th}$ edition). Last issued in 1987 (part 1) and 1990 (part 2), this Pharmacopeia includes 83 individual monographs for plants.

Each monograph of the State Pharmacopoeia of the USSR contains information including plant name (both Russian and Latin), plant part, recommended collection time, macroscopic evaluation (for whole and pulverized plant material), microscopic observation, quantitative data (loss of material on drying, concentration of chemical constituents or biological activity), ash content, ash content that is insoluble in 10% HCl, broken parts, organic and mineral adulteration, qualitative assay (chemical reactions or chromatography), fraction sieve analysis (for pulverised material), packaging, storage conditions, shelf life, and pharmacological group. (Table 1).

Various plant parts are described in the Pharmacopoeia: 20 aerial parts (herb), 15 leafs, 13 fruits, 14 roots and rhizomes, 8 flowers, 3 barks, 3 seeds, 2 buds, 1 mushroom, 1 cone, 1 alga, 1 column with stigmas, and 1 shoot.

Based on the main therapeutic indications, there are 13 expectorants, 8 diuretics, 7 astringents, 6 anti-inflammatory agents, 5 bitter agents (appetite stimulants), 5 laxatives, 3 tonics, 3 cardiotonic agents, 3 cholinolytics, 3 diaphoretics, 2 cardiovascular agents, 2 choleretics, 2 haemostatics, 2 antihelmintics, 2 polyvitamins, 2 sedatives, 1 antiseptic, 1 ambient, and 1 spasmolytic. Three plants have no direct indications in the Pharmacopoeia or in the online State Register of Medicinal Preparations. The term "medicine of natural origin" indicates that a plant has a pharmacological application. Eleven plants have no pharmacological indications in the Pharmacopoeia but have uses claimed in the online State Register of Medicinal Preparations. Among these 11

**Table 1**
Monographs for medicinal plants included in the State Pharmacopoeia of the USSR, 11th edition.

| Monograph title | Latin name of plant, family (as in the State Pharmacopoeia of the USSR) | Pharmacological group |
|---|---|---|
| 1. CORMUS LEDI PALUSTRI | *Ledum palustre* L., *Ericaceae* | Expectorant |
| 2. CORTEX FRANGULAE ALNI | *Frangula alnus* Mill., *Rhamnaceae* | Laxative |
| 3. CORTEX QUERCUS | *Quercus robur* L. *Querqus petrae* Liebl., *Fagaceae* | Astringent |
| 4. CORTEX VIBURNI | *Viburnum opulus* L, *Caprifoliaceae* | Diuretic |
| 5. FLORES CALENDULAE | *Calendula officinalis* L., *Asteraceae* | Antiseptic and anti-inflammatory |
| 6. FLORES CENTAUREAE CYANI | *Centaurea cyanus* L., *Asteraceae* | Diuretic |
| 7. FLORES CHAMOMILLAE | *Chamomilla recutita* (L.) Rauschert (*Matricaria recutita* L., *M. chamomilla* L.), *Asteraceae* | Anti-inflammatory, spasmolytic |
| 8. FLORES CRATAEGI | *Crataegus sanguinea* Pall.; *C. laevigata* (Poir.) DC. [syn. *C. oxyacantha sensu* Pojark.] *C. korolkowii* L. Henry *C. altaica* (Loud.) Lange *C. chlorocarpa* Lenne et *C. Koch* *C. dahurica* Koehne ex Schneid. *C. monogyna* Jacq. *C. alemanniensis* Cin. *C. orientobaltica* Cin. *C. curvisepala* Lindm. *C. X curonica* Cin. *C. X dunensis* Cin. *C. pentagyna* Waldst. et Kit., *Rosaceae* | Cardiovascular |
| 9. FLORES HELICHRYSI ARENARII | *Helichrysum arenarium* (L.) Moench, *Asteraceae* | Choleretic |
| 10. FLORES SAMBUCI NIGRAE | *Sambucus nigra* L., *Caprifoliaceae* | Diaphoretic (sudorific) |
| 11. FLORES TANACETI | *Tanacetum vulgare* L., *Asteraceae* | Antihelminthic and choleretic |
| 12. FLORES TILIAE | *Tilia cordata* Mill. *T. platyphyllos* Scop., *Tiliaceae* | Diaphoretic (sudorific) |
| 13. FOLIA BELLADONNAE | *Atropa bella-donna* L., *Solanaceae* | Cholinolytic (spasmolytic) |
| 14. FOLIA DIGITALIS | *Digitalis purpures* L., *D. grandiflora* Mill. (syn. *D. ambigua* Murr.), *Scrophulareaceae* | Cardiotonic |
| 15. FOLIA EUCALYPTI VIMINALIS | *Eucalyptus viminalis* Labill., *Myrtaceae* | Anti-inflammatory |
| 16. FOLIA FARFARAE | *Tussilago farfara* L., *Asteraceae* | Expectorant |
| 17. FOLIA HYOSCYAMI | *Hyoscyamus niger* L., *Solanaceae* | Cholinolytic (spasmolytic) |
| 18. FOLIA MENTHAE PIPERITAE | *Mentha piperita* L., *Lamiaceae* | Spasmolytic and choleretic |
| 19. FOLIA MENYANTHIDIS TRIFOLIATAE | *Menyanthes trifoliata* L., *Menyanthaceae* | Bitterness (appetite stimulant) and choleretic |
| 20. FOLIA PLANTAGINIS MAJORIS | *Plantago major* L., *Plantaginacea* | Expectorant |
| 21. FOLIA ORTHOSIPHONIS STAMINEI | *Orthosiphon stamineus* Benth., *Lamiaceae* | Diuretic |
| 22. FOLIA SALVIAE | *Salvia officinalis* L., *Lamiaceae* | Anti-inflammatory |
| 23. FOLIA SENNAE | *Cassia acutifolia* Del., *Fabaceae* | Laxative |
| 24. FOLIA STRAMONII | *Datura stramonium* L., *Solanaceae*. | Cholinolytic (spasmolytic) |
| 25. FOLIA URTICAE | *Urtica dioica* L., *Urticaceae* | Haemostatic |
| 26. FOLIA UVAE URSI | *Arctostaphylos uva-ursi* (L.) Spreng., *Ericaceae* | Diuretic |
| 27. FOLIA VITIS-IDAEA | *Vaccinium vitis-idaea* L., *Ericaceae*. | Diuretic |
| 28. FRUCTUS ALNI | *Alnus incana* (L.) Moench *A. glutinosa* (L.) Gaertn., *Betulaceae* | Astringent |
| 29. FRUCTUS ANETHI GRAVEOLENTIS | *Anethum graveolens* L., *Apiaceae* | Not claimed, Spasmolytic* |
| 30. FRUCTUS ANISI VULGARIS | *Pimpinella anisum* L. (*Anisum vulgare* Gaertn.), *Apicae* | Not claimed, Expectorant* |
| 31. FRUCTUS CARVI | *Carum carvi* L. *Apiaceae* | Not claimed, Spasmolytic* |
| 32. FRUCTUS CRATAEGI | *Crataegus laevigata* (Poir.) DC. (*C. oxyacantha sensu* Pojark.) *C. korolkovii* L., Henry *C. altaica* (Lond.) Lange *C. chlorocarpa* Lenne *C. dahurica* Koehne ex Schneid. *C. monogina* Jacq. *C. alemanniensis* Cin. *C. pentagyna* Waldst. et Kit. *C. orientobaltica* Cin. *C. curvisepala* Lindm. *C. x curonica* Cin. *C. x dunensis* Cin., *Rosaceae* | Cardiovascular |
| 33. FRUCTUS FOENICULI | *Foeniculum vulgare* Mill., *Apiaceae* | Not claimed, Spasmolytic* |
| 34. FRUCTUS JUNIPERI | *Juniperus communis* L., *Cupressaceae* | Diuretic |
| 35. FRUCTUS MYRTILLI | *Vaccinium myrtillus* L., *Ericaceae* | Astringent |
| 36. FRUCTUS PADI | *Padus avium* Mill. *P. asiatica* Kom., *Rosaceae* | Astringent |
| 37. FRUCTUS RHAMNI CATHARTICAE | *Rhamnus cathertica* L., *Rhamnaceae* | Laxative |
| 38. FRUCTUS ROSAE | *Rosa majalis* Herrm. (*R. cinnamomea* L.) *R. acicularis* Lindl. *R. davurica* Pall. *R. beggeriana* Schrenk *R. fedtschenkoana* Regel *R. canina* L. *R. corymbifera* Borkh. *R. micrantha* Smith, *R. kokanica* (Regel) Regel ex Juz., *R. psammophila* Chrshan., *R. tomentosa* Smith, *R. zangezura* P. Jarosch., *R. rugosa* Thunb., *Rosaceae* | Polyvitamin |
| 39. FRUCTUS SORBI | *Sorbus aucuparia* L., *Rosaceae* | Polyvitamin |
| 40. FRUCTUS VIBURNI | *Viburnum opulus* L., *Caprifoliaceae* | Diaphoretic, anti-inflammatory |
| 41. GEMMAE BETULAE | *Betula pendula* Roth *B. pubescens* Ehrh., *Betulaceae*. | Diuretic |
| 42. GEMMAE PINI | *Pinus silvestris* L., *Pinaceae* | Expectorant |
| 43. HERBA ADONIDIS VERNALIS | *Adonis vernalis* L., *Ranunculaceae* | Cardiotonic |
| 44. HERBA ARTEMISIAE ABSINTHII, FOLIA ARTEMISIAE ABSINTHII | *Artemisia absinthium* L., *Asteraceae*. | Bitterness (appetite stimulant) and choleretic |
| 45. HERBA BIDENTIS | *Bidens tripartita* L., *Asteraceae*. | Anti-inflammatory for external use |
| 46. HERBA BURSAE PASTORIS | *Capsella bursa - pastoris* (L.) Medik., *Brassicaceae* | Not claimed, Haemostatic* |
| 47. HERBA CHELIDONII | *Chelidonium majus* L., *Papaveraceae* | Anti-inflammatory for external use |
| 48. HERBA CENTAURII | *Centaurium erythraea* Rafn [syn.: *C. minus* Moench, *C.* | Bitterness (appetite stimulant) |

**Table 1** (*continued*)

| Monograph title | Latin name of plant, family (as in the State Pharmacopoeia of the USSR) | Pharmacological group |
|---|---|---|
| | *umbellatum* Gilib., *Erythraea Centaurium* (L.) Borkh] *C. pulchellum* (Sw.) Druce [syn.: *Erythraea pulchella* (Sw.) Hornem], *Centianaceae* | |
| 49. HERBA CONVALLARIAE, FOLIA CONVALLARIAE, FLORES CONVALLARIAE | *Convallaria majalis* L., *C. transcaucasica* Utkin ex Grossh. *C. keiskei* Mig. *Liliaceae* | Cardiotonic |
| 50. HERBA EQUISETI ARVENSIS | *Equisetum arvense* L., *Equisetaceae* | Diuretic |
| 51. HERBA GNAPHALII ULIGINOSI | *Gnaphalium uliginosum* L., *Asteraceae* | Not claimed, Hypotensive, anti-inflammatory, choleretic* |
| 52. HERBA HYPERICI | *Hypericum perforatum* L. *H. maculatum* Crantz (*H. quadrangulum* L.), *Hypericaceae* | Astringent, antiseptic |
| 53. HERBA MILLEFOLII | *Achillea millefolum* L., *Asteracea* | Not claimed, Haemostatic, anti-inflammatory |
| 54. HERBA LEONURI | *Leonurus cardiaca* L. (*L. cardiaca* L. subsp. *villosus* (Desf.) Jav. *Leonurus quinquelobatus* Gilib., *Lamiaceae*. | Sedative |
| 55. HERBA ORIGANI | *Origanum vulgare* L., *Lamiaceae* | Expectorant |
| 56. HERBA POLYGONI AVICULARIS | *Polygonum aviculare* L., *Polygonaceae* | Not claimed, Diuretic* |
| 57. HERBA POLYGONI HYDROPIPERIS | *Polygonum hydropiper* L., *Polygonaceae* | Haemostatic |
| 58. HERBA POLYGONI PERSICARIAE | *Polygonum persicaria* L., *Polygonaceae*. | Not claimed, medicine of natural origin |
| 59. HERBA THERMOPSIDIS LANCEOLATAE | *Thermopsis lanceolata* R. Br., *Fabaceae* | Not claimed, medicine of natural origin |
| 60. HERBA SERPYLLI | *Thymus serpyllum* L., *Lamiaceae*. | Expectorant |
| 61. HERBA THYMI VULGARIS | *Thymus vulgaris* L., *Lamiaceae* | Expectorant |
| 62. HERBA VIOLAE | *Viola tricolor* L. *V. arvensis* Murr., *Violaceae* | Expectorant |
| 63. INONOTUS OBLIQUUS | *Inonotus obliquus* (Pers.) Pil., *Hymenochaetaceae* | Not claimed, Regulation of metabolism, anti-inflammatory* |
| 64. RADICES ALTHAEAE | *Althaea officinalis* L. *A. armeniaca* Ten., *Malvaceae*. | Expectorant |
| 65. RADICES ARALIAE MANDSHURICAE | *Aralia elata* (Miq.) Seem. (*A. mandshurica* Rupr. et maxim.), *Araliaceae*. | Not claimed, Tonic* |
| 66. RADICES GINSENG | *Panax ginseng* C. A. Mey., *Araliaceae* | Tonic |
| 67. RADICUS ONONIDIS | *Ononis arvensis* L., *Fabaceae* | Not claimed, medicine of natural origin |
| 68. RADICES RHEI | *Rheum palmatum* L. var *tanguticum* Maxim., *Polygonaceae* | Laxative |
| 69. RADICES TARAXACI | *Taraxacum officinale* Wigg., *Asteraceae* | Bitterness (appetite stimulant) and choleretic |
| 70. RHIZOMATA BERGENIAE | *Bergenia crassifolia* (L.) Fritsch, *Saxifragaceae*. | Astringent, for external use |
| 71. RHIZOMATA BISTORTAE | *Polygonum bistorta* L. | Astringent |
| 72. RHIZOMATA CALAMI | *Acorus calamus* L., *Araceae* | Bitterness (appetite stimulant) and choleretic |
| 73. RHIZOMATA ET RADICES INULAE | *Inula helenium* L., *Asteraceae* | Expectorant |
| 74. RHIZOMATA CUM RADICIBUS POLEMONII | *Polemonium caeruleum* L., *Polemoniaceae*. | Expectorant |
| 75. RHIZOMATA ET RADICES RHODIOLAE ROSEAE | *Rhodiola rosea* L., *Crassulaceae* | Tonic |
| 76. RHIZOMATA ET RADICES RUBIAE | *Rubia tinctorum* L. *R. iberica* (Fish. ex DC). C. Koch, *Rubiaceae* | Not claimed, Spasmolytic* |
| 77. RHIZOMATA CUM RADICIBUS VALERIANAE | *Valeriana officinalis* L., *Valerianaceae* | Sedative |
| 78. SEMINA CUCURBITAE | *Cucurbita pepo* L., *C. maxima* Duch. *C. moschata* (Duch.) Poir., *Cucurbitaceae* | Antihelminthic |
| 79. SEMINA LINI | *Linum usitatissimum* L., *Linaceae* | Ambient |
| 80. SEMINA SCHISANDRAE | *Schisandra chinensis* (Turcz.) Baill., *Schisandraceae* | Tonic |
| 81. STROBILI PICEAE ABIETIS | *Picea abies* (L.) Karst., *Pinaceae* | Anti-inflammatory |
| 82. STYLI CUM STIGMATIS ZEAE MAYDIS | *Zea mays* L., *Poaceae* | Choleretic |
| 83. THALLI LAMINARIAE | *Laminaria saccharina* (L). Lam., *Laminariaceae* | Laxative |

* Pharmacological group according to the on line State Register of Medicinal preparations.

plants, 4 are claimed as spasmolytics, 2 as haemostatics, one is an expectorant, one is a hypotensive, one is a diuretic, one is a tonic, and one is a metabolism regulator.

Approximately 60% of plants are referenced in the European Pharmacopoeia and have been well studied in Europe, whereas 32 plants are included in the Pharmacopoeia of the USSR only.

In the following section, we discuss the plants that are included only in the Pharmacopoeia of the USSR and focus on their pharmacological effects and on safety, and clinical data.

### 5.1. Anti-inflammatory agents

#### 5.1.1. HERBA BIDENTIS

The annual *Bidens tripartita* L. (*Compositae*) is 30–100 cm in height with yellow flowers (common names include threelobe beggarticks, water agrimony, and burr marigold). In Russian traditional medicine, an infusion of the aerial part of *B. tripartita* L. is widely used in the treatment of catarrhal rhinitis, angina, acute respiratory infection, and as an anti-inflammatory in colitis, gout, and infantile rickets (Sokolov, 2000). This plant is also used in oriental medicine as a diaphoretic and a diuretic in nephrolithiasis (Sezik et al., 2004), as an antiseptic and as a bath for children to treat diathesis (antiallergic action) (Blinova, Yakovlev, 1990).

The safety of this plant has been studied in mice. An aqueous-ethanol extract (1:1) of the aerial parts administered intraperitoneally to mice had a median lethal dose of 750 mg/kg (Bhakuni et al., 1971). No adverse effects were reported in rats after oral

acute administration of aqueous infusion (10 g in 200 mL of water) of *B. tripartita* at doses up to 20 mL/kg (Pozharitskaya et al., 2010). Table 2 summarizes the pharmacological studies that have been undertaken on *B. tripartita* and reported in the literature.

In an open clinical trial without the use of a control group, a 70% EtOH extract of the aerial parts of the plant and an ointment containing 2.5% of the extract were administered to 53 patients with psoriasis. After oral administration of the extract (20 drops three times daily) and simultaneous application of the ointment to the affected areas of the skin once a day, the combination was found to have anti-inflammatory activity as well as the ability to stimulate adrenal function. After one week of treatment, desquamation of the skin was decreased, and a decoloration of the

**Table 2**
Summary of Pharmacological Studies for *B. tripartite*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro.* Mouse leukemia cells L1210, | Not specified | Methylene chloride extract, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 100% growth inhibition | Goun et al., 2002 |
| Anti-inflammatory | *in vivo.* Carrageenan-induced edema in rats | Aerial part | Crude aqueous infusion (1:20 w/v). Active compounds: (±)-catechin, chlorogenic acid, caffeic acid, luteolin-7-O-glucoside, chicoric acid, rosmarinic acid, luteolin, hydroxycinnamic acid, glycoside of luteolin, polyacetylenes | Per oral | 4, 10, 20 mL/kg 12 h and at 2 h before, and immediately after, injection of carrageenan | Negative, Indomethacin, 5 mg/kg | 51.1% inhibition of edema at the dose of 20 mL/kg, comparable to indometacin. Antipyretic effect (normalization of paw temperature) in 1 h | Pozharitskaya et al., 2010 |
| Antimicrobial | *in vitro.* Broth microdilution method in vitro. Disc diffusion test | Dry flower heads and herbs | Aqueous, MeOH/water, acetone/water and MeOH. MeOH extract partitioned between diethyl ether, EtOAc and n-BuOH. Dominating flavonoid in herb: cynaroside; in flower heads – flavanomarein Essential oils by hydrodistyllation | *in vitro.* | No data | Gram-positive: *Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus.* Gram-negative: *Escherichia coli, E. coli* (β-lactamase+), *Klebsiella pneumoniae* (ESBL+), *Pseudomonas aeruginosa,* Fungi: *Candida albicans, C. parapsilosis, Aspergillus fumigatus, A. terreus* | Weak activity against Gram-positive bacteria (MIC > 1.5 mg/mL) no effect on Gram-negative. Oil from flower heads activity four-time higher than from the herb. Fungistatic effect of oils, highest gainst *C. albicans* and *C. parapsilosis* | Tomczykowa et al., 2008 |
| Antioxidant | *in vitro.* DPPH assay | Dry flowers and herb | Aqueous, MeOH/water, acetone/water and MeOH crude extracts | *in vitro.* | | | Radical scavenging for MeOH/water extract of flowers - 68% ; for acetone/ water extract of herb -66% | Wolniak et al. 2007 |
| | *in vitro.* DPPH assay | Aerial part | Isoookanin 7-O-glucoside, luteolin 7-O glucoside, luteolin | *in vitro.* | | | Radical scavenging : 25% for luteolin 7-O glucoside, 41% for luteolin | Wolniak et al. 2007 |
| Antithrombin | *in vitro.* Thrombin solution from bovine plasma | Not specified | Methylene chloride extracts, soxhlet | 96 well plate | 50 μL | Negative control | 100% thrombin inhibition | Goun et al., 2002 |
| Antiulcer | *in vivo.* Aspirin-induced ulcer. Indomethacin-induced ulcer of rats | Aerial part | Crude MeOH and aqueous extracts | Intragastric | 500 mg/kg | No data | Antiulcer activity against aspirin-induced, but not against indomethacin-induced ulcers. | Muto et al., 1994 |
| Hepatoprotective | *in vivo.* $CCl_4$ induced hepatitis of rats | Aerial part | Crude EtOH extract (20-96%), crude chloroform extract | Per oral | 200 mg/kg, 6 days | Negative, Carsil, 100 mg/kg | EtOH extract (40%) was most effective. Decrease of ALT (51%), ALP (40%), TG (53%), increase of glycogen (117%) in liver | Mikaelian et al., 2006 |
| Hypotensive | *in vivo.* Outbreed rats | Aerial part | Crude EtOH extract (40, 96%), crude chloroform extract | Intraperitoneal | 100 mg/kg, single administration | Negative control | Decrease of systolic blood pressure in 35% after 50 min (40% EtOH extract). Decrease of blood pressure 20% during 5-60 min of experiment (chloroform extract) | Stepanova et al., 2006 |

psoriatic plaques was observed. Clinical recovery was recorded in 29 of the patients; an improvement in condition was recorded in 22 patients; and a failure of treatment was recorded in 2 patients (Faraschuk, 1972; Levin et al., 1974).

*Bidens tripartita* was used in a clinical trial to treat 500 cases of dysentery, 65 cases of acute enteritis, and 248 cases of chronic enteritis. Different forms of the herb were used to prepare the medicine; the daily amount was divided into three doses and used in the following ways: 200 grams of fresh whole herb in decoction, taken as three divided doses; 100 grams of dried herb in decoction, taken as three divided doses; granules of aqueous extract, taken 5 grams each time, three times daily; 0.5 gram tablets of aqueous extract, taken 10 tablets each time, three times daily; injections of 2 mL each time, administered 2–3 times daily. The granules and tablets prepared from granules were administered as a total dose of 15 g/day (derived from approximately 75 g of dried herb). The herbal materials in various forms were usually administered for 3–10 days; to patients who had already suffered from diarrhea, the herbs were administered for 7–15 days. In 500 cases of dysentery, 387 cases were reported cured, of whom 13 did not respond in 3 days. In 313 cases of enteritis, all were cured (12 chronic cases relapsed later). The author of the study noted that there had been an epidemic of dysentery in Shandong Province for many years and that practitioners at village clinics and at the county hospital in Jianan County had used bidens as a remedy for approximately 10,000 patients (Zhang, 1989).

*Bidens tripartita* is recommended for internal administration at the dose of 1 tablespoon of the infusion (10 g in 200 mL of water) taken 3–4 times a day and as one glass of an infusion of 10 g of cut herb together with 100 g of cooking salt or sea salt per bath for external use (Sokolov, 2000).

*Bidens tripartita* is a popular herb in Russia, and its safety and efficacy has been confirmed through long use. The special monograph *Herba Bidentis* was included in the World Health Organization (WHO) monographs on medicinal plants commonly used in the Newly Independent States (NIS) in 2010. However, there is a lack of information in the public literature regarding its efficacy. By revealing more information about *Bidens*, broad studies of this plant can lead to an improved appreciation of the extent of the applications of this herb in medicine.

### 5.2. Diaphoretic and anti-inflammatory agents

#### 5.2.1. FRUCTUS VIBURNI

*Viburnum opulus* L., also known as guelder rose, water elder, European cranberrybush, cramp bark, and the snowball tree, is a deciduous shrub of the *Caprifoliaceae* family and grows to 4–5 m tall.

In Russian traditional medicine, an infusion of the fruit has been used for the treatment of hemorrhoids, and the fruit juice has been used as a laxative and for the treatment of colds, either alone or mixed with honey (Utkin, 1931). The berries are recommended as a source of vitamins and for use as a tonic, and a diuretic (Turova, Sapozhnikova, 1989) and as hypotensive, choleretic, anti-inflammatory, and sedative agents for use in hypertension, insomnia, convulsions, and hysteria (Yelina, 1993). The berries are astringent; therefore, they are seldom consumed directly. However, the juice is one of the best-known products on the food market. People living in the Middle Anatolia region of Turkey drink the juice to prevent some stomach and kidney problems (Soylak et al., 2002).

The fruits are non-toxic (Ehrlen, Eriksson, 1993). The dry fruits of *V. opulus* are safe at the recommended dose of 65 mL of decoction (10 g of fruits in 200 mL of water) for use 3–4 times per day and are available in pharmacies without a prescription (Sokolov, 2000). Table 3 summarizes the pharmacological studies that have been undertaken on *V. opulus* fruits and that are reported in the literature.

No clinical data was found regarding *V. opulus* fruits in the available literature. The fruits of *V. opulus* are recommended for internal administration at the dose of 1/3 of a glass of the infusion (10 g in 200 mL of water) 3–4 times a day (Sokolov, 2000).

*V. opulus* fruits can therefore be regarded as a promising and under-explored fruit that has been used as food in Europe and Asia and that might find wider application for medicinal purposes. However, the pharmacological effects of this fruit are not well documented, and further study of this subject might prove interesting.

### 5.3. Hypotensive, anti-inflammatory, and choleretic agents

#### 5.3.1. HERBA GNAPHALII ULIGINOSI

*Gnaphalium uliginosum* L. (syn *Filaginella uliginosa* (L.) Opiz), a member of the *Compositae* also known as Marsh cudweed, is an annual plant widely used in Russian phytotherapy (Blinova, Yakovlev, 1999). In Russian and Bulgarian phytotherapy, this plant is used in the treatment of hypertension and ulcers (Buturlin, 1953; Shchepotin et al., 1984; Ivancheva, Stantcheva, 2000). Decoctions and infusions of the aerial parts of *G. uliginosum* are known to possess anti-inflammatory, astringent, and antiseptic properties (Sokolov, 2000). Some information is available regarding the application of marsh cudweed for the treatment of thrombophlebitis and phlebothrombosis (Turova, Sapozhnikova, 1989; Shikov et al., 2010a). The hypotensive effect of marsh cudweed is associated with a decrease in systolic blood pressure due to a decrease in cardiac output and the inhibition of baroreceptor sensitivity (Turischev, 2008). Oil extracts are used both internally and externally for the treatment of laryngitis, upper respiratory catarrh and tonsillitis (Gammerman et al., 1984). According to Voronina (1952), the aerial parts of the plant are used to treat nervous disease. The aerial parts of *G. uliginosum* were included in the VIIIth Pharmacopoeia of the USSR in 1952.

The herb *G. uliginosum* is generally considered safe when used as infusions at the daily dose of 180–300 mL and is available in pharmacies without a prescription (Sokolov, 2000). The 40% EtOH crude extract did not suppress the growth of human lymphoblastoid Raji cells at concentrations of up to 200 μg/mL (Spiridonov et al., 2005). Table 4 summarizes the pharmacological studies that have been undertaken on *G. uliginosum* and that are reported in the literature.

An original method for the treatment of patients with peptic ulcers involving the combined administration of infusions of *Polemonium caeruleum* and *G. uliginosum* has been reported (Panchenkov, 1950) and is discussed in the part of the article regarding *P. caeruleum*. No other clinical data were found. The aerial parts of *P. caeruleum* are recommended for internal administration at the dose of 1/2 -1/3 of a glass of the infusion (10 g in 200 mL of water) 2–3 times per day for anti-inflammatory and hypothensive use (Sokolov, 2000).

The safety and efficacy of *G. uliginosum* have been confirmed during its long history of use. However, publications regarding its chemistry, pharmacological effects, and safety remain fragmentary. Further study of this herb might prove interesting.

### 5.4. Bitterants (appetite stimulants)

#### 5.4.1. HERBA CENTAURII

In a monograph in the Pharmacopoeia of the USSR, *Herba centaurii* was described as the aerial parts of *Centaurium erythraea* Rafn [syn.: *C. minus* Moench, *Erythraea Centaurium* (L.) Borkh] and *C. pulchellum* (Sw.) Druce, (*Centianaceae*), as collected during the flowering season. In the European Pharmacopoeia, *C. majus* (H. et L.) Zeltner and *C. suffruticosum* (Griseb.) Ronn. (syn.: *Erythraea centaurium* Persoon; *C. umbellatum* Gilibert; *C. minus* Gars.) are also described in the monograph, *Herba centaurii*. Because the

**Table 3**
Summary of Pharmacological Studies for *V. opulus* fruits.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vivo*. Mice, 1,2-dimethyl-hydrazine (DMH)-induced colon cancer | Fruit | Juice (65% pulp, 45% water) | Per oral | Drinking of juice instead of water. 30 weeks after first DMH injection), 18 after last DMH injection | Negative control | Higher number of low-grade dysplasia and lower number of other type lesions (high-grade dysplasia, intramucosal carcinoma and invasive carcinoma) in treated groups indicate that juice prevents progress of established tumors but not chemical induction of colonic tumors. | Ulger et al., 2012. |
| Antimicrobial | *in vitro*. Agar well diffusion method | Fruit | Fresh juice, standardized by phenolics and anthocyanins. | *in vitro*. | Wells with 50 μL of juice | Gram-positive: *S. aureus, S. epidermidis, B. subtilis, Listeria monocytogenes, Enterococcus faecalis, Micrococcus luteus*. Gram-negative: *P. aeruginosa, E. coli, Salmonella typhimurium, S. agona* Yeast: *Debaryomyces hansenii, Trichosporon cutaneum, Kluyveromyces marxianus var. lactis, Torulaspora delbrueckii, Saccharomyces cerevisiae, Candida parapsilosis* | Strong inhibition of *S.typhimurium* (inhibition zone 25.3-30.3 mm), *S. agona* (23.3-27.7 mm), *L. monocytogenes* (26.5 ± 0.35 mm), *E. faecalis* (25.7 mm), and *S. aureus* (24.1 mm). Most resistant: *P. aeruginosa, M. luteus, S. epidermidis*. No or little antifungal activity was observed | Česoniene et al., 2012 |
| Antimicrobial | *in vitro*. Agar well diffusion method | Fruits | MeOH extract (10 and 15%) | *in vitro*. | No data | Negative control. | Most sensitive: *Aeromonas hydrophila*, most resistant *Yersinia enterocolitica* | Sagdic et al., 2006 |
| Antioxidant | *in vitro*. DPPH assay | Fruit | Flesh, standardized by malic, oxalic, citric acids, total phenolic, total flavonoid, and total anthocyanin contents | *in vitro*. | No data | Negative control. | $EC_{50}$=24.56 mg/mg | Cam et al. 2007 |
| | *in vitro*. DPPH assay | Fruit | Seeds, standardized by malic, oxalic, citric acids, total phenolic, total flavonoid, and total anthocyanin contents | *in vitro*. | No data | Negative control. | $EC_{50}$=2.35 mg/mg | Cam et al. 2007 |
| | *in vitro*. ABTS assay, DPPH assay, NO scavenging, superoxide anion scavenging, inhibition of lipid peroxidation | Fruit | Fruit extract (25%) standardized by total phenolic and ascorbic acid contents | *in vitro*. | No data | Negative control. | Inhibition of NO (21.89-25.44%), superoxide anion (25.13-28.50%), and lipid peroxidation (11.20–13.90%). In DPPH test 8.6-9.8 ascorbic acid equivalent/kg of fresh fruits (AAE/kg FM) and 9.1-11.1 AAE/kg FM in ABTS test | Rop et al., 2010 |
| Gastroprotective | *in vivo*. Rats, water immersion restraint stress | Dry fruits | Proanthocyanidins, no composition | Intragastric | 25, 50, 75 mg/kg | Negative control | Potent gastroduodeno-protective activity via an increase in endogenous NO generation, suppression of lipid peroxidation and mobilization of antioxidant activity and changes in glycoconjugate content of the gastroduodenal mucosa of rats | Zayachkivska et al., 2006 |
| Immuno-stimulating | *in vitro*. Peritoneal cells of rats. | Fruit | Water-soluble polysaccharide fractions from the squeezed fruits. Acidic polysaccharides with α-l,4-1inked residues of D-galacturonic acid, galactose, arabinose, and rhamnose. Neutral polysaccharides composed of galactose and mannose. | 96 well plate Activity of myeloperoxidase in the macrophages Petri dishes, phagocytic index of the macrophages by light microscopy | Polisacharides, 10 μg/mL | Negative control | Increase the phagocytic index in 31% and the secretion of lysosomal enzymes with peritoneal macrophages in 68% | Ovodova et al., 2000 |

**Table 4**
Summary of Pharmacological Studies for *G. uliginosum*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro*. Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 45% growth inhibition by methylene chloride extract, 38% growth inhibition by MeOH extract | Goun et al., 2002 |
| Antidiabetic | *in vivo*. Rats, epinephrine induced hyperglycemia. Rats, alloxan induced diabetes | Aerial part | Crude aqueous decoction (1 g in 10 mL) | Intragastric | 25 mL/kg, 6 days | Negative control | The level of glucose was decreased 25%, and glycogen in liver was increased 1.7 fold compared to control the glucose tolerance test (epinephrine induced hyperglycemia). Decrease of glucose 19% but no effect on blood insulin level (alloxan induced diabetes). | Molokovskii et al., 2002 |
| Antithrombin | *in vitro*. Thrombin solution from bovine plasma | Not specified | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 50 μL | Negative control | 75% thrombin inhibition by methylene chloride extract | Goun et al., 2002 |
| Gastroprotective | *in vivo*. Experimental gastric dystrophy by stomach alteration in reserpinized or immobilized mice | Not specified | Isolated gnaphaloside A ([7-(6''-O-caffeoyl]-O-β-D-glucopyranosido-5,4'-dihydroxy-6,3'-dimethoxyflavone) | Per oral | 50 mg/kg Immediately before and 5 h after immobilization or reserpine injection | Negative control | Decrease total number of stomach lesions (by 1.6 fold), including small pulverized (l.7 fold) and large bandlike (2.3 fold) lesions compared with control (reserpinized mice). Decrease of number of lesions of any type (by 2.6 to 3.l fold) and number of animals with various gastric lesions (2.5 fold) compared with control (immobilized mice). | Barnaulov et al., 1984 |
| Hypotensive | *in vivo*. SHR rats | Aerial part | Crude aqueous extract. gnaphaloside A; 6''-caffeyl-7-β-D-glucopyranosyloxy-4',5-dihydroxy-3',6' dimethoxyflavone; 3',4',5,7-tetrahydroxy-6-methoxyflavone 7-0-(6''-O-caffeyl-β-D-glucopyranoside); 6-methoxyluteolin, 6-hydroxyluteolin 7-O- β -D-glucopyranoside | Per oral | 50 mg/kg, 14 days | Negative control. Positive control: enalapril, 2 mg/kg, atenolol 10 mg/kg | Decrease of systolic pressure by 12% and 19% after 3 and 6 h each day. Decrease of diastolic pressure by 34% and 37% after 3 and 6 h each day. Cumulative affect after 10 days. | Makarova, Makarov, 2010 |

**Table 5**
Summary of Pharmacological Studies for *A. incana*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | in vitro, Human cervix adenocarcinoma HeLa cell | Catkins | MeOH extract, soxhlet with 381.3 ± 7.2 mg gallic acid equivalents/g extract | 96 well plate | 200, 100, 50, 25, and 12.5 μg/mL, | Negative control. Positive control: Cisplatin | $IC_{50}$ = 39.9 μg/mL | Stević et al., 2010 |
| Anti-inflammatory | in vivo Rats, chloroquine induced irritation of mucous membrane accompanied with emotional-painful stress | Catkins | Polyphenolic extract (ellagic and gallic acid) | Per oral | 1 mg/kg, 30 days | Negative control | Positive effect on structures of vessels of the microcirculatory bloodstream, subepithelial connective tissue and integumentary epithelium of tunica mucosa. Effect by endocellular regeneration in combination with expressed compensatory hypertrophy of part epithelium integument cells. | Moiseyev et al., 2008 |
| Anti-inflammatory (photoprotective) | in vivo. Guinea pigs; ultraviolet-induced erythema | Catkins | Polyphenolic extract (ellagic and gallic acid) | Intragastric | 1 mg/kg, 40 min before and 2 h after UV irradiation | Negative control. Positive control: methyluracil, sea buckthorn oil | Decrease of erythema (61%) accompanied with decrease of lipid conjugated dienes and increase of superoxide (39%)dismutase and catalase (16%) compared to control group | Zvyagintseva et al., 2009 |
| Anti-inflammatory (radioprotective) | in vivo. Rats, ionizing radiation of skin (dose 80 Gy) | Catkins | Polyphenolic extract (ellagic and gallic acid) | Intragastric | 1 mg/kg, 40 min before and during 10 days after irradiation | Negative control. Positive control: methyluracil | Decrease of malonyl-dialdehyde and lipid conjugated dienes, increase of antioxidant enzymes activity and quick epithelization and healing of skin comparing with control group | Myronchenko and Zvyagintseva, 2008 |
| Antimicrobial | in vivo. Newborn rat. Gastroenterocolitis induced by *Klebsiella pneumoniae* | Catkins | Polyphenolic extract (ellagic and gallic acid) | Per oral | 1.0, 2.5, 5.0, 10.0, 20.0 mg/kg 14 days | Negative control | Bacteriostatic effect at 1.0 and 2.5 mg/kg (31.5 % and 62.5% survival of rats resp.) Bactericidal effect at 10.0 and 20.0 mg/kg; 100% survival of rats. No effect on normal microflora at 1.0-20.0 mg/kg | Rikalo, 2005 |
| Antimicrobial | in vitro. Broth microdilution method | Catkins | MeOH extract, Soxhlet with ca. 381.3 mg of gallic acid equivalents/g of extract | 96 well plate | No data | *E. coli, Salmonella typhimurium, Enterobacter cloacae, P. aeruginosa, P. tolaasii, Proteus mirabilis,* Gram-positive *S. aureus, S. epidermidis, Streptococcus faecalis, B. subtilis Micrococcus luteus, M. flavus, Sarcina lutea, Listeria monocytogenes*; yeast: *C. albicans*. Negative control, streptomycin, nystatin | MIC = 0.117-0.129 mg/mL | Stević et al., 2010 |
| Antioxidant | *in vitro*. DPPH assay, phospholipid degradation | Catkins | MeOH extract, Soxhlet with ca.381.3 mg of gallic acid equivalents/g of extract | *in vitro.* | 100 μL | Negative control. Positive control: Trolox | $IC_{50}$ = 18.9 μg/mL (DPPH), $IC_{50}$ = 48.6 μg/mL (phospholipid) | Stević et al., 2010 |

**Table 5** (*continued*)

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| | *in vitro*. DPPH assay | Catkin | Crude 70% aqueous EtOH (1:40, w/v) extract; pedunculagin, glutinoin, praecoxin D | 96-well microplate | 10 mg/mL | Negative control. Positive control: Gallic acid Ascorbic acid | $IC_{50}$= 2.7 ± 0.1 μg/mL (crude extract) $IC_{50}$= 1.0 ± 0.1 μg/mL for individual compounds) | Ivanov et al., 2012 |
| Hepatoprotective | *in vivo*. Rats, $CCl_4$ induced hepatitis | Catkins | Polyphenolic extract (ellagic and gallic acid) | Intragastric | 1 mg/kg | Negative control. Positive control: Carsil. | It limits choleopoiesis disorder, has an anti-inflammatory and membrane stabilizing effect, recovers physiological antioxidant system, increase of bile secretion and cholesterol content in bile. | Buniatian et al., 1998 |
| Hepatoprotective | *in vivo*. Rats $CCl_4$ induced hepatitis, EtOH-induced hepatitis | Catkins | Polyphenolic extract (ellagic and gallic acid) | Intragastric | 1 mg/kg | Negative control | Repaired functional activity of mitochondria to the intact level in EtOH-induced hepatitis and increased microsome hydroxylase activity in $CCl_4$ induced hepatitis | Gordienko, Yakovleva, 1999 |

pharmacological effects of the plants found in the European Pharmacopoeia are similar to those of *C. pulchellum*, this review will not discuss the pharmacological effects of *C. pulchellum.*

### 5.5. Astringents

#### 5.5.1. FRUCTUS ALNI

*Fructus alni* consists of the catkins of *Alnus incana* (L.) Moench (grey alder or speckled alder) or *A. glutinosa* (L.) Gaertn. (European black alder; *Betulaceae*), a small to medium tree that is 15-20 m in height. Alder catkins are collected during late autumn and winter. Decoctions of alder catkins are used in Russian traditional medicine for the treatment of stomach pain, diarrhea, and dysentery (Nosal, Nosal, 1960).

In 1942, *A. incana* catkins were introduced in officinal medicine by Prof. D.M. Rossijsky Rossijsky, 1942; Vereschagin et al., 1959), and a dry extract of *A. glutinosa* catkin was developed by V.E. Shatadze (Turova, Sapozhnikova, 1989). Due to their astringent properties, extracts of these catkins have been recommended for the treatment of ailments of the gastrointestinal tract. Recently, it was shown that *Fructus alni* has anti-inflammatory and UV- and radioprotective properties (Sokolov, 2000).

The acute and chronic toxicity of a polyphenolic extract of *A. glutinosa* catkins has been studied in rodents after oral administration. The $LD_{50}$ values measured in acute toxicity studies were 5,420 mg/kg in mice and 8,500 mg/kg in rats, respectively. In the chronic toxicity study, the extract used exhibited hepatotoxicity in rats after 6 months of administration at the dose of 50 mg/kg; the recommended dose for therapeutic use is 1 mg/kg (Maloshtan, Serbina, 1999). MeOH extracts of *A. incana* exhibited very low toxicity and did not cause significant brine shrimp (*Artemia salina*) mortality, even when used at 200 μg/mL (Stević et al., 2010). Table 5 summarizes the pharmacological studies that have been undertaken on *Fructus alni* that are reported in the literature.

A group of 50 patients (32 females and 18 males, 19–78 years) suffering from salmonellosis was included in a clinical trial. Group 1 (25 patients) was treated with drug therapy (control) and group 2 was treated with a polyphenol-rich extract of *A. glutinosa* catkins at a dose of 20 mg, 3 times per day for 8 days. The publication did not give a full description of the controls, making it difficult to assess the results of this trial. The levels of malonyl-dialdehyde and lipid-conjugated dienes and the activity of superoxide dismutase in the blood serum of the patients were statistically significantly decreased (33%, 44% and 10%, respectively) and were similar to normal levels found in healthy persons. The levels of malonyl-dialdehyde, lipid-conjugated dienes and superoxide dismutase in group 1 decreased by 16%, 17% and 30%, respectively, compared to untreated levels. Based on the results, the extract was recommended for the treatment of patients with salmonellosis (Popova, 2002).

Considering the literature data and the results of applications of *Fructus alni* in the USSR and Russia, this material may be considered safe and effective. *Fructus alni* is recommended for internal administration at the dose of 1/2 - 1/3 of a glass of the infusion (10 g in 200 mL of water) 2–3 times a day for use as an astringent (Sokolov, 2000). "Altan" tablets, which include 0.01 g of a polyphenolic extract of *A. glutinosa* catkins, are registered in Ukraine as an over-the-counter medicine. Future study of alnus catkins should contribute to increasing their medicinal application.

#### 5.5.2. HERBA HYPERICI

In a monograph in the Pharmacopoeia of the USSR, *Herba hyperici* is described as the aerial parts of *Hypericum perforatum* L., *H. maculatum* Crantz (syn. *H. quadrangulum* L.), *Hypericaceae*, as

collected during the flowering season. Because the pharmacological effects of *H. maculatum* are similar to those of *H. perforatum,* which is included in the European Pharmacopoeia, the pharmacological effects of *H. maculatum* will not be discussed in this review.

#### 5.5.3. RHIZOMATA BERGENIAE

*Bergenia crassifolia* (L.) Fritsch (*Saxifragaceae*), commonly known as badan, Siberian tea, Mongolian tea, leather bergenia, or elephant's ears, is an evergreen perennial plant with rhizomes up to 1 meter long, 10–50 cm long leather-like large leaves, and pink flowers.

Infusions of *Bergenia* rhizomes have been used in Russian traditional medicine for the treatment of colds, gastritis, enterocolitis, headache, diarrhea, and fever (Gammerman et al., 1984). In Russian ethnomedicine, the leaves are widely used as a beverage. Buryats and Mongols are known to have used *B. crassifolia* leaves to make tea. However, in Altai, old blackened wintered leaves, known as chagirsky tea, are preferred for this purpose because the green leaves contain higher amounts of tannins (Vereschagin et al. 1959). In officinal medicine, the rhizomes are claimed as haemostatic, astringent, anti-inflammatory, and antimicrobial agents. Infusions are recommended in gynecology for excessive menstruation, bleeding after abortions, and cervical erosion treatment (Turova, Sapozhnikova, 1989). The rhizome is claimed to strengthen capillary walls, to exhibit local vasodilatation activity, to decrease arterial blood pressure and to increase heart rate (Sokolov, 2000). *Bergenia* rhizomes are used to treat the following oral diseases: periodontal disease, stomatitis, gingivitis, and bleeding gums (Lukomsky, 1955). *Bergenia crassifolia* appears to meet the criteria required for consideration as an adaptogen (Suslov et al., 2002; Panossian, 2003).

The rhizomes of *B. crassifolia* are safe at the daily dose of 50–100 mL of decoction (10 g in 200 mL of water) and are available in pharmacies without a prescription (Sokolov, 2000). Infusions of both the black and fermented leaves of *B. crassifolia* (10 g in 100 mL of water) have been found to be safe in mice after 7 days of continuous per oral administration at the dose of 9 mL/kg (Shikov et al., 2010b). At a single oral dose (50 mg/kg per day) of dry extracts of black and green leaves, no signs of toxicity were observed in rats after one week (Shikov et al., 2012). Bergenin and norbergenin, the main coumarins of *Bergenia*, were found to be safe up to 2,000 mg/kg weight in mice after per oral acute administration, and no sign of mortality or change in behavioral pattern was observed (Nazir et al., 2007). The bergenan - pectic polysaccharide from *B. crassifolia* green leaves was found to be nontoxic and failed to influence the body weight or the length and weight of the intestine (Popov et al., 2005). The $LD_{50}$ for sulfated pectin derivatives of *B. crassifolia* after a single intraperitoneal injection was more than 1,000 mg/kg (Vityazev et al., 2012). Table 6 summarizes the pharmacological studies that have been undertaken on *B. crassifolia* and that are reported in the literature.

In the available literature, no clinical data for *B. crassifolia* were found. Rhizomes of *B. crassifolia* are recommended for internal administration at the dose of 1–2 tablespoons of the decoction (10 g in 200 mL of water) taken 3 times per day as an astringent, a haemostatic, or an anti-inflammatory agent (Sokolov, 2000). Claims of antimicrobial activity are not supported by antimicrobial assays, which only show activity at very high concentrations. Anti-inflammatory activity might be associated with high concentrations of polyphenols, polysaccharides, and α-bisabololoxide B (Popov et al., 2005; Chernetsova et al., 2012; 2014).

It is interesting that the black leaves and rhizomes have been used in traditional medicine, but the use of rhizomes is only referred to in the Pharmacopoeia of the USSR. The safety and efficacy of *B. crassifolia* (both leaves and rhizomes) are confirmed by their long period of traditional application. However, publications regarding their chemistry, pharmacological effects and safety remain fragmentary. This plant should be an interesting subject for further investigations, especially with respect to its adaptogenic properties.

### 5.6. Choleretic agents

#### 5.6.1. FLORES HELICHRYSI ARENARII

*Helichrysum arenarium* (L.) Moench (Compositae), also known as dwarf everlast, is a perennial grows to an average height of 15–40 cm.

The inflorescence of *H. arenarium* has been used in the popular medicine of Russia for its choleretic, diuretic, anti-inflammatory, and detoxifying properties and has been applied in the form of infusions for treating cystitis, arthritis, rheumatism, and gout; for stimulating gastric secretion; and for the treatment of gallbladder disorders (Shass, 1952; Vereschagin et al., 1959). The choleretic, cholagogue, hepatoprotective, and detoxifying activity of the inflorescence of *H. arenarium* has been recognized for a long time in Europe (Kroeber, 1951; Szadowska, 1962; Wagner, 1993).

The administration of *H. arenarium* at recommended dose (decoction, 1:20, 100 mL, 2–3 times per day) or the use of "Flamin" tablets (purified flavonoids) at a therapeutic dose of 50 mg, 3 times per day for 40 days, is safe. However, longer administration may lead to the development of bile congestion (Sokolov, 2000).

*Helichrysi flos* has cholagogue and choleretic activity and stimulates the secretion of gastric juice (Krivenko et al., 1989; Litvinenko et al., 1992). "Flamin" tablets are used in cases of cholecystopathy and affect the chemical composition of bile (by increasing the cholesterol cholate coefficient), regulate the function of the gastrointestinal tract, and increase diuresis (Petrovsky et al., 1953; Skakun, Stepanov, 1988). Table 7 summarizes the pharmacological studies that have been undertaken on *H. arenarium* and that are reported in the literature.

Increased bile secretion and decreased bilirubin and cholesterol levels were observed in patients with cholecystitis, cholangitis, gallstones, and hepatitis when treated with *H. arenarium. Helichrysum arenarium* prevents the stagnation of bile, improves the metabolic function of the liver, and decreases the viscosity and relative density of bile. This plant also promotes the leaching of sand and small stones in patients with chronic calculous cholecystitis (Sokolov, 2000). However, no more details are available.

The aerial parts of *H. arenarium* are recommended for internal administration at the dose of 100 mL of the decoction (10 g in 200 mL of water), 2–3 times per day as a choleretic. "Flamin" tablets containing 0.05 g of flavonoids are recommended for internal administration at the dose of 1 tablet 3 times daily for 10–40 days in patients with cholecystitis (Sokolov, 2000).

A special monograph on *Flos Helichrysi arenarii* was included in the WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS) in 2010. However, publications regarding the chemistry and pharmacological effects of this plant are fragmentary, and no special publication is available regarding its safety. This plant is an interesting subject for further investigations.

### 5.7. Antihelmintic and choleretic agents

#### 5.7.1. FLORES TANACETI

*Tanacetum vulgare* L., (common name, tansy) is a flowering herbaceous plant (*Compositae*) with finely divided compound leaves and yellow, button-like flowers; the plant is 50–150 cm tall.

In Russian traditional medicine, tansy has been used to treat intestinal worms (ascaris and enterobius), diarrhea and digestive problems and has been used as an antipyretic and as a diaphoretic (Nosal, Nosal, 1960). Tansy has been proposed for use as an insect repellent. Powdered aerial parts of this plant cause 100% paralysis in

**Table 6**
Summary of Pharmacological Studies for *B. crassifolia*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Adaptogenic | *in vivo*. Mice, forced swimming test. | Leaves, black and fermented | Aqueous infusion (1:10, w/v), fingerprint by arbutin, bergenin, ellagic, gallic, protocatechuic acids, hydroquinone. | Per oral | 9.0 mL/kg, 7 days | Negative control. Positive control: *Rhodiola rosea* extract | 2 fold Enhanced swimming time, increased glucose utilization and decreased lactate levels compared to control . Increased fat utilization and a decreased body weight of 15–18% in groups treated with black and fermented leaves. | Shikov et al., 2010b |
| Anticancer | *in vitro*. Human lymphoblastoid Raji cells | Rhizomes, green leaves | Crude EtOH (40%) extract | *in vitro* | 10, 50, 200 μg/mL | Positive control: methotrexate fluorouracil, cyclophos-phamide, vinblastine. Negative control | 99% inhibition at 200 μg/mL by rhizomes extract; 82% inhibition by leaves extract. | Spiridonov et al., 2005 |
| Antimicrobial | *in vitro*. Liquid dilution method | Rhizomes, leaves | EtOH (80%) extract | *in vitro*. | No data | *B. cereus, E. coli, P. aeruginosa, S. aureus, C. albicans*. Positive control: erythromycin, gentamicin, amphotericin B | MIC (mg/mL) for leaves/rhizomes: *B. cereus:* 62.50 / 15.63; *E. coli:* 62.50/15.63; *P. aeruginosa,* 15.63/ 62.50; *S. aureus:* 62.50/62.50; *C. albicans*: 250.00/ 15.63 | Kokoska et al., 2002 |
| Anti-inflammatory | *in vivo*. Mice, adjuvant-induced arthritis | Not specified | Bergenin (main coumarine) of plant | Per oral | 5, 10, 20, 40, 80 mg/ kg | Positive control: prednisolone | Inhibition production proinflammatory Th1 cytokines (IL-2, IFN-γ and TNF-α). | Nazir et al., 2007 |
| Anti-inflammatory | *in vivo*. Mice, immobilization stress or cyclophosphamide injections | Rhizomes | Dry extract standardized by arbutine min 18%. | Per oral | 50 mg/kg, 5 days | Negative control. Positive control: enalapril, 2 mg/kg, atenolol 10 mg/kg | Extract normalized content antibody-forming cells in spleen after stimulation by antigen in both immunodepression models. Extract decreased expression inflammatory processes under delayed hypersensitivity reaction conditions, by preventing accumulation of T-lymphocytes in the inflammation focus and reducing the ability of cells to produce anti-inflammatory cytokines | Churin et al., 2005 |
| Antiobesity | *in vivo*. Rats with high-calorie diet- induced obesity | Leaves, black and fermented | Crude aqueous extract standardized by arbutin, bergenin, ellagic, gallic, protocatechuic acids, hydroquinone. | Per oral | 50 mg/kg, 7 days | Negative control. Positive control: sibutramine hydrochloride | Daily dietary intake reduced to 40% compared with control. Improvement in glucose tolerance after 7 d treatment. Black leaves extract reduced serum triglyceride level by 45% compared to control in rats. | Shikov et al., 2012 |
| Antioxidant | *in situ*. DPPH assay after HPTLC separation. | Leaves, green, brown, black. | MeOH extract, with arbutin, bergenin, ellagic, gallic acids, hydroquinone. | *in vitro*. | 1 mg/mL | Negative control. Positive control: ascorbic acid | $ID_{50}$ (nmol) gallic acid 0.49; ellagic acid 0.94; arbutin 0.88; hydroquinone 1.23. | Pozharitskaya et al. 2007 |
| | *in vitro*. DPPH assay. | Rhizomes | EtOH (70%) extract, (+)-catechin 3,5-di-O-gallate, (+)-catechin 3-O-gallate | *in vitro*. | 10 mg/mL | Negative control. Positive control: gallic acid, catechin, 2,6-di-tertbutyl-4-methylphenol | $SC_{50}$ (μg/mL) 3.7 for extract, 1.0 for (+)-catechin 3,5-di-O-gallate, 1.3 for (+)-catechin 3-O-gallate. | Ivanov et al., 2011 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Antioxidant | *in vitro*. Human pancreatic lipase inhibition | Rhizomes | EtOH (70%) extract, (+)-catechin 3,5-di-O-gallate, (+)-catechin 3-O-gallate | 96-well plate | 25 μL | Negative control. Positive control: (-)-Catechin 3-O-gallate, (-)-Epicatechin 3-O-gallate | $IC_{50}$ (μg/mL) 3.4 ± 0.2 for extract, 0.42 ± 0.04 for (+)-catechin 3,5-di-O-gallate, 2.02 ± 0.11 for (+)-catechin 3-O-gallate. | Ivanov et al., 2011 |
| Cerebro-protective | *in vivo*. Hypoxia in rats, | Leaves | Dry extract | Intragastric | 300 mg/kg, 5 days | Negative control. Positive control: piracetam | Extract prevented the death of rats which occurred in 33–45% cases of control group after hypoxic exposure. Extract exerted cerebroprotective effect by preventing inhibition of the succinate oxidaze system. | Khazanov, Smirnova 2000 |
| Immuno-stimulating | *in vivo*. Mice, delayed type hypersensitivity (DTH) reaction to aggregated ovalbumin on footpad swelling. in vitro. phagocytic activity of human blood neutrophils. *in vitro*. Mouse peritoneal cells. | Green leaves | Isolated bergenan – polysaccharide comprise mainly D-galacturonic acid, galactose, rhamnose, arabinose, glucose residues; appeared to be pectin. | Per oral | 2 mg/mL in drinking water *ad libitum* (6 mg/day) 3 weeks. 10 μL for phagocytic activity. 50 μL for peritoneal cells assay. | Negative control. Positive control: apple pectin | Increase of DTH reaction in vivo. Bergenan enhanced uptake capacity of human neutrophils at 10 μg/mL and stimulated generation of oxygen radicals by mouse peritoneal macrophages in vitro. Bergenan increased spontaneous adhesion of peritoneal leukocytes but did not influence adhesion stimulated by PMA or adhesion of peritoneal leukocytes. | Popov et al. 2005 |
| Hypotensive | in vivo. SHR rats | Leaves | Dry aqueous extract. | Per oral | 50 mg/kg, 14 days | Negative control. Positive control: enalapril, 2 mg/kg, atenolol 10 mg/kg | Decrease of systolic pressure by 20–25 mmHg after 3–6 h after each daily administration. Decrease of diastolic pressure by 20–25 mmHg after 1 h each day. Cumulative effect after 7 days. | Makarova, Makarov, 2010 |

flies within 15 minutes (Zemlinsky, 1949). This plant is also mentioned regarding its use in treating hysteria, migraine, neuralgia, rheumatism, kidney weakness, stomach problems, and fever. *Tanacetum vulgare* has antihelminthic, carminative, antispasmodic, stimulant (to the abdominal viscera), tonic, emmenagogue, antidiabetic, diuretic, and antihypertensive properties. In larger doses, the plant can be used to induce abortion. Externally, tansy is used as a poultice on swellings, sprains, gout, contusions, and some eruptive skin diseases and to kill lice and fleas and treat scabies (Abad et al., 1995; Sokolov, 2000). Tanacechol®, a purified complex extract of flavonoids and phenolcarbonic acids extracted from tansy flowers (0.05 g/ tablet), is registered in Russia as a choleretic and as a spasmolytic agent for chronic cholecystitis and biliary dyskinesia (Sokolov, 2000).

The acute and chronic toxic effects of a lyophilized aqueous extract of tansy were studied in rodents. The no-observed-adverse-effect levels (NOAELs) of crude aqueous tansy extract in mice when given by the oral and intraperitoneal routes are 7.0 g/kg and 1.0 g/kg, respectively, and the lowest-observed-adverse-effect levels (LOAELs) are 9.0 g/kg and 1.5 g/kg, respectively. Mortality increased with increasing dosage; the $LD_{50}$ values were 9.9 g/kg and 2.8 g/kg for the oral and intraperitoneal modes of administration, respectively. The $LD_{50}$ values were lower for female mice (oral dose: 8.70 g/kg; intraperitoneal dose: 2.25 g/kg) than for male mice (oral dose: 11.30 g/kg; intraperitoneal dose: 3.25 g/kg). In the chronic study in rats, daily oral administration of the crude aqueous extract of tansy up to 600 mg/kg for 90 days did not result in death or significant changes in the biological (except for hypoglycemia) or hematological parameters (Lahlou et al., 2008a).

The safety of Tanacechol® has been tested in rats, mice, dogs, and guinea pigs. The $LD_{50}$ was 1.27 g/kg in rats after intraperitoneal administration and 7.42 g/kg in mice after intragastric administration. This drug was not toxic, and no histopathological effects were detected after 90 days of administration in rats and dogs at the dose of 100 mg/kg. No allergenic effects were observed in guinea pigs (Vichkanova et al., 2009). Table 8 summarizes the pharmacological studies that have been undertaken on *T. vulgare* and that are reported in the literature.

The effects of oral treatment with Tanacechol® have been studied in 291 patients with chronic cholecystitis. Patients were treated with Tanacechol® tablets (0.05 g) at the dose of 2 tablets 3 times per day, 20–30 min before ingestion of food, for 25 days. The report did not fully describe the controls used, which makes it practically difficult to assess the outcome of this trial. A positive effect was registered in 74.9% of the patients studied. The treatment led to a decrease in bitter taste in the mouth and nausea after 6–7 days, reduced pain in the right-upper quadrant after 9–10 days, and dyspepsia disappeared after 15–20 days. No side effects were observed (Vichkanova et al., 2009).

The flowers of *T. vulgare* are recommended for internal administration at the dose of 1 tablespoon of the decoction (10 g in 200 mL of water), 3 times per day, as a choleretic and an antihelmintic. Tanacechol® tablets containing 0.05 g of a purified complex extract of flavonoids and phenolcarbonic acids are recommended for internal administration at the dose of 1–2 tablets, 3–4 times per day, for 20–30 days in patients with biliary system and liver diseases (Sokolov, 2000). However, publications regarding the pharmacological effects and clinical trials of these tablets are far too limited to allow conclusions regarding its therapeutic potential. This botanical drug is clearly an interesting subject for further investigations, especially within a clinical context.

### 5.8. Expectorants

#### 5.8.1. CORMUS LEDI PALUSTRI

*Ledum palustre* L. (syn. *Rhododendron tomentosum* Harmaja), commonly known as marsh Labrador tea, northern Labrador tea or

**Table 7**
Summary of Pharmacological Studies for *H. arenarium*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antibacterial | *in vitro*, agar-well diffusion method | Aerial part | MeOH extract, Soxhlet with gallic, *p*-hydroxybenzoic, chlorogenic, caffeic, syringic, *p*-coumaric, ferulic, rosmarinic acids, catechin, epicatechin, rutin, resveratrol, hesperidin, apigenin- 7-glucoside, eriodictyol, quercetin, naringenin, luteolin, apigenin, and acacetin. | *in vitro.* | 100, 50, 25, 10 μg/mL | *Aeromonas hydrophila*, *Bacillus brevis*, *B. cereus*, *B. subtilis*, *E. coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Mycobacterium smegmatis*, *Proteus mirabilis*, *P. aeruginosa*, *S. aureus*, *Yersinia enterocolitica*, *C. albicans*, *Saccharomyces cerevisiae.* Positive control: amoxicillin, and 11 other antibiotics. | No activity against *E. coli*, *B. subtilis*, *M. morganii*, *M. smegmatis*, *P. mirabilis*, *Y. enterocolitica*, *S. cerevisiae.* Inhibition diameter (mm at 100 μg/mL): *A. hydrophila* (28.0), *B. brevis* (22.5), *B. cereus* (22.5), *K. pneumoniae* (17.0), *P. aeruginosa* (28.0), *S. Aureus* (23.5). | Albayrak et al., 2010 |
| Anticancer | *in vitro.* Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 96% growth inhibition by methylene chloride extract, 85% growth inhibition by MeOH extract | Goun et al., 2002 |
| Anticoagulant | *in vitro.* Clotting assays of activated partial thromboplastin time (APTT) and of prothrombin time (PT) | Flowers | Crude extract with polyphenolic-polysaccharide fraction | *in vitro.* | 0.1–12.5 mg/mL | Negative control | APTT > 600 sec at 12.5 mg/mL and 479 sec at 6.25 mg/mL. Pt 81.7 sec at 12.5 mg/mL | Pawlaczyk et al., 2009 |
| Anti-inflammatory | *in vitro,* TNF-α, 1 ng/mL induced cytotoxicity in L929 cells | Flowers | MeOH extract, 50 constituents including new flavanone and chalcone glycosides named arenariumosides I, II, III, IV. | 96-well microplate | 3–100 μM | Negative control. Positive control: sylibin, piperine. | 20.8-40.7 % inhibition of TNF-α -induced cytotoxicity in L929 cells at 30 μM by naringenin 7-*O*-β-D-glucopyranoside, apigenin 7-*O*-β-D-glucopyranoside, apigenin 7-*O*-gentiobioside, apigenin 7,4'-di-*O*-β-D-glucopyranoside. | Morikawa et al., 2009 |
| Antioxidant | *in vitro.* DPPH assay, reducing iron(III), $H_2O_2$: OH– luminol–micropero-xidase system | Inflo-rescences | Crude aqueous infusion (5 g in 200 mL), lyophilizates (fingerprint by TLC: apigenin, naringenin, kaempferol, luteolin, quercetin, caffeic acid, helichrysin, apigenin-7-*O*-glucoside, luteolin- 7-*O*-glucoside, quercetin-3-*O*-glucoside, chlorogenic acid) | *in vitro* | 1 mg/mL | Negative control. Positive control: silibinin | For lyophilizates: $IC_{50}$ =0.14 mg (DPPH), 380-1049 asc. acid equivalents/mg, $IC_{90}$ =0.154 μg ($H_2O_2$/OH luminol-microperoxidase system) | Czinner et al., 2000 |
| | *in vitro.* DPPH assay, phospho-molybdenum method | Aerial part | MeOH extract, Soxhlet with gallic, *p*-hydroxybenzoic, chlorogenic, caffeic, syringic, *p*-coumaric, ferulic, rosmarinic acids, catechin, epicatechin, rutin, resveratrol, hesperidin, apigenin- 7-glucoside, eriodictyol, quercetin, naringenin, luteolin, apigenin, and acacetin. | *in vitro* | 1 mg/mL | Negative control. Positive control: butylated hydroxy-toluene, ascorbic acid | $IC_{50}$=23-48 μg/mL (DPPH) 106–162 mg asc. acid equivalents/g | Albayrak et al., 2010 |
| | *in vitro.* Lipid peroxidation in rats liver microsomes | Inflores-cences. | Lyophilized water extracts standardized by polyphenols and flavonoids | *in vitro* | 0.01–0.02 mg/mL | Negative control. Positive control: sylibin. | MDA production was decreased in 23-50%, cytochrome *c* reductase activity was increased in 20-50% | Czinner et al., 2001 |
| Antiviral | *in vitro.* Agar diffusion, method. HeLa cells | Flowers | 10% aqueous extract | Petri dishes | 0.02 mL | Herpes virus Hominis HVP 75 (type 2), influenza virus A2 (Manheim 57), Vaccini virus, poliovirus type 1. Negative control. | Virusatic effect with inhibition zone 15-30 mm for all viruses, inactive against poliovirus type 1. | May, Willuhn, 1978 |
| Hypothensive | *in vivo.* Rats, dogs | Aerial part | Ether, EtOH, aqueous extracts | Intravenous | 50 mg/kg (dogs), 500 mg/kg (rats) | Negative control | Hypotensive effect | Szadowska, 1962 |
| Spasmolytic | *in vivo.* Rats | Aerial part | Aqueous solutions of naringenin-5-glucoside, kaempferol-3-glucoside), apigenin dissolved in phosphate-buffered sodium hydroxide. EtOH extract containing all fl avonoids and aqueous extract containing no flavonoids. | Intravenous | 4 mg/100 g bw 50 mg/100 g bw | Negative control. Positive control: dehydrocholic acid | Spasmolytic activity and choleretic effects (approximately 33% of that of dehydrocholic acid) for individual compounds. The flavonoids extract demonstrated spasmolytic activity similar to individual compounds. The flavonoids free extract elicited a spastic response in smooth muscles from rat intestine and gall-bladder. | Szadowska, 1962 |

wild rosemary, is a low shrub growing to 50 cm (rarely up to 120 cm) tall with evergreen leaves, belonging to the *Ericaceae*.

In Russian traditional medicine, the shoots are used as an aqueous infusion or decoction. This infusion has been used to treat a wide range of respiratory and lung disorders including bronchitis, tuberculosis, (whooping) cough, and asthma, as well as for lowering blood pressure and preventing seizures (Shass, 1952; Vereschagin et. al., 1959); the decoction is used as an anthelmintic (Utkin, 1931), and an ointment is prepared using an animal fat base, which is used topically for eczema, scabies, and insect stings (Vereschagin et. al., 1959). In Swedish traditional medicine, this plant has been used to treat headache, toothache, pain, and shingles (Tunón et al., 1995). The leaves are also used as marsh tea, which is considered to act as an abortifacient, diaphoretic, diuretic, emetic, expectorant, and lactagogue (Jin et al., 1999). In the Norwegian Sami community, a decoction of dried "guohcarassi" ("stinking plant") was considered a good remedy for cold and whooping cough, for rheumatism as a pain reliever, for frost damage of the joints, to lower blood pressure, and for bladder catarrh and diphtheria (Alm, Iversen, 2010). *Ledum palustre* leaves and shoots are used in China to treat coughs and asthma, to decrease blood pressure, and as an antifungal agent (Li, 2002).

*Ledum palustre* is regarded as poisonous due to the presence of toxic volatile compounds, especially the sesquiterpenoid ledol. Ledol can affect the central nervous system, initially leading to psychomotor stimulation, then to seizures and cramps, finally to paralysis, breathing problems and even death (Dampc, Luczkiewicz, 2013). As has been suggested, chronic and extended exposure to ledol and presumably its overdosage is crucial to causing serious adverse reactions, such as dizziness, exhaustion, nausea, vomiting and loss of consciousness (Dampc, Luczkiewicz, 2013). The essential oil of wild rosemary when applied orally can irritate the kidneys, urinary tract, and the gastrointestinal tract, causing vomiting and diarrhea (Aronson, 2009; Habermehl, 1998). However, the only side effects reported for "Ledin", an USSR medicine for coughs containing 50 mg of ledol per tablet, when used at the recommended total daily dose of 50–100 mg divided over 3–5 administrations per day for 3–10 days, are allergic reactions (Mashkovskii, 2002). The maximal tolerated dose of *L. palustre* extract in mice after oral administration is greater than 30 g/kg. At doses of 2.5, 5.0 and 10.0 g/kg, the extract had no observable genotoxicity in mice and was found to inhibit cyclophosphamide, a well-known anti-tumor drug, and induced genotoxicity in mice (Jing et al., 2011).

The acute toxicities of a 40% EtOH extract of *L. palustre* shoots and of chloroform and hexane fractions of the EtOH extract were studied in mice. The $LD_{50}$ for the 40% EtOH extract was 2,800–3,200 mg/kg after intraperitoneal administration, and no mortality of mice was observed after intragastric administration of the extract at the dose of 10g/kg. The $LD_{50}$ values for the chloroform fraction were 350 mg/kg (intraperitoneal) and 2,600 mg/kg (intragastric), and the $LD_{50}$ values for the hexane fraction were 420 mg/kg (intraperitoneal) and 5,100 mg/kg (intragastric), respectively (Basova, 2004).

The acute toxicity of ursolic acid as extracted from *L. palustre* was tested in mice. The $LD_{50}$ after oral administration was determined to be 9.26 g/ kg. The frequencies of micronuclei in mice administered with high, medium and low doses of the ursolic acid extract were 2.0, 2.0 and 1.8, respectively. No significant differences in the frequency of micronuclei were observed between mice administered with the ursolic acid extract and untreated mice. Chromosomal aberration rates in mice administered with high, medium, and low doses of the ursolic acid extracts were 1.2%, 1.2% and 1.0%, respectively, and were not significantly different from those found in normal mice. The results suggest that the ursolic acid extract from *L. palustre* is safe and has low acute toxicity and no genetic toxicity (Jing et al., 2009).

The pharmacological properties of *L. palustre* shoots depend on the essential oil, which are partially excreted after intragastric administration through the mucous membranes of the respiratory system. Volatile compounds of *L. palustre*, which are eliminated through the bronchi, have a moderate effect on the local irritation of mucous membranes, increasing the secretion of the bronchial glands and increasing the activity of the ciliated airway epithelium. A spasmolytic effect of *L. palustre* on airway smooth muscle has been observed (Sokolov 2000). It has been reported that the expectorant and antitussive effects of *L. palustre* are caused by ledol (Belousov et al., 1998). Table 9 summarizes the pharmacological studies that have been undertaken on *L. palustre* and that are reported in the literature.

The traditional applications of *L. palustre* shoots in various countries are mostly for coughs, bronchitis, lung disorders, and lowering blood pressure. The effects and safety of *L. palustre* has been demonstrated in a number of experiments, and this material is recommended in Russian officinal medicine as an effective expectorant for the treatment of bronchitis and other lung diseases that are accompanied with cough in the form of an infusion (10 g in 200 mL of water) at the dose of ¼ of a glass, 2–3 times per day (Sokolov, 2000). The film-coated tablets “Ledin” (which contain 50 mg of ledol) are recommended for acute and chronic bronchitis, pneumonia and bronchitis that is caused by chemicals, gases, fumes and vapors and for asthma, pulmonary tuberculosis, cystic fibrosis and frequent, mostly dry coughs at the dose of 1–2 tablets, 3–5 times a day, for 3–10 days (Mashkovskii, 2002). However, additional studies regarding its safety (in particular, its chronic toxicity) and efficacy are needed.

#### 5.8.2. FOLIA FARFARAE

*Tussilago farfara* L. (*Compositae*), commonly known as coltsfoot, is a perennial herbaceous species that grows 10–30 cm in height. The leaves of *T. farfara* are traditionally used in Russia to treat respiratory illnesses such as asthma, bronchitis, or the common cold as an expectorant and as a sedative. Additional uses of this material include the improvement of digestion, the treatment of diarrhea, its topical application for furunculosis, and its use as an analgesic (Vereschagin et al., 1959). The leaves are components of pectoral and diaphoretic teas (Gammerman et al., 1984). In China, the dried flower buds of *T. farfara* are used to treat coughs, bronchitis, and asthmatic conditions (Committee for the Pharmacopoeia of People’s Republic of China, 2010).

The safety of *T. farfara* is extensively discussed in the literature. In addition to the presence of acidic polysaccharides, which are considered responsible for the cough-relieving effect (Franz, 1969), *T. farfara* contains (generally comparatively low levels of) pyrrolizidine alkaloids, which are known to be toxic to the liver. The main alkaloid is senkirkine, and traces of senecionine are also present. The content of senkirkine in samples of *T. farfara* flowers was found to vary from 19.5 ppm to 46.6 ppm (Jiang et al., 2009). The concentration of senkirkine in commercial samples of coltsfoot leaves was 2.5–11.2 ppm, as determined using capillary zone electrophoresis, depending on the method of extraction used. The level of senecionine in the leaves was either below the detection limit (by gas chromatography) or less than 0.9 ppm when measured using capillary zone electrophoresis (Lebada et al., 2000).

A small lifetime study was performed in rats that were fed 32% young, pre-blooming flowers of coltsfoot in their diet for 4 days, and subsequently, as 16% of their diet until 380 days after the beginning of treatment. All of the rats survived beyond 380 days after the start of feeding, but 8 out of 12 developed hemangioendothelial sarcoma in the liver (Hirono et al., 1976). In the absence of epidemiological data, the International Agency for

**Table 8**
Summary of Pharmacological Studies for *T. vulgare*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro*. Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 99% growth inhibition by methylene chloride extract, 95% growth inhibition by MeOH extract | Goun et al., 2002 |
| Antihelminthic | *in vitro*. Egg hatching assay (*Ascaris suum*), larval migration inhibition (L3 larvae from *Trichostron-gylus colubriformis*) | Aerial part | EtOH (80%) extract. | 96 well plate. | 62.5-2000 μg/mL | Negative control. Positive control: albendazole | 46% ovicidal effect on *A. suum* eggs at 2000 μg/mL; 49.5% larval migration inhibition at 2000 μg/mL | Urban et al., 2008 |
| Anti-inflammatory | *in vivo*, mouse-ear edema induced by 12-0-tetradecano-ylphorbol 13-acetate; carrageenan-induced mouse paw edema | Aerial part | Dichlormethane, MeOH, chloroform extracts; parthenolide, methoxyflavones jaceosidin, eupatorin, chrysoeriol, diosmetin. | Topical application in ear. Per oral. | 0.5 mg/ear 100 mg/kg per oral | Negative control. Positive control: indometacin, phenylbutazone | 93% edema inhibition $ID_{50}$=0.18 μmol/ear by parthenolide; 92% inhibition by chloroform extract; 80% inhibition with $ID_{50}$=0.50 μmol/ear by jaceosidin. 24% paw edema reduction after 1 h. by parthenolide. | Schinella et al., 1998 |
| | *in vivo*, Rats, formalin induced edema | Inflore-scence | Polysaccharide complex (ammonium oxalate extract) | Intragastric | 0.3 g/kg, 7 days | Negative control. Positive control: indometacin. | 61.9% oedema inhibition after 4 h, 100% inhibition after 3 days of treatment. Concentration leucocytes and erythrocyte sedimentation rate was equivalent to control group after 7 days. | Kirichenko et al., 2012 |
| Antioxidant | *in vitro*. DPPH assay, | Aerial part | MeOH crude extract, 3,5-*O*-dicaffeoylquinic acid, axillarin, luteolin | *in vitro*. | 1 mg/mL | Positive control: quercetin | $EC_{50}$= 37 μg/mL (MeOH extract); $IC_{50}$=9.7 μmol for 3,5-*O*-dicaffeoylquinic acid | Juan-Badaturuge et al., 2009 |
| Antithrombin | *in vitro*. Thrombin solution from bovine plasma | Aerial part | MeOH extracts, soxhlet | 96 well plate | 50 μL | Negative control | 87% thrombin inhibition | Goun et al., 2002 |
| Antiviral | *in vitro*, antiviral and time-of-addition assay | Aerial part | Crude MeOH extract, fractionation using: petroleum ether, chloroform, EtOAc, BuOH, water; 3,5-*O*-dicaffeoylquinic acid, axillarin, luteolin, parthenolide. | 96 well plate | 5–500 μg/mL | Herpes simplex viruses HSV-1, HSV-2. Positive control: acyclovir | $CE_{50}$=31.1 μg/mL, 69.9 μg/mL, 95.7 μg/mL for 3,5-*O*-dicaffeoylqu-inic acid, petroleum ether and EtOAc extracts respectively against HSV-1. $CE_{50}$=42.7 μg/mL, 47.0 μg/mL, 58.4 μg/mL, 61.1 μg/mL for axillarin, 3,5-*O*-dicaffeoylquinic acid, EtOAc, and petroleum ether extracts respectively against HSV-2. | Alvarez et al., 2011 |
| Choleretic | *in vivo*. Rats, $CCl_4$ induced hepatitis | Aerial part | Tanacechol® | Per oral. | 50, 100 mg/kg, single administration | Negative control. | Effect in rats treated with 50 mg/kg observed during 3 h. After administration of 100 mg/g bile volume increased 80.9% after 1 h, and 76.2% after 2 h. Concentration of bile acids increased in 2.7, 2.1 and 1.8 fold compared to control after 1, 2, and 3 h. | Vichkanova et al., 2009 |
| Gastroprotective | *in vivo*. Rats, EtOH-induced gastric ulcer | Aerial part | Chloroform extracts; parthenolide | Per oral. | 2.5–80 mg/kg (chloroform extract), 5–40 mg/kg parthenolide, single dose. | Negative control. | 100% inhibition of damage for extract (10 mg/kg) and parthenolide (40 mg/kg). Administration extract (80 mg/kg) or parthenolide (40 mg/kg) 24 h before EtOH treatment restored numbers | Tournier et al., 1999 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mucosal -SH groups to values near controls | |
| Immunomodulatory | *in vitro*. Activation of NF-κB; NO, ROS, and TNF-α production. | Flowers | Polysaccharides with $M_r$=326, 151, 64 and 9 kDa | 96 well plate | 0–1600 μg/mL | Negative control. Positive control: LPS. | Potent macrophage-activating properties, resulting in modulation of NO, ROS, and TNF-α production. Polysaccharides stimulated neutrophil MPO release and activated NF-κB signaling in monocytic cells. | Xie et al., 2007 |
| Spasmolytic | *in vitro*. Rats isolated aorta | Aerial part | Crude aqueous decoction, lyophilized. | *in vitro*. | 50, 100, 200, 400, 800 μg/mL | Negative control. | Biphasic concentration-dependent relaxation: a first rapid effect within 10 min after addition of extract (50 μg/mL) and maximum at 200 μg/mL, which relaxed contraction by about 30% | Lahlou et al., 2008b |
| | *in vitro*. Serotonin release inhibition. | Leaves | EtOH extract, parthenolide | *in vitro*. | 1200–24000 μg/mL for EtOH extract; 1.14-6.04 μM for parthenolide | Negative control. | Serotonin release inhibition with $IC_{50}$= 9797 μg/mL fresh weight for EtOH extract and $IC_{50}$= 3.03 μmol for parthenolide | Marles et al., 1992 |

Research on Cancer listed senkirkine as an agent that was not classifiable as carcinogenic to humans (Group 3) (Barceloux, 2008).

Roulet et al. (1988) reported a case of a newborn female infant from Switzerland with fatal hepatic vaso-occlusive disease. Her mother revealed the occasional consumption of cannabis and hallucinogenic mushrooms some months before the actual pregnancy and the daily consumption of a single cup of herbal tea representing a toxic amount of senecionine (0.60 mg/kg dry weight) during her entire pregnancy. The exact composition of the incriminated cough tea was obtained from the manufacturer; of the 10 different plants used in this preparation, *T. farfara* leaves comprised 9% (w/w). In a comment responding to this article, Roder assumed that the herb containing pyrrolizidine alkaloids was not *Tussilago* but petasites, because the typical leading alkaloid of *Tussilago*, senkirkine, was not found by the authors (Roder, 1988). Roder argued that petasites leaves had most likely been confused with *Tussilago* because both plants grow wild in alpine regions and can be easily confused when gathered after the flowering period. The results of later research showed that the cough tea, contrary to the representation made in the publication of Roulet, contained not only leaves and flowers of *T. farfara*, but also the roots of *Petasites hybridus* (L.) G. Gaertn., B. Mey. & Scherb. (described as *Petasites officinalis* by Moench) (Spang, 1989). Another report, published in 1995, concerned an 18-month-old boy from the Southern Tyrol with reversible hepatic veno-occlusive disease caused by over 15 months consumption of herbal tea, which contained large amounts of seneciphylline (approximately 60 μg/kg body weight per day). *Adenostyles alliariae* (alpendost) leaves were mistaken for those of *T. farfara* (coltsfoot) by the parents; these two plants can easily be confused, especially after the flowering period. The child was given conservative treatment only and recovered completely within 2 months (Sperl et al., 1995). Both clinical cases were due to the adulteration of coltsfoot with other, more toxic plants.

However, to avoid any risk for consumers, the German public health authorities (Bundesgesundheitsamt, 1992) have limited the daily intake of toxic pyrrolizidine alkaloids to 1 μg.

Intravenous injection of the alcoholic extracts or decoctions of *T. farfara* to cats induced a primary blood pressure depression effect, which was followed by a more rapid acute rise in mean blood pressure and finally a sustained pressor response for several minutes. No tachyphylaxis was observed. This blood pressure response was associated with increases in heart rate and respiratory stimulation. It was suggested that the mechanism of action of *Tussilago* on blood pressure might be due to stimulation of the vasomotor center of the medulla and the vascular α-receptor and to constriction of the peripheral blood vessels (Wang, 1979). The juice prepared from fresh *T. farfara* leaves (at dilutions of 1:10 and 1:100) was observed to exhibit significant antimutagenic activity against the genotoxic compound nalidixic acid in an SOS chromotest (Karamova et al., 2010). Water-soluble polysaccharides present in coltsfoot reduce the toxic effect of paclitaxel on the blood system in mice that have Lewis lung carcinoma (Safonova et al., 2010). Table 10 summarizes the pharmacological studies that have been undertaken on *T. farfara* and that are reported in the literature.

Mixtures with *T. farfara* have been found efficaceous in the complex treatment of rhinosinusitis in miners with chronic bronchitis (Lavrenov et al., 1988). However, no details were provided by the authors.

The leaves of *T. farfara* are used in Russian traditional medicine and were included in the VIIIth Pharmacopoeia of the USSR in 1952. Since this time, no adverse effects or toxicity have been reported in Russian publications. Considering the long history of the application of this plant in traditional medicine, infusions of *T. farfara* leaves (5 g in 300 mL of water) can be considered safe at the recommended therapeutical dose of 1/2-1/3 of a glass, 2–3

times per day, for use as an expectorant (Sokolov, 2000). The possibilities of adulteration must, however, be carefully monitored (Roulet et al. 1988, Sperl et al. 1995). Publications reporting the chemistry and pharmacological effects of this plant remain fragmentary, and further study of this plant would provide useful results.

### 5.8.3. FOLIA PLANTAGINIS MAJORIS

*Plantago major* L. is a perennial plant that belongs to the family *Plantaginaceae*. The leaves of *P. major* have long been used in Russia for wound healing and as an expectorant, antiphlogistic, pain-relieving herb (Turova, Sapozhnikova, 1989; Sokolov, 2000). Whole or fragmented dried leaves and scapes of *Plantago lanceolata* L. are approved by the European Pharmacopoeia.

Because the pharmacological effects of *P. major* are similar to those of *Plantago lanceolata*, the pharmacological effects of *P. major* are not discussed in this review.

### 5.8.4. GEMMAE PINI

*Gemmae pini* consist of the buds of *Pinus silvestris* L. (of the *Pinaceae* family), which are collected during early spring. Pine buds are widely used in Russian traditional medicine as an expectorant and a weak diuretic for the treatment of chronic bronchitis and tuberculosis. This material can be used for aromatic baths that improve skin conditions and support the treatment of arthritis (Vereschagin et. al., 1959; Gammerman et al., 1984).

Pine buds are safe, available without a prescription, and are recommended for use as a decoction (10 g of buds in 200 mL of water) or by inhalation. The decoction is used at a dose of 60-100 mL, 2–3 times per day, as an expectorant (Sokolov, 2000). Pine buds are used as the raw material for the steam distillation of an essential oil. *Pini sylvestris* aetheroleum is included in the European Pharmacopoeia and will therefore not be discussed further here.

### 5.8.5. RHIZOMATA ET RADICES INULAE

Elecampane (*Inula helenium* L.), also called horse-heal, is a perennial plant from 90 cm to 150 cm high belonging to the *Compositae* family. In Russia, elecampane roots are used as an expectorant for treating chronic respiratory diseases, including bronchitis, tracheitis, tuberculosis, and bronchitis with lots of mucus (Turova, Sapozhnikova, 1989). A decoction made from elecampane roots is often prescribed as an antiphlogistic and as a haemostatic for treating problems of the gastrointestinal tract. This root increases stomach and intestinal secretions, thus stimulating the appetite and improving digestion (Zevin et al., 1997). Preparations of the roots are used in the folk medicine of several ethnic groups to treat a variety of ailments including asthma, (whooping) cough, bronchitis, lung disorders, tuberculosis, indigestion, chronic enterogastritis, and infectious and helminthic diseases (List and Horhammer, 1976; Cantrell et al., 1999; Huo et al., 2008).

The safety of elecampane has been evaluated in mice, rats, rabbits, and other animals. The $LD_{50}$ of infusions, tinctures, and liquid extracts of *I. helenium* roots were found to be greater than 5,000 mg/g in both mice and rats. The median lethal dose of the tincture was found to be 14,043 mg/kg for mice and 12,684 mg/kg for rats. The median lethal dose of the liquid extract was found to be 13,230 mg/kg for mice and 12,285 mg/kg for rats (Gurskaya et al., 2009a). The safety of the infusion, tincture, liquid and dry extracts of *I. helenium* was evaluated in irritation tests on guinea pigs, rabbits, sheep and piglets. There was no irritating effect after the transdermal application of all forms of *I. helenium*. The irritating activity of the infusion after application to the eye conjunctiva was evaluated as light, whereas the effect of the dry extract (10-20% suspension in water) was estimated as limited and disappeared in 24 hours. The irritating activities of the tincture and liquid extract (70% EtOH) were evaluated as pronounced and did not disappear within 24 hours (Gurskaya et al., 2009b). Table 11 summarizes the pharmacological studies that have been undertaken on *I. helenium* and that are reported in the literature.

A clinically tested and approved extract of *I. helenium* root (standardized based on the total amount of sesquiterpene lactones), which has been marketed in Russia under the name "Alanton" since 1979, is prescribed for the treatment of acute and chronic infectious and inflammatory diseases of the respiratory system that are accompanied by a persistent cough with thick viscous mucus, to stimulate blood circulation in the stomach and to accelerate the healing of stomach ulcers (Mashkovskii, 2002). In an open clinical trial without a control group, "Alanton" tablets were administered to 24 patients with peptic ulcers. After oral administration of the tablets (0.1 g, three times daily, for 3 weeks), clinical recovery was recorded for all of the studied patients. The level of blood serum protein, primarily albumin, and γ-globulins, was increased. Decreases in pyrosis, nausea, and vomiting were registered after 7–10 days, patient appetite was improved, and body weight was increased by approximately 3 kg. The treatment resulted in regeneration of the gastric epithelium and decreased the size of the ulcers. It was concluded that "Alanton" has anti-inflammatory activity and contributes to mucus production and mucus membrane regeneration (Luchkova, 1978).

*Inula helenium* roots are recommended for internal administration at a dose of 100 mL of the decoction (16:200), 2–3 times per day, for use as an expectorant in upper respiratory tract infections. "Alanton" tablets that contain 0.1 g of total sesquiterpene lactone content are recommended for internal administration at the dose of 1 tablet, 3 times per day, for 6–8 weeks by patients with inflamed or scarred stomach ulcers (Sokolov, 2000). The extracts and isolated compounds of *I. helenium* have been determined to have interesting biological activities, suggesting that *Radix Inulae* could lead to the development of further drugs.

### 5.8.6. RHIZOMATA CUM RADICIBUS POLEMONII

*Polemonium caeruleum* L., (Jacob's ladder or Greek valerian; *Polemoniaceae*) is a hardy perennial flowering plant, which grows to a height of approximately 35–140 centimeters; this plant has been used in Russian traditional medicine as a sedative that is similar to valerian and to treat tuberculosis and whooping cough. In Ukraine, this plant was used to prepare childrens' baths. An infusion of the roots is used as a drink to treat fever (Turova, Sapozhnikova, 1989, Sokolov, 1990). In modern medicine, this plant is recommended as an expectorant for bronchitis, neurosis, and stomach and intestinal ulcers in combination with *Gnaphalium uliginosum* L. (Mashkovskii, 2002).

Varlakov first studied this plant in 1932 in connection with the medicinal flora of Eastern Sayan and proposed its use as an expectorant to replace imported *Polygala senega* L. (Varlakov, 1943). In experiments on rabbits with cholesterol-induced atherosclerosis, it was shown that saponins of *P. caeruleum* have a hypocholesterolemic effect, decrease the development of atherosclerosis and reduce lipid levels in the skin, aorta and liver (Sokolov, 1990). *Rhizomata cum Radicibus Polemoni* was included in the State Pharmacopoeia of the USSR in 1961 (Maltseva, Sorokina, 2010), and a limited number of pharmacological studies are available (Table 12).

No toxicity was observed after treating patients with 45 mL of an infusion of *P. caeruleum* (6 g of roots in 200 mL of water) per day for two weeks; however, because some irritating effects are possible, this infusion should be taken after a meal (Panchenkov, 1950; Turova, Sapozhnikova, 1989).

**Table 9**
Summary of Pharmacological Studies for *L. palustre*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antibacterial | *in vitro.* Broth dilution method. | Shoots | Aqueous extract and isolated polysaccharide complex | *in vitro* | 1/20-1/160 | Tested microbes *S. aureus, E. coli, P. aeruginosa, Klebsiella pneumoniae* | Bacteriostatic effect at 1/160 dilution, excluding to *P. aeruginosa* (1/20 dilution) for polysaccharide complex. | Belousov et al., 2006 |
| Anticancer | *in vitro.* Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, Soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 99% growth inhibition by methylene chloride extract. This extract is not attractive as a potential source of drugs because of the possibility of causing necrosis of the cells. 71% growth inhibition by MeOH extract. | Goun et al., 2002 |
| Anticancer | *in vitro.* Human lympho-blastoid Raji cells | Aerial part | Crude EtOH (40%) extract | *in vitro* | 10, 50, 200 μg/mL | Positive control: methotrexate fluorouracil, cyclophos-phamide, vinblastine. Negative control | 99% inhibition at 200 μg/mL | Spiridonov et al., 2005 |
| Antidiabetic | *in vitro.* C2C12 murine skeletal myoblasts and the 3T3-L1 murine preadipocyte cell lines | Leaves | EtOH (80%, 1:10) extract with 153.5 μg/mg total phenolic | *in vitro.* | 1.1 mmol/L (glucose deprivation) or 150 mmol/L glucose (glucose toxicity) | Negative control. Positive control rosiglitazone | Cytoprotective properties under conditions of glucose toxicity and glucose deprivation at 6.25 μg/mL. Exhibited the effect on the basal and insulin stimulated 3H-deoxy-glucose uptake in differentiated 3T3-L1 Adipocytes at 50 μg/mL. Triglyceride level was increased by 3-fold. Effect was comparable with levels induced by10 mmol/L rosiglitazone | Harbilas et al., 2009 |
| Antidiabetic | *in vitro.* Caco-2/15 cells; western blot analysis. *in vivo.* Rats, oral glucose tolerance test | Leaves | EtOH (80%, 1:10) extract with 153.5 μg/mg total phenolic | | 25–100 μg/mL (*in vitro*); 250 mg/kg (*in vivo*) | Negative control. Positive control: cytochalasin B, phlorizin, phloretin. | 100 μg/mL instantaneous inhibition of differentiated Caco2/15 intestinal cells glucose absorption. Reduced SGLT1 protein expression. *in vivo* reduction AUC of blood glucose levels compared with control in the periods 0–30 min, 0–50 min, 0–120 min after glucose administration. | Nistor Baldea et al., 2010 |
| Antifungal | *in vitro.* Micro-broth dilution method. | Leaves | Quercetin 3-β-D-(6-p-coumaroyl) galactoside and quercetin 3-β-D-(6-p-hydroxy-benzoyl) | 96 well plate | 100 μL | *Cryptococcus neoformans, Saccharomyces Cerevisiae, Aspergillus niger, C. albicans.* Positive control amphotericin B, fluconazole | MIC = 16-63 μg/mL for *C. neoformans, S. cerevisiae* and *A. niger*. MIC = 0.16–10 μg/mL for amphotericin B and fluconazole. MIC = 250 μg/mL for *C. albicans*. | Jin et al., 1999 |

**Table 9** (*continued*)

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anti-inflammatory | *in vitro.* Prostaglandin biosynthesis assay; PAF-induced exocytosis | Aerial part | Aqueous extract, lyophilized. | *in vitro* | 0.2 mg/mL (for prostaglandin) 0.25 mg/mL (for PAF) | Negative control. Positive control: indometacin, eugenol, quercetin, saligenin. | Moderate inhibition of prostaglandin biosynthesis (50%) and platelet activating factor (PAF)- induced exocytosis (71%) | Tunón et al., 1995 |
| Anti-inflammatory | *in vitro.* Prostaglandin-synthesizing cyclooxygenase system from sheep seminal vesicles and HPLC separation | Aerial part | Essential oil | *in vitro.* | 37 μMol | Positive control: eugenol, carvacrol, thymol, guajazulen, urushiol, curcumin, piperin, capsaicin, apiol, cubebin, isoalantolacton, ledol | Ether oil inhibited cyclooxygenase *in vitro* with 46.6% and carvacrol was reported to be one of the compounds responsible with 94% inhibition. However, ledol, did not inhibit the enzyme. | Wagner et al., 1986 |
| Anti-inflammatory | *in vivo*. Carrageenan-induced edema in rats | Shots | Dry extract aqueous, EtOH 40%, EtOH 70% | Per oral | 50 mg/kg / Single dose | Negative, Positive control: butadione, 50 mg/kg | $51.5 \pm 4.6\%$ inhibition of edema by EtOH 40% extract, comparable to butadione. | Belousov et al., 2006 |
| Antioxidant | *in vitro.* DPPH assay, $Fe^{3+}$-EDTA-$H_2O_2$ deoxyribose assay, nonenzymatic lipid peroxidation of rat liver homogenate | Aerial part | Essential oil. 37 compounds identified among them sabinene (16-17%), terpinen-4-ol (7.6%), myrtenal (3.5%), β-Selinene, α-selinene, γ-elemene, α -caryo-phyllene (2-6% range) | *in vitro.* | Not indicated | Negative control. | $IC_{50}=1.6$ μg/mL in DPPH assay; $IC_{50}=2.7$ μg/mL in $Fe^{3+}$-EDTA-$H_2O_2$ deoxyribose system; $IC_{50}=13.5$ μg/mL in nonenzymatic lipid peroxidation of rat liver homogenate | Kim, Nam, 2006 |
| Antithrombin | *in vitro.* Thrombin solution from bovine plasma | Aerial part | MeOH extract, soxhlet | 96 well plate | 50 μL | Negative control | 88% thrombin inhibition | Goun et al., 2002 |
| Hepato-protective | *in vivo.* Rats, mice, $CCl_4$ intoxication | Shots | Dry extract (EtOH 40%) | Per oral | 100 mg/kg / Single dose | Negative control. | Extract reduces hexobarbital sleeping time in 1.4 (rats), and 3.2 (mice) folds. Improves functional-metabolic and morphological parameters of liver. | Belousov et al., 2007 |
| Radioprotective | *in vivo.* Mice irradiated with γ-irradiation | Aerial part | Combination of *Archangelica officinalis* and *L. palustre* extracts | Single injection | Not indicated, 5–15 min before lethal dose irradiation | Negative control. | 100% of animals survived after a dose of 6 Gy ($LD_{50/30}$); 70% survived after a dose of 7.5 Gy ($LD_{90/30}$), and 25% after a dose of 8 Gy ($LD_{100/12}$) by day 30. | Narimanov et al., 1991 |
| | *in vivo.* 30 days albino mongrel male mice irradiated with γ-irradiation ($LD_{90/30}$) | Aerial part | Combination of *Archangelica officinalis* and *L. palustre* extracts | Single injection | Not indicated | Negative control: nonirradiated animals | Offspring were obtained from 11 of 12 experimental males. The number of mouse pups was $10.2 \pm 0.6$ and $7.4 \pm 0.7$ in experimental and nonirradiated groups respectively. The number of both sexes in the posterity of nonirradiated parents was equal, in offspring of experimental groups, the number of female pups was 2.3 times larger than that of males. | Narimanov, 1992 |

In an open clinical trial without a control group, a group of patients with tuberculosis, acute and chronic bronchitis, and lung abscess was treated with 0.75 mL of *P. caeruleum* liquid extract (taken 3 times a day) and 45–75 mL of infusion (6 g of roots in 200 mL of water) for 30 days. Therapeutic effects were observed in 60% of the patients, but no clear scale for primary outcome parameters appears to have been defined. Patient treatment resulted in increased phlegm and the facilitation of its evacuation. Catarrhal conditions of the lungs were improved, and coughing diminished (Turova, 1955). A different group of patients with psychiatric disorders was treated with 15 mL of an infusion of *P. caeruleum* (6 g of roots in 200 mL of water) to be taken three time a day after a meal for a 2-week period. A sedative effect was observed in all patients (Turova, Sapozhnikova, 1989), but the details remain lacking.

A specific method has been reported for the treatment of patients with peptic ulcers that involves the combined administration of infusions of *P. caeruleum* and *G. uliginosum*. The rationale behind this therapy is due to the sedative effect provided by *P. caeruleum* and a local effect of *G. uliginosum* that accelerates ulcer healing. Seventy patients with ulcers were treated with 15 mL of an infusion of *P. caeruleum* (6 g of roots in 200 mL of water) and 50 mL of an infusion of *G. uliginosum* (10 g in 200 mL of water) to be taken three times a day after a meal for 2 weeks. No side effects were observed. Most of the patients exhibited diminished gastric pain and less blood in the stool. Based on radiographic examination, the gastric ulcer lesions (called 'niches') disappeared, and the gastric pH was usually normalized. Treatment of patients with either of the infusions alone was not effective (Panchenkov, 1950).

The roots and rhizomes of *P. caeruleum* are recommended for internal administration at the dose of 20 mL of the infusion (6 g in 200 mL of water), 3–5 times per day, for use as an expectorant and at the dose of 20 mL, 3 times per day, together with an infusion of the aerial parts of *G. uliginosum* for use as an anti-inflammatory agent for the treatment of stomach ulcers (Sokolov, 2000). *Polemonium caeruleum* has been used clinically for a long time, and the roots and rhizomes are available without a prescription. However, the chemical and pharmacological evidence needed to support the medical applications of this plant, especially for its use as an expectorant, dates from the early part of the last century and needs further confirmation.

### 5.9. Diuretic agents

#### 5.9.1. CORTEX VIBURNI

*Viburnum opulus* L. (*Adoxaceae)*, also known as the guelder rose, water elder, European cranberrybush, cramp bark, and snowball tree, is a deciduous shrub growing to 4–5 m high.

An infusion of the bark is used in Russian traditional medicine to treat scrofula in children, asphyxia, colds, and uterine, gastric and hemorrhoidal bleeding (Vereschagin et al. 1959). The bark has been used to treat high blood pressure, heart trouble, tuberculosis, shortness of breath, stomach pain, digestive troubles, duodenal ulcers and bleeding, kidney and bladder afflictions, and coughs and colds, and this infusion also has astringent activity (Smirnova, Iadrova, 1968, Velioglu et al., 2006, Zayachkivska et al., 2006; Sokolov, 2000). The tannins of *V. opulus* bark bind mucous proteins after intragastric administration, causing them to precipitate and thereby cover and protect sensitive stomach cells. Consequently, local pain is decreased, blood vessels are constricted, the secretion of gastric juice is decreased, and membrane density is increased, resulting in decreased inflammation. In 1952, the bark was included in the State Pharmacopoeia of the USSR (Vereschagin et al. 1959).

In the available literature, there is no data regarding the toxic effects of *V. opulus* bark. The bark is available without a prescription in Russian pharmacies and is considered safe in decoction form at the dose of 18–36 mL, 3–4 times per day (Sokolov, 2000). Table 13 summarizes the pharmacological studies that have been undertaken on *V. opulus* bark and that are reported in the literature.

In the literature, no clinical data are reported. The bark of *V. opulus* is recommended for internal administration at the dose of 1–2 tablespoons of the decoction (10 g in 200 mL of water), taken 3–4 times per day as a diuretic or an antiseptic. The bark has been used clinically for a long time as a non-prescription medicine. However, the information available regarding its chemical and pharmacological effects is insufficient, and the bark should be studied in greater detail.

#### 5.9.2. FLORES CENTAUREAE CYANI

*Centaurea cyanus* L. *(Compositae)* also called blue cornflower or bachelor's button has grey-green branched stems. The flowers are used in Russian traditional medicine as a diuretic and for the treatment of cystitis, coughs, nervous and gastric diseases, uterine bleeding and in children against diarrhea and as an eye-wash (Vereschagin et al., 1959). The flowerheads are a well-known crude drug used in European traditional medicine to treat minor ocular inflammation (Bruneton, 1995), fever, gynecological problems, digestive complaints (Kern et al., 1972; Hansel et al., 1992), and wounds and dermatological complaints (Pieroni et al., 2004). The dried flowers of *C. cyanus* are used to relieve diarrhea, increase energy and appetite, and to relieve chest tightness (Arif et al., 2004). *Centaurea cyanus* is recommended as a component of herbal mixtures for the treatment of edema associated with kidney disease, as well as diseases of the urinary tract (nephritis, cystitis, and urethritis), and diseases of the liver and biliary tract (Turova, Sapozhnikova, 1989).

No data regarding the toxicity of *C. cyanus* is available in the literature. In a recently published review of retrospective observational case reports of ocular side effects or systemic side effects of eye medications involving herbal medicines and nutritional supplements, Fraunfelder (2004) mentioned that cornflower is used for the treatment of conjunctivitis and ophthalmia. No side effects of *C. cyanus* were found in reports submitted to the WHO, the Food and Drug Administration, and the National Registry of Drug- Induced Ocular Side Effects (Fraunfelder, 2004). The dry flowers of *C. cyanus* are available without a prescription in Russian pharmacies and are safe in decoctions at the dose of 18 mL, administered 3 times a day (Sokolov, 2000). Few pharmacological studies of *C. cyanus* are available and summarized in Table 14.

No clinical data were found regarding *C. cyanus*. Flowerheads of *C. cyanus* are recommended for internal administration at the dose of 1 tablespoon of the infusion (10 g in 200 mL of water), 3 times per day, for use as a diuretic. This material has been used clinically for a long time without prescription. However, information regarding the chemical and pharmacological effects of this material is limited and warrants further study.

#### 5.9.3. FOLIA VITIS-IDAEA

*Vaccinium vitis-idaea* L., (lingonberry, or cowberry, *Ericaceae*) is a short evergreen shrub up to 25 cm tall, with leathery evergreen leaves. In Russian traditional medicine, infusions or decoctions made from the leaves have been used as an astringent and as a diuretic for the leaching of kidney stones and in cases of stomach pain, diarrhea, and rheumatism (Vereschagin et al., 1959; Nosal, Nosal, 1960). *Vaccinium vitis-idaea* leaves are used as an anti-inflammatory medicine in China to treat respiratory system infections (Wang et al., 2005). A decoction of *V. vitis-idaea* leaves is recommended in modern Russian medicine for use as a diuretic, a cholagogue, an antiseptic, and as an astringent for the treatment of kidney and bladder diseases, gastroenteritis, diarrhea, as well as

**Table 10**
Summary of Pharmacological Studies for *T. farfara*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro*. Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 92% growth inhibition by methylene chloride extract. 71% growth inhibition by MeOH extract. | Goun et al., 2002 |
| Anti-inflammatory | *in vitro*. Murine macrophage cell line (RAW 264.7), lipopolysac-charide-activated macrophages | Flower buds | Isolated 1α,5α -bisacetoxy-8-angeloyloxy-3β,4β-epoxy-bisabola-7 (14),- 10-dien-2-one | 96 well plate | No data | Negative, Positive control: $N^G$-monomethyl -L-arginine | Inhibition of arachidonic acid metabolism and i-NOS (71.1%) with IC50 =8.9 μM. | Ryu et al., 1999 |
| Anti-inflammatory | *in vitro*. Murine macrophage cell line (RAW 264.7), lipopolysac-charide-activated macrophages | Flower buds | Isolated tussilagone | 96 well plate | 0–30 μM | Negative, Positive control: zinc protoporphyrin IX, copper protoporphyrin IX | Inhibition of production of NO, TNF-α, and PGE2 aswell as i-NOS and COX-2 LPS-stimulated RAW264.7 cells and murine peritoneal macrophages | Hwangbo et al., 2009 |
| Antimicrobial | *in vitro*. Liquid dilution method | Aerial part, rhizome | EtOH (80%) extract | *in vitro*. | No data | *B. cereus, E. coli, P. aeruginosa, S. aureus, C. albicans*. Positive control: erythromycin, gentamicin, amphotericin B | MIC (mg/mL) for aerial part/rhizome *B. cereus*: 16.63/62.5; *S. aureus:* 62.50/62.5 | Kokoska et al., 2002 |
| Antioxidant | *in vitro*. Lipid peroxidation in rat brain homogenates, DPPH assay. | Flower buds | EtOAc fraction from MeOH extract | *in vitro*. | Not indicated | Negative control. | $IC_{50}$=6.3 μg/mL in lipid peroxidation assay, $IC_{50}$=14.3 μg/mL in DPPH assay | Cho et al., 2005 |
| Antioxidant | *in vitro*. DPPH assay, pyrogallol autoxidation assay | Flower buds | EtOAc, BuOH, aqueous fractions from EtOH (70% extract). Main compounds: chlorogenic and 3, 5-*O*-dicaffeoylquinic acids. | *in vitro* | 5–8 mg/mL | Negative control. | EtOAc and BuOH fractions exhibited more potent activities than aqueous fraction in all tested concentrations. The scavenging activity of all extracts was found in a concentration-dependent manner | Li et al., 2012a |
| Antitussive | *in vivo*. Mice, ammonia induced coughing. | Flower buds and rachis | Aqueous extract | Per oral | Flower bud (2.8 g/kg), rachis (3.5 g/kg). 5 days. | Negative control. Positive control: pentoxyverine | After treatment with flower bud extract latent period of cough was prolonged in 47% and cough frequency was decreased in 48% compared to control. Rachis extract has no significant effect. | Li et al., 2012b |
| Expectorant | *in vivo*. Mice, intraperitoneal injection of phenol red solution. | Flower buds and rachis | Aqueous extract | Per oral | Flower bud (2.8 g/kg), rachis (3.5 g/kg). 5 days. | Negative control. Positive control: ammonium chloride | Flower bud enhance tracheal phenolsulpho-nphthalein excretion in 42% compared to control, indicating strong expectorant effect. No effect for the rachis extract | Li et al., 2012b |
| Neuro-protective | *in vitro*. Cortical cell cultures | Flower buds | EtOAc fraction from MeOH extract | *in vitro*. | Not indicated | Negative control. | Inhibition of neuronal damage induced by arachidonic acid with $IC_{50}$= 0.64 μg/mL. Attenuated neuronal damage induced by spermine NONOate. Cell viability increased to 30-40% at 10 μg/mL and above. Inhibited $A_{\beta\ (25\text{-}35)}$-induced neurotoxicity with $IC_{50}$= 30.9 μg/mL and glutamate- or *N*-methyl-D-aspartic acid-induced excitotoxicity was inhibited with $IC_{50}$= 76.3 and 53.7 μg/mL respectively. 90% of cells were protected from $Fe2^+$/ascorbic acid-induced damage at 30 μg/mL. $H_2O_2$-induced damage was not inhibited until 300 μg/mL. Viability of cells exposed to xanthine/ xanthine oxidase was increased at 30 μg/mL and above. | Cho et al., 2005 |

for rheumatism, gout and arthritis (Sokolov, 2000). The leaves of *V. vitis-idaea* were included in the VIIIth Pharmacopoeia of the USSR in 1952.

No literature data is available regarding the toxic effects of *V. vitis-idaea* leaves. The acute toxicity of the polyherbal mixture "Brusniver", which contains 50% *V. vitis-idaea* leaves, 20% *Hypericum perforatum* L. (*Hypericaceae*) aerial parts, 20% *Rosa* spp. L (*Rosaceae*) pseudo-fruits and 10% *Bidens tripartita* L (*Compositae*) aerial parts, has been studied in mice. Regarding acute toxicity, intragastric administration of the infusion was found to be safe; no mortality was observed after administration of the extract at the dose of 30 g/kg (equivalents of dry mixture) in mice, and the $LD_{50}$ was not reached. No signs of toxicity were observed in female rats after intragastric administration of infusions (20 and 40%) of the mixture at doses up to 8 g/kg administered for 21 days (Vichkanova et al., 2004). Table 15 summarizes the pharmacological studies that have been undertaken on *V. vitis-idaea* and that are reported in the literature.

The effect of an oral treatment with an infusion of Brusniver® (200 mL/day, administered for 14 days) was studied in 31 patients with pyelonephritis, urolithiasis, and urethritis. The report did not give a full description of the controls used, which makes it difficult to assess the outcome of this trial. A positive effect was registered in 83.8% of patients; however, it appears that no clear primary outcome parameters were defined. All patients tolerated the treatment well, and no side effects were observed (Vichkanova et al., 2004).

*Vaccinium vitis-idaea* leaves are available in Russia in pharmacies without a prescription and are recommended for internal use at a dose of 1/2 - 1/3 glass of the decoction (6 g in 200 mL of water), 2–3 times per day, for use as a diuretic, a cholagogue and as an antiseptic (Sokolov, 2000). However, insufficient information is available regarding the chemical and pharmacological effects of this material, which therefore warrants further study.

#### 5.9.4. GEMMAE BETULAE

*Gemmae betulae* consists of the buds of *Betula pendula* Roth and *B. pubescens* Ehrh. (*Betulaceae*). Birch buds are widely used in Russian traditional medicine as a diuretic, expectorant, cholagogue, diaphoretic, blood-purifier, and analgesic; as an anti-infective agent and an antiseptic for wound healing; to treat furunculosis; and as a wash to remove skin spots (Vereschagin et al., 1959; Nosal, Nosal, 1960; Zevin et al., 1997). Infusions and decoctions of birch buds are used in stomatology and otolaryngology for their anti-inflammatory properties, to treat stomatitis, gingivitis, periodontitis, glossitis, sore throat, chronic tonsillitis, acute respiratory diseases, and as a rinse applied to gauze pads, which are moistened with infusions or decoctions (Lavrenova, Lavrenov, 1997).

Birch buds have been used for centuries; in adequate doses, this material presents no toxicity or contraindications except for ingestion, due to the presence of ether oils in the buds. However, we did not find any data regarding the toxic effects of *Gemmae betulae* in the available literature. Table 16 summarizes the pharmacological studies that have been undertaken on *Gemmae betulae* and that are reported in the literature.

A group of 108 patients with purulent wounds (83 had superficial wounds, 10 had deep wounds, and 15 had cavitary wounds) was treated with a 20% tincture of birch buds in 70% EtOH. The publication did not give a full description of the controls; thus, it is practically difficult to assess the outcome of this trial. Positive results were obtained after using the birch-bud tincture in all of the patients, including patients with antibiotic-resistant microbial floras; however, it appears that no clear primary outcome parameters were defined (Zakharov et al., 1980). Birch buds have been used in patients with edema of cardiac origin as a diuretic. A significant increase in diuresis (urine production) and a sharp decrease in edema were observed. However, in case of functional kidney failure, this type of treatment is not recommended due to possible irritation of the renal tissue by the resinous substances (Sokolov, 2000). Birch buds were shown to exert a beneficial effect in the treatment of patients with acute and chronic forms of eczema (Pevzner, Raitsina, 1954).

Birch buds are available in Russia pharmacies without a prescription and are recommended for internal administration at the dose of 1/2 - 1/3 glass of the infusion (10 g in 200 mL of water), taken 2–3 times per day as a diuretic and a cholagogue (Sokolov, 2000). However, insufficient information is available regarding its chemical composition and pharmacological effects, and thus, this material warrants further study.

### 5.10. Cardiotonic agents

#### 5.10.1. HERBA ADONIDIS VERNALIS

*Adonis vernalis* L., also known as pheasant's eye, spring pheasant's eye, yellow pheasant's eye and false hellebore, among others, is a perennial flowering plant of the *Ranunculaceae*. This plant is included in the German Homoeopathic Pharmacopoeia.

In Siberia, an aqueous infusion of the aerial parts has traditionally been used against malaria, edema, cardiac edema, and several other heart-related problems, and against kidney diseases (Utkin, 1931; Nosal, Nosal, 1960). In 1879, alcoholic extracts of *A. vernalis* were first introduced into medicine by the Russian medical doctor, N.O. Bubnow, who employed these extracts as a cardiac stimulant (Heyl et al., 1918). In 1898, the famous Russian neurologist Vladimir Bekhterev suggested using a mixture of *A. vernalis* with sodium bromide (or potassium bromide) or codeine to treat light forms of heart failure, panic disorder, dystonia, and epilepsy (Bekhterev, 1898). The biological activity of *A. vernalis* aerial parts (1:20 EtOH 95% extract) was defined as 50–66 frog units or 6.3-8.0 cat units according to the State Pharmacopoeia of the USSR, 11th edn.

The toxicity of *A. vernalis* leaves was assayed using the one-hour frog method, which is officially used to test tinctures of digitalis, strophanthus, and squill. The average minimum dose producing a permanent systole (M.S.D.) of the frog's ventricle at the end of exactly one hour was 0.0045 mL/g frog for the *A. vernalis* tincture (1:10, 95% EtOH) (Heyl et al., 1918). The $LD_{50}$ of cymarin (one of the active glycosides present) after intravenous injection in rats was found to be $24.8 \pm 1.8$ mg/kg (Vogel, Kluge, 1961) and the $LD_{50}$ after intravenous injection in cats was found to be $95.4 \pm 3.0$ μg/kg (Chen et al., 1942). The M.S.D. values for adonitoxin and cymarin are $0.621 \pm 0.046$ g/g and $0.880 \pm 0070$ g/g frog, respectively (Chen, Anderson, 1947). The $LD_{50}$ for adonitoxin after intravenous injection in cats was found to be $191.3 \pm 17.5$ μg/kg (Chen, Anderson, 1947).

Preparations of *Adonis* slow, regulate and strengthen heart contractions, increase blood pressure, and exert a mild diuretic action. This material reduces dyspnea and relaxes smooth muscle in the lungs, allowing deeper breathing, and is especially indicated in congestive heart failure with arrhythmia, and for feeble contractions with dyspnea and dropsy. In heart failure accompanied by cardiac conduction disturbance, *Adonis* can be as effective as *Digitalis*; however, the effects of *Adonis* are not cumulative and do not cause the phenomenon of a cardiac arrest, as does *Digitalis* (Turova, Sapozhnikova, 1989). Table 17 summarizes the pharmacological studies that have been undertaken on *A. vernalis* and that are reported in the literature.

In the first half of the twentieth century, the pharmacological effects of *A. vernalis* were studied extensively in Russia; however, the literature from that time is poorly accessible. The novo-galenic preparation "Adonisid" (a specific extract of *A. vernalis*) was

**Table 11**
Summary of Pharmacological Studies for *I. helenium*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro* Human lymphobla stoid Raji cells | Root | Crude EtOH (40%) extract helenin (40% alantolactone and 60% isoalantolactone) | *in vitro* | 10, 50, 200 μg/mL | Positive control: methotrexate fluorouracil, cyclophos-phamide, vinblastine. Negative control | 100% inhibition at 50 μg/mL by EtOH extract; and at 10 μg/mL by helenin. Helenin exceeded activity cyclophosphamide and fluorouracil and approached the activity of methotrexate. | Spiridonov et al., 2005 |
| | *in vitro.* Human tumor cell lines HT-29, MCF-7, Capan-2 and G1. MTT assay for adherent cell lines and propidium iodide staining and FACS analysis for PBL | Root | Acetone: MeOH (2:1 v/v) extract | 96 well plate | 10, 1, 0.1, 0.05, 0.01, 0.005 μL/mL | Negative control | Cytotoxic effect with $LD_{50}$ (μL/mL) of 0.015 for HT-29, of 0.017 for MCF-7, of 0.020 for Capan-2 and of 0.018 for G1 and $LD_{90}$ (μL/mL) of 0.05 for HT-29, of 0.20 for MCF-7, of 0.10 for Capan-2 and of 0.10 for G1. The cytotoxicity on healthy human PBLs has $LD_{50}$ of 2.4- 3.0 (μL/mL) and $LD_{90}$=8.0-9.0 (μL/mL) Cytotoxicity over 100-times higher in tumor cell lines than in PBLs. | Dorn et al., 2006 |
| Antihelmintic | *in vitro.* Egg hatching assay (eggs *Ascaris sum)* larval migration inhibition (LMI) (*Trichostron gylus colubriformis)* | Rhizomes and roots | EtOH (80%) extract | 96 well plates | 62.5–2000 μg/mL | Positive control: albendazole. Negative control. | Athelmintic effect on the egg embryo-genesis at 250-000 μg/mL. LMI at the dose of 125 μg/mL and higher. | Urban et al., 2008 |
| | *in vivo.* Rabbits infected with *Clonorchis sinensis* | Root | Boiled water extract | *in vivo.* | 30 days, beginning at the end of 3rd day of inoculation. | Negative control. | Recovery rates of worms from rabbits was 2%. Degeneration, atrophy, necrosis, dilatation, etc. of viscera of the worms was observed | Rhee et al. 1985 |
| Antihypoxant | *in vivo.* Mice, single hemic hypoxia, repeated hemic hypoxia, single tissue hypoxia, repeated tissue hypoxia, single circulatory hypoxia, repeated circulatory hypoxia. | Stem | Tincture (1:10) by EtOH 40%. Contain 1.63% of flavonoids, dry residue > 2.25% | Injection | 2.5 mL/kg, 5 days and 1 h before the hypoxic exposure. | Negative control | Life-span of mice increased by 35% after single hemic hypoxia and by 76% after repeated hypoxia. Stress-protective effect was realized through prevention of adrenal hypertrophy and splenic involution. The life-span after single intoxication with sodium fluoride was prolonged by 59%, of those exposed to repeated hypoxia by 29%. Severity of stress decreased by 5 and 4 points, respectively, compared to control due to the protective effect on gastric mucosa. | Zelenskaya et al., 2005 |
| Antimicrobial | *in vitro.* Broth dilution assay | Root | Helenin (a crystalline mixture of eudesmanolides) | *in vitro.* | 10–750 μg/mL | Negative control. Several strains of *S. aureus, E. coli, P. aeruginosa, C. albicans* | The MIC (μg/mL) against several strains of *S. aureus* was 10-400, *E. coli* and *P. aeruginosa* 200-750, *C. albicans* - 200-750. | Kowalewski et al., 1976 |
| | *in vitro.* Broth microdilution method | Root | Stepwise supercritical fluid extract (SFE), hydrodistillate (HD). Main compounds: alantolactone, isoalantolactone and β -elemene | *in vitro.* | 10–750 μg/mL | Negative control. Positive control: streptomycin, bifonazole | MIC from 0.009 mg/mL to > 14 mg/mL. HD and SFE extracts active against *Bacillus cereus*, *S. aureus*, *Enterococcus faecium* clinical strain resistant to ampicillin, erythromycin, penicillin and tetracycline (MIC > 0.03 mg/mL). *Candida* strains were most | Deriu et al., 2008 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | susceptible, with MIC= 0.009–0.12 mg/mL. | |
| | *in vitro.* Radiorespirometric bioassay against *Mycobacterium tuberculosis* | Root | Isolated alantolactone, isoalantolactone, 11αH, 13-dihydro-isoalanto-lactone | *in vitro.* | | Negative control. Positive control: encelin from *Montanoa speciosa* | MIC for alantolactone and isoalantolactone was 32 μg/mL. | Cantrell et al. 1999 |
| | *in vivo.* Mice inoculated with *S. aureus* suspension in the left nare | Root | Isoalantolactone | Subcuta-neously | 50 mg/kg, 2 h after infection with *S. aureus* and at 12-h intervals thereafter for a total of 6 doses. | Negative control: phosphate-buffered saline | Marked alleviation of pulmonary inflammation; treated mice less accumulation of cellular infiltrates in alveolar space. | Qiu et al., 2011 |
| Anti-proliferative | *in vitro.* MK-1, HeLa, B16F10 cell lines, MTT assay | Root | MeOH extract , isolated 1,3,11(13)-elematrien-8β,12-olide, igalan; 5α-epoxyalantolac-tone; 4 β, 5α -epoxy-1(10),11 (13)-germacradiene-8,12-olide; alantolactone, isoalantolactone, 11 α,13-dihyd-roalantolactone, 11α,13-dihydroisoalanto-lactone | *in vitro.* | | Negative control. Positive control: 5-fluorouracil | $GI_{50}$ (μM) for 5α-epoxyalan-tolactone was 3.6-6.9, for alantolactone – 4.7-6.9. 1,3,11(13)-elematrien-8β,12-olide, igalan exhibited almost the same potency, but $GI_{50}$ against HeLa cells was 2 folds lower. | Konishi et al., 2002 |
| Antithrombin | *in vitro.* Thrombin solution from bovine plasma | Not specified | Methylene chloride extract, soxhlet | 96 well plate | 50 μL | Negative control | 100% thrombin inhibition | Goun et al., 2002 |

**Table 12**
Summary of Pharmacological Studies for *P. caeruleum*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Hypoglycemic | *in vivo*. Mice, glucose tolerance test. | Roots with rhizome | EtOH 70% extract with 65% saponins | Intraperitoneal | 10 mg/kg | Negative control. Positive control: extract of roots of *Beta vulgaris* | Glucose concentration in the blood decreased by half in 30 min after glucose injection. Maximum of glucose in the blood was in 50 min after injection. | Boyeva et al., 2007. |
| | *in vivo*. Mice, glucose tolerance test. | Roots with rhizome | EtOH 70% extract with 65% saponins | Intraperitoneal | 10, 30 mg/kg | Negative control. | Glucose concentration in the blood was decreased by half after injection of 10 mg/kg of extract in 30 min after glucose injection. | Sorokina et al., 2010. |
| Hypotensive | *in vivo*. Rabbits with experimental atherosclerosis | Roots with rhizome | Isolated saponins, no details | Per oral | Not provided | Negative control. | Decrease of cholesterol and blood pressure. According to histological evaluation, saponins reduce lipid cell infiltration of the aortic intima and large vessels | Turova, 1955 |
| Sedative | *in vivo*. Mice exited with phenamine. | Roots with rhizome | Infusion | Per oral | 0.01-0.03 g (equivalents of dry mass) | Negative control. Positive control: valerian infusion | Sedative effect was 8–10 times stronger compared with valerian and more pronounced in mice exited with phenamine. | Zofina, 1946 |
| Sedative | *in vivo*. Rats, prolongation of soporific effect of sodium ethaminal | Roots with rhizome | Dry powder | Intragastric | 30, 60, 120 mg/kg | Negative control. Positive control: *V. officinalis* powder | Combination of *P. caeruleum* and *V. officinalis* (1:1, 60 mg/kg) prolonged the soporific effect of sodium ethaminal in 2.5 fold. | Khishova et al., 2013 |

**Table 13**
Summary of Pharmacological Studies for *V. opulus* bark.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antispasmodic | *in vitro*. Single uterine horns from virgin Holtzman rats | Bark | MeOH extract with yield 4%. | *in vitro* | 0.4 g/mL | No data | Complete relaxation of muscle at 1 mL | Jarboe et al., 1966 |
| | *in vitro*. Single uterine horns from virgin Holtzman rats | Bark | Isolated scopoletin | *in vitro* | 0.025–0.150 mg/mL | No data | Relaxation of muscle tension and spasms in uterus, $IC_{50}$=0.09 mg/mL | Jarboe et al., 1967 |
| | *in vitro*. Barium stimulated rat uterus. | Bark | Isolated viopudial | *in vitro* | No data | No data | $ED_{50}$ for spasmolytic effect 24 μg/ml | Nicholson et al., 1972 |
| Hypotensive | *in vivo*. Rats, cats, dogs. | Bark | Isolated viopudial | Intravenous | 250 μg/kg -2 mg/kg | Negative control | In rats hypotensive effect at 250 μg/kg. At 1 mg/kg effects were sustained and decrease in blood pressure with decrease in heart beat. In dogs and cats effective dose 2 mg/kg. | Nicholson et al., 1972 |

produced in USSR in the form of tablets, but this preparation is currently excluded from the State Register of drugs. "Adonisid" is used in modern medicine as a part of the complex phytomedicine "Cardiovalen" (which consists of 17.2 mL of the pressed juice of *Erysimum diffusum* Ehrh. (*Brassicaceae*), 30.3 ml of "Adonisid" containing 85 frog units in 1 mL, 48.6 mL of a tincture of *Valeriana officinalis* L. (*Valerianaceae*), 2.2 mL of a liquid extract of Crataegus, 0.4 g of camphor, and 2 g of NaBr).

The aerial parts of *A. vernalis* are prescribed in Russia for internal use at the dose of 1 tablespoon of the infusion (7:200), 3–5 times per day, when taken as a cardiotonic. "Cardiovalen" is prescribed at the dose of 15–20 drops, taken 1–2 times per day (Sokolov, 2000).

### 5.10.2. HERBA CONVALLARIAE et FOLIA CONVALLARIAE et FLORES CONVALLARIAE

In the Pharmacopoeia of the USSR, *Herba Convallariae, Folia Convallariae* and *Flores Convallariae* consists of the whole or cut dried aerial parts, leaves or flowers, respectively, of *Convallaria majalis* L. (*syn: C. transcaucasica* Utkin ex Grossh.), *C. keiskei* Miq. (Asparagaceae), which are harvested during or at the beginning (for the leaves) of the flowering period. Depending on region, the harvesting time can be shifted to obtain high-quality raw plant material. Particularly in the St-Petersburg region, the optimal harvesting time for *Herba Convallariae* is during the late budding and early flowering stages (Borisova et al., 1984). *Convallaria majalis* is commonly known as the lily of the valley, and has been recognized by clinicians for its antiarrhythmic effect. Felter found it particularly useful for treating tachycardia and mitral insufficiency but found it less useful for addressing aortic valve problems (Felter, 1922). Unlike the much stronger and more dangerous *Digitalis* spp., lily of the valley glycosides do not accumulate in the body, are safer, and produce milder effects (Yarnell, Abascal, 2003). The flavonoids of *C. majalis* are also considered important for the activity of the botanical drug, supporting the use of the whole plant rather than isolated cardiac glycosides (Weiss, 1988). The flowers of *C. majalis* have been used in Russian traditional medicine to treat epilepsy, cardiac dropsy, and mild congestive heart failure (Nosal, Nosal, 1960; Gammerman et al., 1984).

According to the State Pharmacopoeia of the USSR, 11th edn., the biological activity of *C. majalis* should be at least 120 frog units or 20 cat units for the aerial parts (1:20 EtOH 95% extract), 200 frog units or 33 cat units for the flowers (1:20 EtOH 95% extract), or 90 frog units or 15 cat units for the leaves (1:20 EtOH 95% extract).

*Convallaria majalis* has been reported to be toxic due to the presence of the cardioactive glycosides, convallarin, and convallamarin. The $LD_{50}$ for convallarin in rabbits after intravenous administration was found to be 1,500 μg/kg (Marhold, 1986). The lowest published lethal dose for convallarin in rabbits after subcutaneous administration is 10 mg/kg, that in frogs after oral administration is 200 mg/kg, and that after subcutaneous administration in frogs is 15 mg/kg (Abderhalden, 1935). The $LD_{50}$ for convallarin in rabbits after oral administration was found to be 320 mg/kg (Marhold, 1986). Table 18 summarizes the pharmacological studies that have been undertaken on *Convallaria* and that are reported in the literature.

The novo-galenic preparation "Corglycon" (an 0.06% aqueous solution of purified total glycosides from *C. majalis* leaves) was developed in Ukraine SSR during the Soviet period. This preparation is clinically approved and standardized to 11–16 frog units, or 1.8–2.2 cat units per 1 mL. The pharmacological effect of "Corglycon" is similar to that of strophanthin but is more prolonged. The preparation is prescribed for patients with acute and chronic class II and III heart failure, cardiac decompensation, and for the cupping of paroxysmal tachycardia (Mashkovskii, 2002).

A group of 34 patients having stage II-III atherosclerotic dyscirculatory encephalopathy with coexisting ischemic heart disease in the presence of stenosing and occlusive lesions of major brain arteries were evaluated to examine the effects of pentoxiphyllin and corglycon on the clinical course of this medical condition and on systemic and cerebral haemodynamics. In this series, 82.7 % of patients derived benefit from a single intravenous infusion of pentoxiphyllin and corglycon, and a course of treatment with this drug preparation resulted in an improvement in the parameters of the systemic and cerebral hemodynamics and in the regression of the neurological symptomatology. The results of these studies were used as a basis for recommending the use of pentoxiphyllin in combination with corglycon for the treatment of patients with eukinetic and hypokinetic systemic haemodynamics, whereas the use of pentoxiphyllin alone is recommended for those with hyperkinetic haemodynamics, considering its cardiodepressive effects (Ishchenko et al., 1996). The publication did not fully describe the controls used, which makes it difficult to assess the outcome of this trial.

Crude drug preparations of *Convallaria* are not available in Russian pharmacies, but the tincture (10 g in 100 mL of EtOH 70%) is prescribed in Russia for internal use at the dose of 15–20 drops, taken 2–3 times per day as a cardiotonic. "Corglycon" is used for intravenous injection at the dose of 0.5–1.0 mL in 10–20 mL of glucose (20 or 40% solution), administered 1–2 times per day (Sokolov, 2000).

### 5.11. Cardiovascular agents

#### 5.11.1. FLORES CRATAEGI et FRUCTUS CRATAEGI

According to the Pharmacopoeia of the USSR, *Flores crataegi* and *Fructus crataegi* consists of the flowers of *Crataegus sanguinea* Pall. and the flowers and fruits of *C. laevigata* (Poir.) DC., *C. chlorosarca* Maxim (syn. *C. korolkowii* hort. ex Dippel), *C. wattiana* Hemsl. & Lace (syn. *C. altaica* (Loud.) Lange), *C. chlorocarpa* Lenn, & K. Koch, and *C. dahurica* Koehne ex C.K. Schneid, *C. monogyna* Jacq. (syn. *C. alemanniensis* Cinovskis, *C. orientobaltica* Cinovskis), *C. rhipidophylla* Gand. (syn. *C. curvisepala* Lindm.), *C. rhipidophylla* var. lindmanii (Hrabětová) K.I.Chr. (syn. *C. X dunensis* Cinovskis), and *C. pentagyna* Waldst. & Kit. ex Willd. (all *Rosaceae*).

Dried false fruits and the whole or cut, dried, flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm.), *C. laevigata* (Poir.) D.C. (synonym: *C. oxyacantha* L.) or their hybrids or a mixture of these false fruits and the whole or cut, dried, flower-bearing branches of other European *Crataegus* species, including *C. pentagyna* Waldst. et Kit. ex Willd., *C. nigra* Waldst. et Kit., *C. azarolus* L., are included in the European Pharmacopoeia.

The pharmacological profile and indications of *Crataegus* are similar in Russia and Europe. Therefore, these plants will be not discussed further in this review.

### 5.12. Haemostatic agents

#### 5.12.1. HERBA POLYGONI HYDROPIPERIS

*Persicaria hydropiper* (L.) Delarbre (syn. *Polygonum hydropiper* L., Polygonaceae), also known as water pepper, is an annual that grows to 0.8 m tall; in Russian popular medicine, the leaves are used to stop bleeding and to treat haemorrhoids (Turova, Sapozhnikova, 1989). Water pepper has been used for a long time as a haemostatic agent in uterine bleeding, and for heavy and painful menstruation, abortion, and postpartum bleeding (Kravkov, 1912, Rossijsky, 1934). The leaves of this plant have been used to treat cancer, colds, and coughs (Onitsev, 1962). The infusion has been prescribed for treating rheumatism, chronic ulcers, haemorrhoid, tympanitis, and erysipelas (Yang et al., 2012). Women in Assam (India) have traditionally used the powdered dry root of *P. hydropiper* to prevent unwanted pregnancies (Hazarika, Sarma, 2006). Water pepper is a hot-tasting spice known in China, Japan, and Europe. The sprout of water pepper, called "mejiso" or "benitade" in Japanese, is a well-known relish for "sashimi," and the seeds were occasionally used as a substitute for pepper in Europe (Matsumoto, Tokuda, 1990). "Hydropiperinum", a chemically characterized extract of *P. hydropiper* leaves containing flavonoid glycosides, increases blood clotting, reduces the duration of bleeding, and strengthens uterine contractions (Fedukovich, 1960). Since 1946, the aerial parts and a liquid extract of *P. hydropiper* have been included in the State Pharmacopoeia of the USSR (Vereschagin et al. 1959).

The $LD_{50}$ for the chloroform extract of *P. hydropiper* leaves was determined to be 760 mg/kg in male albino mice. Subcutaneous injection of a sub-lethal dose of extract into male mice once a week for 6 weeks failed to show any significant influence on white and red blood cell counts or blood cholesterol levels (Rahman et al., 2005). A subchronic toxicity study of water pepper extract (WPE) was conducted in groups of 10 male and 10 female F344 rats fed powdered diets containing 62.5, 250, 1,000 or 4,000 ppm concentrations of WPE for 13 weeks. WPE was prepared using a two-step extraction method from leaves of *P. hydropiper*; the leaves were first extracted with N-hexane and then with EtOH, resulting in a solution containing 7.0% polygodial as the main component. Suppression of body weight gain due to decreased food consumption was observed in both sexes at concentrations of 4,000 ppm of WPE. At this dose, slight increases of blood urea nitrogen in both sexes and of serum alanine aminotransferase, Na and Cl in females were observed; these increases are suggestive of weak hepatic and renal toxicity, at least in females. The same females also exhibited slight decreases in the number of red blood cells and haematocrit, slight increases in mean corpuscular volume and mean corpuscular haemoglobin, and minimal increases of splenic haemosiderin deposition, providing evidence of slight haemolytic anemia. In addition, an enhanced mast cell accumulation in the mesenteric lymph nodes induced by WPE treatment might be related to the complex biological effects of polygodial and/or related ingredients included in this extract on the gastrointestinal environment. The no-observed-adverse-effect level of WPE was 1,000 ppm, which corresponds to 57.4 and 62.9 mg/kg/day for male and female rats, respectively (Kuroiwa

**Table 14**
Summary of Pharmacological Studies for *C. cyanus*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anti-inflammatory | *in vivo*. Rats, carrageenan-induced and zymosan-induced edema. Mice, croton oil-induced inflammation of ear. | Flower-heads | Water-soluble EtOH-insoluble polysaccharides fraction | Intraperito-neal topical application | 30, 60, 80 mg/kg; 30 min before edema induction. 100, 200, 400 and 800 μg per ear | Negative control. Positive control: indomethacin, acetylsalicylic acid, | Reduction of carrageenan-induced edema by 40% at 30 mg/kg, by 69% at 60 mg/kg. Reduction of zymosan-induced edema by 52% at 400 μg. | Garbacki et al. 1999 |
| Anti-inflammatory | *in vitro*. Haemolytic activity of complement. Anaphylatoxin activity in rat serum | Flower-heads | Water-soluble EtOH-insoluble polysaccharides fraction | *in vitro*. | 10, 50, 250, 1000 μg/mL (haemolytic) 0.01, 0.1, 0.5, 1, 5, 10 mg/mL (anaphy-latoxin) | Negative control. Positive control: rosmarinic acid | Induced the formation of an anaphylatoxin-like activity from 10 μg/mL. At higher concentrations (1000 μg/mL), reduced haemolytic activity of rat serum. | Garbacki et al. 1999 |
| Gastroprotective | *in vivo*. Rats with stress-induced ulcer (immersion and immo-bilization of rats into cold water, on dorsal position) | Herb, flowers | Vegetal product (combination of polysac-charides and polyphenols fractions) | Per oral | 500 mg/kg, one h before stress | Negative control. Positive control: ranitidine. | Gastroprotective effect was 100%, 89% and 83% respectively, in the specific case of deep, medium and superficial gastric lesions, respectively, superior to that of ranitidine (89%, 59%, and 54% respectively on the same type of lesions. | Pirvu et al., 2012 |
| Diuretic | *in vivo*. Dogs with chronic fistula of urinary and gall bladders. | Flower-heads | Infusion (1:10) and EtOH extract | Intragastric | No details | No details. | Stimulation of diuresis and choleresis. | Bashmurin, 1951 |

et al., 2006). Table 19 summarizes the pharmacological studies that have been undertaken on *Polygonum hydropiper* and that are reported in the literature.

No clinical data were found regarding *P. hydropiper* in the available literature. The aerial parts and an extract (70% EtOH) are available in Russia in pharmacies without a prescription and are recommended for internal administration at the dose of 1/3 of a glass of the infusion (10 g in 100 mL of water), 3–4 times a day, or 30–40 drops of the extract, 3–4 times a day, when used as a haemostatic agent (Sokolov, 2000). *Polygonum hydropiper* is a popular herb in Russia, and its safety and efficacy are confirmed by its long history of use. However, there is lack of information in the literature regarding the efficacy of this material. Further clinical studies are required to evaluate the claimed activity in patients, and more details on the safety of this drug would be desirable.

### 5.13. Spasmolytic agents

#### 5.13.1. FRUCTUS ANETHI GRAVEOLENTIS

*Anethum graveolens* L (dill, Apiaceae) grows to a height of 40–60 cm. The fruits (seeds) of *A. graveolens* have had diverse uses in Russian traditional medicine: in powder and tincture forms as a carminative, expectorant, and diuretic; in decoction form as an antispasmodic, sedative, and galactagogue; and in infusion form as a hypotensive agent (Gammerman et al., 1984; Lavrenova, Lavrenov, 1997). Dill is a common household plant with a history of more than 2,000 years of use as a spice and a condiment in food because of its flavor and preservative qualities. Dill water is believed to have a soothing effect and is given to babies to treat influenza and relieve hiccups and colics. Chewing the seeds reduces bad breath. Dill is a galactagogue that is known to increase the flow of milk in nursing mothers and is passed to the baby via the milk to help prevent colics. Dill can be used to help regulate the menstrual cycle and has been reported to possess antihyperlipidaemic and antihypercholesterolaemic activity (Heamalatha et al., 2011).

The toxicity of *A. graveolens* has been studied in mice after intraperitoneal injection. The maximum non-fatal doses of aqueous and EtOH extracts of *A. graveolens* seeds were 0.45 g/kg and 5 g/kg (i.p.), respectively. The $LD_{50}$ values of the aqueous and EtOH extracts were 3 g/kg, and 7 g/kg, respectively (Hosseinzadeh et al., 2002). Table 20 summarizes the pharmacological studies that have been undertaken on *A. graveolens* and that are reported in the literature.

A prospective randomized clinical trial was carried out on 30 hyperlipidemic patients of both sexes with an age range 44–63 years and a disease duration of 5–10 years. Patients were allocated into two groups: Group A comprised 15 patients who were treated with lovastatin tablets at the dose of 20 mg once daily for four weeks; Group B comprised 15 patients who were treated with 500 mg of finely powdered leaves of *A. graveolens*, which was administered twice daily for four weeks; in addition, 15 healthy subjects served as a control group. Treatment of the patients with powdered dill leaves resulted in highly significant ($P \leq 0.01$) decreases in the values of total cholesterol (TC) (19.9%), triglyceride (29.5%), LDL-Chol (22.2%) and VLDL-Chol (25.2%). Statistically significant ($P \leq 0.05$) decreases were observed in TC/HDL-Chol and LDL-Chol/HDL-Chol levels after four weeks of treatment, and TG/HDL-Chol was decreased to less than that of the healthy control group. In contrast, treatment with lovastatin significantly ($P \leq 0.05$) decreased all lipid ratios in hyperlipidemic patients after four weeks. During the course of treatment, no side effects were recorded, indicating the safety and tolerability of the administered agent (Sahib et al., 2012).

Considering the literature data and the common use of *Fructus anethi graveolentis* in Russia and other countries, the drug and its

**Table 15**
Summary of Pharmacological Studies for V. *vitis-idaea*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antidiabetic | *in vitro*. Caco-2/15 intestinal cells; western blot analysis. *in vivo*. Rats, oral glucose tolerance test (OGTT) | Not indicated | EtOH (80%, 1:10) extract | *in vitro* 96-well plate. *in vivo* per oral | 25–100 μg/mL (*in vitro*); 250 mg/kg (*in vivo*) | Negative control. Positive control: cytochalasin B, phlorizin, phloretin. | 100 μg/mL instantaneous inhibition glucose absorption inCaco2/15 cells. *in vivo* No effect in OGTT. | Nistor Baldea et al., 2010 |
| Anti-inflammatory | *in vitro*. Prostaglandin biosynthesis assay; PAF-induced exocytosis | Leaves | Aqueous extract, lyophilized. | *in vitro* | 0.2 mg/mL (for prostaglandin) 0.25 mg/mL (for PAF) | Negative control. Positive control: indometacin, eugenol, quercetin, saligenin. | Moderate inhibition prostaglandin biosynthesis (45% ) and strong inhibition PAF- induced exocytosis (96% ) | Tunón et al., 1995 |
| Anti-inflammatory | *in vivo*. Mice, acetic acid-induced vascular permeability test. | Stems and leaves | EtOH extract, isolated arbutin, fraxin | Per oral. | 5 g/kg (extract), 0.25 g/kg, 0.5 g/kg (arbutin, fraxin) | Negative control. Positive control: dexamethasone | Decrease in vascular permeability by fraxin (0.5 g/kg) similar todexamethasone (1 g/kg). | Wang et al., 2005 |
| Antimicrobial | *in vitro*. Agar dilution assay, *Porphyromonas gingivalis*, *Prevotella intermedia* | Leaves | Isolated procyanidin B-1, procyanidin, B-3, proanthocyanidin A-1, cinnamtannin B1, epicatechin-(4β-8)-epicatechin-(4β-8, 2β-O-7)-catechin, epicatechin-(4β-6)-epicatechin-(4β-8, 2β-O-7)-catechin. | *in vitro*. | 0–100 μg/mL | Negative control. Positive control: tetracycline | Epicatechin-(4β-8)-epicatechin-(4β-8, 2β-O-7)-catechin, had strong antimicrobial activity against *Porphyromonas gingivalis* and *Prevotella intermedia* with MIC of 25 μg/ml. | Ho et al., 2001 |
| Antimicrobial | *in vitro*. Tube dilution assay, eleven strains of *E. coli*. | Leaves | Aqueous, EtOAc, EtOH extracts | *in vitro*. | 0–100 μg/mL | Negative control. Positive control: amoxicillin | MIC=5 mg/mL for aqueous extract. MBC= 5 mg/mL for nine strains. | Vučić et al., 2009 |
| Antioxidant | *in vitro*. Anti-lipid peroxidation activity (thiobarbituric acid test). Anti-superoxide formation: xanthine oxidase inhibition test. Free radical scavenger activity: cytochrome C test | Leaves. | Isolated procyanidin B-1, procyanidin B-3, proanthocyanidin A-1, cinnamtannin B1, epicatechin-(4β-8)-epicatechin-(4β-8, 2β-O-7)-catechin, epicatechin-(4β-6)-epicatechin-(4β-8, 2β-O-7)-catechin. | *in vitro*. | No data | Negative control | Cinnamtannin B1 strongest anti-lipid peroxidation activity $IC_{50}$=2.25 μM, proanthocyanidin A-1 strongest superoxide scavenging activity $IC_{50}$=10.14 μM, picatechin-(4β-6)-epicatechin-(4β-8, 2β-O-7)-catechin strongest antisuperoxide formation effect $IC_{50}$=308 μM | Ho et al., 1999 |
| Antithrombin | *in vitro*. Thrombin solution from bovine plasma | Not specified | MeOH extract, soxhlet | 96 well plate | 50 μL | Negative control | 94% thrombin inhibition | Goun et al., 2002 |
| Antiviral | *in vitro*. Cells infected with HSV-2. XTT assay. Plaque reduction assay | Dried whole plants | Isolated proanthocyanidin A-1 | 96 well plate, 24 well plate | 0.5–200 μMol | Negative control. Positive control: acyclovir | Proanthocyanidin A-1 anti-HSV-2 activity. $IC_{50}$=73.3 μMol for XTT assay. $IC_{50}$=41.9 μMol $IC_{90}$=62.8 μMol for plaque reduction assay 100.0 μMol proanthocyanidin A-1 completely suppressed HSV-2 replication when added at 12 h post-infection. | Cheng et al., 2005 |

**Table 15** (*continued*)

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Cough-suppresant | *in vivo*. Mice, in upset beaker saturated with 25 % $NH_4OH$ | Stems and leaves | EtOH extract, isolated arbutin, fraxin | Per oral. | 5 g/kg (extract), 0.25 g/kg, 0.5 g/kg (arbutin, fraxin) | Negative control. Positive control: carbetapentane citrate | Number of coughing decreased 43%, latency period increased 53% compared to control (EtOH extract). Effect of fraxin (0.5 g/kg)similar to carbetapentane citrate | Wang et al., 2005 |
| Diuretic | *in vivo*. Rats, 5 and 17 h diuresis with 5% water load | Leaves | Infusion of polyherbal mixture Brusniver® | Per oral. | 0.5 mL/100 g, 1 mL/100 g | Negative control. | Increase of diuresis in 11.9% comparing to the control group. | Vichkanova et al., 1992 |
| Phlegm removing | *in vivo*. Mice, injected with phenol red solution. | Stems and leaves | EtOH extract, isolated arbutin, fraxin | Per oral. | 5 g/kg (extract), 0.25 g/kg, 0.5 g/kg (arbutin, fraxin) | Negative control. Positive control: $NH_4Cl$ | EtOH extract and fraxin (0.5 g/kg) showed the strongest phlegm-removing effect. The phlegm-removing effect of arbutin (0.5 g/kg) was similar to that of $NH_4Cl$ (1 g/kg). | Wang et al., 2005 |

preparations should be considered safe and effective. Seeds of *A. graveolens* are available in Russia in pharmacies without a prescription and are recommended for internal administration at the dose of 1/3 of glass of the infusion (10 g in 200 mL of water), 3–4 times per day, as a spasmolytic (Sokolov, 2000). However, publications regarding clinical trials are far too limited to allow conclusions regarding the therapeutic potential of this plant. This botanical drug exhibits clear potential and warrants further clinical testing.

### 5.13.2. *RHIZOMATA ET RADICES RUBIAE*

In a monograph in the Pharmacopoeia of the USSR, *Rhizomata et radices Rubiae* is described as the rhizome and roots of *Rubia tinctorum* L. (syn. *R. iberica* (Fish. ex DC) K. Koch). *Rubia tinctorum*, the common madder or dyer's madder, is a perennial plant species in the *Rubiaceae* that grows to a height of 60-100 cm. Roots of *R. iberica* have been used in traditional medicine in the Caucasus region and Middle Asia as a diuretic (Gammerman et al., 1984). Extracts of *Rubia* have been reported to decrease the tension and increase the amplitude of renal pelvic and ureter contractions. This extract promotes the motility of stones and their elimination from the kidney and the urinary tract (Turova, Sapozhnikova, 1989).

The safety of *R. tinctorum* was evaluated in mice, rats, and cats. The acute toxicity of an aqueous extract of madder root was studied during 14 days of administration by gavage to (C57Bl/$6 \times$ C3H)$F_1$ mice. The maximum tolerated dose of extract was between 3,500 and 5,000 mg/kg body weight. A subacute toxicity test was performed using 62 mice of each sex, mixing their diets with *R. tinctorum* extract at concentrations of 0, 0.3, 0.6, 1.25, 2.5, and 5% for 90 days. All mice tolerated these doses well. The body weight gains of either sex were not affected by the treatment. None of the mice treated with the extract exhibited clinical signs of toxicity. Histopathological examination showed retention cysts of the kidneys and epidermal vaginal cysts in a few of the treated and control mice. No hyperplastic, preneoplastic, or neoplastic lesions and no pathological findings of toxicity were found. It was concluded that dietary exposure to madder root extract at the doses tested had no significant acute or subacute toxic effects on mice (Ino et al., 1995). Acute intragastric administration of the dry extract of *R. tinctorum* root at doses of 125–15,000 mg/g in mice was safe, and no side effects were observed. No side effects were registered after 12 days of intragastric administration of the dry extract of madder roots (100 mg/kg) in rats. The extract was safe for cats at doses of 20–200 mg/kg (intragastric). However, an increased dose of up to 400 mg/kg was followed by vomiting, excitation for 3 hours, and subsequent sleeping. The physiological conditions became normalized after 5 hours (Vichkanova et al., 2009).

Male and female ACI/SegHsd rats weighing 150–200 g received a diet supplemented with 1 or 10% *R. tinctorum* root for 780 days. This root contained lucidin (0.34%), alizarin (0.67%; 1,2-dihydroxyanthraquinone) and the primeverosides of both compounds. In the groups receiving the 10% madder root diet, 2/16 males and 3/17 females developed hepatocellular adenomas, whereas none were observed in the controls or the 1% madder root group of either sex. Renal tubule-cell adenomas were observed in 1/16 males and in 2/16 females in the 10% madder root group, and a renal tubule-cell carcinoma was observed in 1/14 males in the 1% madder root group (Westendorf et al., 1998). Male and female F344 rats were fed diets containing 0%, 2.5%, and 5.0% of a 50% EtOH extract of madder root for 104 weeks. Body weights were significantly decreased in the treated groups of both sexes throughout the feeding period. However, survival rates at week 104 were higher in the treated groups of both sexes than in the controls. The relative weights of the kidneys and liver were

**Table 16**
Summary of Pharmacological Studies for *Gemmae betulae*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro.* Human lympho-blastoid Raji cells | Buds | Crude EtOH (40%) extract | *in vitro* | 10, 50, 200 μg/ mL | Positive control: methotrexate fluorouracil, cyclophos-phamide, vinblastine. Negative control | 63% inhibition at 50 μg/mL and 95% inhibition at 200 μg/ mL, | Spiridonov et al., 2005 |
| Anticancer | *in vitro.* Mouse leukemia cells L1210 | Not specified | Methylene chloride, MeOH extracts, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 99% growth inhibition by m ethylene chloride extract and 91% growth inhibition by MeOH extract. | Goun et al., 2002 |
| Antimicrobial | *in vitro. B. subtilis, S. aureus, E. coli, P. aeruginosa.* Agar diffusion assay, agar dilution assay. | Buds | Acetone extract (1:5), re-extracted with MeOH, decoction (1:10) | *in vitro.* | 0.039- 5% | Negative control. Positive control: ciprofloxacin, gentamicin sulphate, penicillin | Inhibition zones for MeOH extract and decoction were against *S. aureus:* 11.2 and 10.2 mm, against *B. subtilis*: 11 and 8 mm, against *P. aeruginosa:* 11.6 and 0 mm. MIC for MeOH extract against *P. aeruginosa*: 1.25%, against *B. subtilis:* 2.5%, against *S. aureus:* 2.5%. | Duric et al., 2013 |
| Antimicrobial | *in vitro.* Agar dilution assay, antibiotic-resistant forms of 144 strains of *Staphylococci* isolated from patients with mastitis, furunculosis, abscesses, peritonitis. | Buds | EtOH (70%) tincture (1:5) | *in vitro.* | | Negative control. | Antibacterial activity was observed for all strains with MIC in dilution 1:90-1:100 | Nikolaeva, Khokhlova, 1981 |
| Antioxidant | *in vitro.* DPPH assay, $ABTS^{+}$ assay, | Buds | EtOH extract | *in vitro* | 0.01–1.0 mg/mL | Negative control. Positive control: trolox, ascorbic acid | $IC_{50}$=0.511 mg/mL in DPPH assay, $IC_{50}$=0.290 mg/mL in $ABTS^{+}\cdot$ assay. | Mashentseva et al., 2011 |
| Antioxidant | *in vivo.* Mice, acute hypoxia. Phospholipids level in brain. | Buds | EtOH extract | Per oral | 5.0 mg/kg, 20 days | Negative control. Positive control: tocopheryl acetate. | Preventive administration of extract resulted in normalization of phospholipid level. Effect was comparable with tocopheryl acetate. | Mashentseva et al., 2011 |
| Diuretic | *in vivo.* Wistar rats, after NaCl solution load (25 mL/kg) | Buds | 6% aqueous extract | Intraperitoneal | 1 mL per animal, single injection | Negative control. Positive control: furosemid | Increase of uric acid elimination in 5 folds comparing to control group and effect was similar compared to furosemid. | Peev et al., 2010 |
| Heavy metals binding | *in vivo.* Wistar rats, feed normal diet with additional 25 mg/kg of Pb and 25 mg/kg of Cd during 10 days | Buds. | EtOH extract, no details about concentration and method. | Per oral. | 0.5 mL/kg, 32 days after 10 days of intoxication by heavy metals | Negative control. | The Pb concentration in animal organs and tissues was decreased by 45.7-71.3% and Cd, by 10.4-92.2% compared with control. | Bokova, Vasil'tsova, 2011 |

**Table 17**
Summary of Pharmacological Studies for *A. vernalis*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anti-inflammatory | *in vitro*, human whole blood cell culture system stimulated with lipopolysac-charide – activated macrophages. | Aerial part | MeOH 50% extract. | 96 well plate | 500 μL/mL | Negative control. | 35% inhibition TNF-α production | Das et al., 2007 |
| Antiviral | *in vitro*. Agar diffusion, method. HeLa cells | Aerial part | 10% aqueous extract | Petri dishes | 0.02 mL | Herpes virus Hominis HVP 75 (type 2), influenza virus A2 (Manheim 57), Vaccini virus, poliovirus type 1. Negative control. | Cytotoxic effect with inhibition zone 15-30 mm, virustatic effect with inhibition zone over 30 mm for all viruses, | May, Willuhn, 1978 |
| Cardiac inotropic and constrictor | *in vivo*. Cats | Not mentioned. | SCOA, a product which contains extracts from *Scilla, Convallaria, Oleander* and *Adonis* | Intravenous | 21.5–100 GPU/kg (GPU = guinea-pig units, i.e. cardiotoxic equivalents related to 1 g body weight of guinea-pigs) | Positive control: cymarin, convallatoxin, proscillaridin, and scillaren | Positive inotropic and constrictor effect on veins and arteries. Pure glycosides cymarin, convallatoxin, proscillaridin, and scillaren exert equal effects. Effect on veins and on the heart may differ for the glycosides tested. Effect equal guinea-pig units of *Adonis* extract on capacitance vessels twice as much as Scilla, *Oleander* and *Convallaria* extracts. Cymarin (main glycoside of *Adonis*), has stronger effect on veins than expected from its cardiotoxic effect. | Lehmann, 1984 |

significantly increased in the treated groups of both sexes. Histopathologically, karyomegaly and atypical tubules/hyperplasias, as well as renal cell adenomas and carcinomas were significantly increased in the treated groups of both sexes, and this result was dose-dependent. The obtained results indicate that the extract has carcinogenic potential in the kidney and liver, even at the lower dose studied (Inoue et al., 2009).

A number of genotoxicity studies of madder color (50% EtOH extract of madder root) and its constituents have been conducted. Madder color (MC) was found to give negative results in bacterial DNA repair assays but positive results in reverse mutation assays with or without an S9 mix in TA98, TA100 and TA1537 strains (Hachiya et al., 1985). The anthraquinone constituents of MC, such as lucidin-3-O-primeveroside and its deglycosylated metabolite, lucidin, caused the formation of DNA adducts in rodents (Westendorf et al., 1998). Mollugin, 1-hydroxy-2-methylanthraquinone, 2-ethoxymethyl-anthraquinone, rubiadin, 1,3-dihydroxyanthraquinone, 7-hydroxy-2-methylanthraquinone, lucidin, 1-methoxymethylanthraquinone, and lucidin-3-O-primeveroside, which were isolated from the roots of *R. tinctorum*, exhibited mutagenicity with *Salmonella typhimirium* TA 100 and/or TA 98 (Kawasaki et al., 1992). Alizarin, a metabolite of 1-hydroxyanthraquinone, was weakly mutagenic in *S. typhimurium* TA1537 in the presence of S9 and in rat hepatocyte DNA-repair assays but was consistently inactive in transformation experiments conducted with C3H/M2 mouse fibroblasts and in *Hprt* mutation assays conducted with Chinese hamster V79 cells (Westendorf et al., 1990).

Considering the literature data, the International Agency for Research of Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2002) has concluded that limited evidence in experimental animals exists for the carcinogenicity of *R. tinctorum*; thus, this material is not classifiable with regard to its carcinogenicity in humans (Group 3). However, 1-hydroxyanthraquinone is possibly carcinogenic to humans (Group 2B). Nevertheless, the possibility of a human cancer hazard must be considered when madder is used chronically for therapeutic purposes. Table 21 summarizes the pharmacological studies that have been undertaken on *Rhizomata et radices Rubiae* and that are reported in the literature.

Alizarin, a constituent of madder root, is employed in phytotherapy to prevent recurrences of calcium-containing urinary stones. Pharmacokinetic studies have been carried out in human subjects. After a single oral dose of 210 mg of alizarin was administered, two maxima were observed in the serum concentration curves: the first at 2–4 h and the second at 6–8 h. Alizarin and its glucuronide conjugate were detected in both maxima using TLC. The mean elimination half-life was 12 h. The amounts excreted in the urine within 6 days ranged from 18.1 to 36.3%, and the amounts excreted in the feces within 6 days ranged from 21.6 to 33.0% (total recovery: 40-60%). In bile from a patient who had undergone cholecystectomy, only 0.6% of the dose was recovered. To exclude any possibility that alizarin might be bound to calcium ions in bone, bone trephine specimens were examined from patients with oxalate stones who had previously been treated with alizarin for several years. No alizarin was detectable in these samples (Lorenz et al., 1985).

A group of patients (15 male and female, 29–63 years old) with renal pelvis stones (1.5–7 cm) was treated with 0.5 g of *R. tinctorum* root extract, to be taken three times a day for 30 days. The resulting therapeutic results were observed in 11 patients. The report did not give a full description of the controls, which makes it difficult to assess the outcome of this trial. The treatment of the patients resulted in the removal of sand and small stones and in the reduction of pyuria. However, the extract was not effective in 4 patients who had large stones. In another study, tablets (0.25 g) of the dry extract of *R. tinctorum* were used in a clinical trial to treat 22 patients with nephrolithiasis with various urinary stone

**Table 18**
Summary of Pharmacological Studies for *Convallaria.*

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anti-tumor | *in vivo,* Balb/c mice induced by human kidney tumor cells and by sarcoma L1 cells | Rhizomes and roots | Convallamaroside, the steroidal saponin. | Per oral | 5, 10, 20, 50, 100 μg of convallamaroside / 3 days | Negative control. | Antitumor effect on human kidney tumors, and mouse sarcoma through inhibition angiogenesis | Nartowska et al., 2004 |
| Antiviral | *in vitro.* Agar diffusion, method. HeLa cells | Leaves | Aqueous extract (1:10) | *in vitro* | 0.02 mL | Herpes virus Hominis HVP 75 (type 2), influenza virus A2 (Manheim 57), Vaccini virus, poliovirus type 1. Negative control. | Cytotoxic effect with inhibition zone 15-30 mm, virustatic effect with inhibition zone over 30 mm for all viruses excluding poliovirus | May, Willuhn, 1978 |
| Cardiac inotropic | *in vivo,* beating rabbit atria | Aerial part | Aqueous extract (1:5), dry, convallatoxin | *ex vivo* | 0.003; 0.03 mg/ mL for extract and 0.0001 mM for convallatoxin | Negative control. | Extract significantly increased atrial stroke volume, pulse pressure, and cAMP efflux. and markedly increase the $K^+$ concentration in the beating atria-derived perfusate. Convallatoxin increased atrial stroke volume and pulse pressure but did not alter the cAMP efflux level. | Choi et al., 2006 |
| Cardiac inotropic | *in vitro.* Rabbit erythrocytes, $(Na^+ + K^+)$-ATPase, from hog cerebral cortex | Not specified | Convallatoxin. | *in vitro.* | 0.01–10 μM | Negative control. Positive control: ouabain, digoxin, digitoxin. | Inhibition of palytoxin-induced $K^+$ release with $IC_{50}=0.9$ μM. Inhibition of $Na^+ + K^+$ ATPase with $IC_{50}=0.84$ μM. No inhibition by aglycones, even at 10 μM | Ozaki et al. 1985 |
| Cardiac inotropic and constrictor | *in vivo.* Cats | Not specified. | SCOA, a product which contains extracts from *Scilla, Convallaria, Oleander* and *Adonis* | Intravenous | 21.5–100 GPU/kg | Positive control: cymarin, convallatoxin, proscillaridin, and scillaren | Positive inotropic and moderately strong vasoconstrictor effect on veins and arteries. Pure glycoside convallatoxin, exert equal effects. | Lehmann, 1984 |
| Cardiotonic | *in vivo.* Cats wit modulated ischemia | Leaves | Tincture, no details about preparation | Intravenous | 0.2 mL | Negative control. Positive control: tinctures of *A. vernalis, Digitalis purpurea, Narium oleander.* | The maximal increase in the amplitude of ischemic skeletal muscle contractions and has lower lethal dose comparing with positive control. | Pardo et al., 1951 |
| Cardiotonic | *in vivo.* Cats, and isolated papillary muscle of the cat heart. | Leaves | Convara – an aqueous extract, treated with ferric hydroxide, concentrated under reduced pressure until 1 g was equivalent to 30 g of dried leaves. | Extract direct addition to the Locke's solution. | 0.1 g | Negative control. | Increased strength isometric contractions of isolated papillary muscle. | Weeks, Holck, 1943 |

localizations: kidney (11 patients), urethra (9 patients), and bladder (2 patients). The tablets were administered 3 times per day at the dose of 0.5 g (2 tablets) for 25 days. Positive effects were observed in 5 patients. The treatment led to the removal of sand with the urine and to pain reduction. However, no size decrease of large stones was seen in X-ray examinations. No side effects were recorded during either trial (Vichkanova et al., 2009).

Tablets (0.25 g of dry extract standardized with a minimum of 8% of ruberitrinic acid) of *R. tinctorum* root are available in Russian pharmacies without a prescription and are recommended for internal administration at the dose of 1 tablet to be taken 3 times per day (maximum 3 tablets, 3 times per day) in 100 mL of warm water as a spasmolytic (Sokolov, 2000). However, the information regarding the chemical composition and pharmacological effects of this material is insufficient and warrants further study.

### 5.14. Sedatives

#### 5.14.1. HERBA LEONURI

According to the Pharmacopoeia of the USSR, *Herba Leonuri* (motherwort) consists of the aerial parts of *Leonurus cardiaca* L. and *Leonurus quinquelobatus* Gilib. (syn. *Leonurus cardiaca* L. subsp. villosus (Desf. ex d'Urv.) Hyl.), Lamiaceae, as collected during the flowering season. The two species are similar in morphology, the only difference being the degree of hairiness. *L. quinquelobatus* has hairs all around the stem, not only on the angles, and the hairs are 1 mm in length and erect. Because the pharmacological effects of both plants are similar and *L. cardiaca* is included in the European Pharmacopoeia, the pharmacological effects of *L. quinquelobatus* will not be discussed in this review.

### 5.15. Polyvitamins

#### 5.15.1. FRUCTUS SORBI

*Sorbus aucuparia* L. (rowan, European rowan, mountain-ash, or European mountain-ash), is a small to medium deciduous tree typically growing to 8–10 m tall and is a member of the Rosaceae. The fruit is a small pome of ca. 6–9 mm (rarely up to 14 mm) in diameter. The edible fruits of *S. aucuparia* have been traditionally used in Russia for their diuretic, anti-inflammatory, anti-diarrheal, vasoprotective, and vasorelaxant properties and as a vitamin source (Turova, Sapozhnikova, 1989; Sokolov, 2000). In Central and Lower Valais (Switzerland), rowan fruits are used for the treatment of the gastrointestinal tract as antiflatulent and anti-bloating agents and against colics (Abbet et al., 2014). As documented in the VOLKSMED database, the fruits of *S. aucuparia* are used in Austria as teas, syrups, jellies or liqueurs for the treatment of respiratory tract-related ailments, such as infections, colds, and influenza, as well as fever, rheumatism and gout (Vogl et al., 2013). Rowanberry is a good source of vitamin C (up to 490 mg/kg) (Häkkinen et al., 1999) and has been used to prepare dietary jellies and jams, as a component of syrups and polyherbal mixtures (Shass, 1952).

Rowanberry is considered of low toxicity. The toxicity is related to the cyanogenic glycoside amygdalin and to parascorbic acid, which irritates mucous membranes. These compounds are present in very low concentrations and therefore rarely cause more than gastrointestinal effects (Campbell, Chapman, 2000). Table 22 summarizes the pharmacological studies that have been undertaken on *S. aucuparia* and that are reported in the literature.

A capillary protective effect of *S. aucuparia* when taken in combination with vitamin C and rutin was shown in patients with myocardial infarct and angina pectoris (Golubenko, 1967). However, no details are available. No other clinical data were found in the literature.

Dry fruits of *S. aucuparia* are available in Russia in pharmacies without a prescription and are recommended for internal administration at the dose of 1/2 of glass of the infusion (10 g in 200 mL of water), taken 2 times a day as a polyvitamin (Mashkovskii, 2002). *S. aucuparia* fruits can be regarded as a promising and under-explored fruit that has been used in food in Europe and Asia and that might find wider application for medicinal purposes. However, the pharmacological effects of this fruit are not well documented and warrant further study.

### 5.16. Regulation of metabolism and anti-inflammatory agents

#### 5.16.1. INONOTUS OBLIQUUS

According to systematic classification methods, Chaga - also known as birch fungus (*Fungus betulinus*) - is the terrestrial polypore fungus *Inonotus obliquus* (Pers.) Pil (Polyporaceae). Chaga must be collected only from living or freshly cut old birch trees. On dry standing and fallen trees, Chaga is destroyed, and the content of active compounds decreases dramatically (Shashkina et al., 2006).

Since the 12$^{th}$ century, chaga has traditionally been used in Russia for the treatment of gastrointestinal disorders, cardiovascular diseases, diabetes, and even cancer. Allegedly, the Russian duke Vladimir Monomach was cured of lip cancer using chaga (Artemova, 2001). Chaga (in various combinations with other medicinal plants) has been used for the treatment of gastric and duodenal ulcers and for various forms of gastritis (Artemova, 2001; Kaukin, 2002). Chaga tea increases general stamina, relieves pain and is used to treat heart, stomach, and liver diseases (Gammerman et al., 1984; Saar, 1991).

The safety of chaga extract was tested in mice, rabbits, dogs, and cats. The extract was well tolerated in large doses; the $LD_{50}$ for mice was 6.5 g/kg body weight. The extract administered *per os* in doses up to 1.0 g/kg did not cause any change in the behavior of rabbits, dogs, and cats (Lazovskaya, 1959). In a chronic administration test, rats and rabbits received a chaga extract in a daily dose of 1.0 and 0.3 g/kg body weight, respectively, over 5–6 months. It was concluded that chaga is tolerated well in the doses indicated and does not exhibit accumulative toxic effects. The same tests showed no evidence of pyrogenicity upon per oral administration of chaga in rabbits (Lazovskaya, 1959). Table 23 summarizes the pharmacological studies undertaken on I. obliquus and reported in the literature.

Clinical data indicate that when chaga is administered for extended periods, it has beneficial effects in the treatment of patients with stage III – IV of cancer, irrespective of the tumor location. In most of these patients without pronounced cachexia, a 3- to 4-week administration of chaga led to a decrease and a termination of the pain syndrome, which allowed the administration of narcotic drugs to be stopped (Bulatov et al., 1959; Pyaskovskii, Rikhter, 1961; Shashkina et al., 2006).

The commercial chaga extract Befungin® contains an EtOH (10%) extract of chaga with 1.76% of cobalt chloride or 2.0% cobalt sulfate and is manufactured in 8 factories in Russia. A group of 50 patients (14 women and 36 men) suffering from psoriasis were treated with Befungin® and chaga extract paste. In 37 of these patients, the development of psoriasis was preceded by diseases of the gastrointestinal tract or liver (hyperacid or hypoacid gastritis, hepatocholecystitis, gastric ulcer or duodenal ulcer, or colitis). In 9 patients, these gastrointestinal tract problems appeared during the existing psoriasis condition, and another 4 patients had accompanying chronic pharyngonasal cavity conditions. Almost all patients with gastrointestinal disorders complaining regarding pyrosis, belching, unstable stool, intolerance to fatty foods, pain in the right upper quadrant of the epigastric area etc. The patients noted that the exacerbation of psoriasis often coincided with the

**Table 19**
Summary of Pharmacological Studies for *P. hydropiper.*

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vivo.* Mice initiated with 7,12-dimethylbenz [α]anthracene (DMBA) and promoted with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) | Fresh sprouts | Isolated warburganal and polygodial | Transder-mal | 1.7, 17, 170 nM / 1 h prior to each promotion with TPA | Negative control. Positive control: Salicylaldehyde | Delayed the formation of papillomas, and markedly reduced rate of papilloma-bearing mice and the number of papillomas per mouse. | Matsumoto, Tokuda, 1990 |
| Antifertility | *in vivo.* Pregnancy rats. | Roots | EtOH (90%) extract | Per oral | 100–200 mg/kg/ single dose | Negative control. | 66% antifertility in early pregnancy | Prakash, 1985 |
| Anti-inflammatory | *in vitro.* Murine macrophage cell line (RAW 264.7), lipopolysac-charide-activated macrophages | Leaves | Commercial MeOH extract (99% purity) | 96 well plate | 0–200 μg/mL | Negative control. | Suppressed release of NO, TNF-α, and prostaglandin PGE2. Inhibited mRNA expression of pro-inflammatory genes such as iNO synthase, COX-2, and TNF-α by suppressing the activation of NF-κB, activator protein (AP-1), and cAMP responsive element binding protein (CREB), and simultaneously inhibited its upstream inflammatory signaling cascades, including cascades involving Syk, Src, and IRAK1 | Yang et al., 2012 |
| Anti-inflammatory | *in vivo.* Mice with dextran sulphate sodium (DSS)-induced colitis | Leaves | Commercial MeOH extract (99% purity) | Per oral | 100 mg/kg/ 7 days | Negative control,DSS | Extract strongly ameliorated the DSS-induced decrease in colon length that had been triggered by DSS-induced colon inflammation | Yang et al., 2012 |
| Antimicrobial | *in vitro.* Broth microdilution method. | Leaves | Confertifolin isolated from essential oil. | *in vitro.* | Initial concentration 0.5 mg/mL | Negative control. Positive control: fluconazole, ketoconazole, streptomycin | MIC (μg/mL ) was 1.56 against *Erwinia sp,* 6.25 against *S. aureus* and *K. pneumoniae,* 7.82 against *E. floccosum, C. Lunata, and Scopulariopsis* sp., and 16.62 against *T. mentagrophytes* and *T. rubrum* | Duraipandiyan et al., 2010 |
| Antinociceptive | *in vivo.* Mice, acetic acid-induced writhing | Aerial part | Hexane, EtOAc MeOH extracts (yield 1.22, 1.81, 2.28% of dried plant material). | Per oral | 250, 500 mg/kg, | Negative control. Positive control: aminopyrine 50 mg/kg | Suppression of the number of writhing in 19-55%. Maximal effect for EtOAc extract at 500 mg/kg. | Rahman et al., 2002 |
| Antioxidant | *in vitro.* DPPH assay | Aerial part | Hidropiperoside B and vanicosides A isolated from MeOH extract | 96 well plate | No data | Negative control. | $IC_{50}$=23.4 μg/mL for hidropiperoside B, 26.7 μg/mL, for vanicosides A. | Kiem et al., 2008 |
| | *in vitro.* Ferric thiocyanate method | Leaves | Isolated 7,4'-dimethylquercetin, 3'-methylquercetin | *in vitro.* | 0–10 ppm | Negative control. Positive control: α-tocopherol | $ID_{50}$= 1.5 ppm for 4'-dimethylquercetin and 3.0 ppm for 3'-methylquercetin. | Haraguchi, 1992 |
| Citotoxic | *in vitro.* Sensitized sheep erythrocytes and guinea pig serum (complement) | Leaves | Isolated drimane-type sesquiterpene dialdehyde polygodial. | Microtiter plates | No data | Negative control. | Anticomplement activity at 10.5 μg/ mL. | Fukuyama et al., 1980 |
| Estrogenic | *in vivo.* Ovary-intact and ovariectomized (OVX) rats | Roots | MeOH extract | Per oral | 1000 mg/kg / 12 days | Negative control. Positive control: estradiol-17β (E2) | In uterine tissues of ovary-intact and OVX rats, extract induced hyperplasia in places of luminal epithelium and degeneration of endometrial glands. In OVX rats, the effect of extract on uterine endometrium was corroborative with the effect of E2. | Hazarika, Sarma, 2006 |

**Table 20**
Summary of Pharmacological Studies for *A. graveolens*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antibacterial | *in vitro* Agar diffusion assay. | Seeds | Aqueous, hexane, EtOAc, acetone, EtOH extracts | *in vitro.* | 0.1 mL | Negative control. Positive control: ampicillin, cefixime, chloramphenicol, co-trimoxazole, gentamicin, imipenem, pipericillin/tazobactam, tobramycin | Antibacterial activity against *E. faecalis, S. aureus, E. coli, P. aeruginosa, S. typhi, S. typhimurium, S. flexneri* with MIC = 5-10 mg/mL for acetone extract and 20-50 mg/mL for aqueous extract. | Kaur, Arora, 2009 |
| Antibacterial | *in vitro.* Microdilution assay. *E. coli*, *P. aeruginosa*, *Proteus mirabilis*, *K. pneumoniae*, *Acinetobacter baumannii S. aureus*, *Enterococcus faecalis*, *B. subtilis,* and clinical isolates. *C. albicans, C. parapsilosis* | Aerial part | Essential oil by hydrodistil-lation | Microplates | No data. | Negative control. Positive control: ampicillin, gentamicin, ofloxacin, levofloxacin, ketoconazole, fluconazole; | MIC = 1-4 μg/mL for all microbes (excluding clinical isolates) and 9-18 μg/mL for all fungi. | Erdoğan Orhan et al., 2012. |
| Antibacterial | *in vitro.* Broth dilution method. *S. aureus*, *E. coli.* | Not specified | Commercial essential oil | 96 well plate | 0-0.5% (v/v) | Negative control. | MIC(v/v) = 0.37% against *S. aureus* and 0.47% against *E. coli* | Delaquis et al., 2002 |
| Anticancer | *in vitro.* Mouse leukemia cells L1210, | Aerial part | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg per well concentration of the extract | Positive control Methotrexate Negative control | 98% growth inhibition by methylene chloride extract, | Goun et al., 2002 |
| Anti-inflammatory | *in vivo,* Mice, formalin induced inflammation | Aerial part, seeds | Hydroalchoholic extract | Intraperito-neal | 300 mg/kg | Negative control. Positive control: morphine. | Analgesic effect 15–45 min after formaline injection by both extracts. | Rezaee-Asl et al., 2013 |
| | *in vivo,* Rats, formalin induced edema | Fresh aerial part | Sesame oil extract (10:4) | Topical application on paw | 100 mg/ 8 days | Negative control. Positive control: diclofenac gel 0.01%. | Reducing of the paw inflammation even stronger than application of diclofenac. | Naseri et al., 2012 |
| Antispasmodic | *in vitro.* Rats isolated ileum contractions induced by KCl, acetylcholine and $BaCl_2$ | Seeds | EtOH (70%) extract | Direct addition of extract to the media with ileum | 0.1, 1, 2, 4 mg/mL /cumulative | Negative control. | Maximal spasmolytic effect was for $BaCl_2$ induced contraction with $IC_{50}$ = 0.96 mg/mL. | Gharib Naseri, Heidari, 2007 |
| Antiviral | *in vitro*, antiviral | Aerial part | Essential oil by hydrodistil-lation | 96 well plate | 0.025–0.8 μg/mL | Herpes simplex viruses HSV-1, parainfluenza type-3 (PI-3). Positive control: acyclovir, oseltamivir | Antiviral activity against HSV-1 at 0.025–0.8 μg/mL and against PI-3 at 0.4–0.8 μg/mL. | Erdoğan Orhan et al., 2012. |
| Diuretic | *in vivo.* Mongrel dogs. | Seeds | EtOH (70%) extract. Volatile oil by steam distillation. | Intrave-nous. | Volatile oil 0.004 mL/kg. Extract 12.5, 25 mg/kg. | Negative control. | Increase in urine flow 2.2 folds at 12.5 mg/kg no effect on blood pressure. 25 mg/kg produced a further but insignificant increase in urine flow accompanied by a marked hypotension that lasted for 1 h. Volatile oil increased $Na^+$ and $Cl^-$ excretion | Mahran et al., 1991). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Gastroprotective | *in vivo.* Rats, EtOH and HCl-induced gastric ulcer | Seeds | Aqueous and EtOH (70%) extracts | Per oral, intraperito-neal. | 0.05–0.45 g/kg aqueous extract, 0.5–5 g/kg EtOH extract. | Negative control. Positive control: sucralfate, cimetidine | Decreased gastric lesions induced by HCl with $ED_{50}$= 0.12 g/kg for both extracts, induced by EtOH with $ED_{50}$=0.34 g/kg for aqueous and 1.73 g/kg for EtOH extracts. Both extracts at higher doses antisecretory activity as effective as cimetidine. | Hosseinzadeh et al., 2002 |
| | *in vivo.* Rats, indomethacin induced gastric ulcer after ligation of pylorus. *in vitro* pepsin binding. | Seeds | Dry powder, aqueous and EtOH (95%) extracts. | Per oral. | 1, 1.5, 2 g/kg of powder. Aqueous and EtOH extracts equivalent of 2 g/kg of powder. 14 days. | Negative control. Positive control: indomethacin | The powder of seeds dose dependent decrease gastric acid output, increase pH, and reduce gastric ulcer index. Effects of aqueous and EtOH extracts were significant but lower. Pepsin binding capacity of powder was 70.4% at 0.5 g/mL. | Rifat-uz-Zaman et al., 2004 |
| Hypolipidemic | *in vivo.* Rats fed with high cholesterol (Chol) diet, rats with normal diet. | Aerial part | Essential oil by hydro-distillation with α-phellandrene (32%), limonene (28%) and carvone (28%). Dry powder. | Per oral | Essential oil: 45, 90, 180 mg/kg for high Chol diet rats. Dry powder: 10% (w/w) addition for normal diet rats / 2 weeks | Negative control. Positive control: clofibrate | Treatment with essential oil resulted in dose-dependent reduction of total Chol, triglyceride and LDL-Chol and increase of HDL-Chol by 24- 33%. Addition of powder reduced the total Chol in 20%, LDL-Chol in 2 folds and triglyceride in 14% and increased the HDL-Chol concentration in 30% compared to control. | Hajhashemiand Abbasi, 2008 |
| Regulation of menstrual cycle | *in vivo.* Rats in estrus phase of estrous cycle. | Seeds | Aqueous and EtOH (80%) extracts. | Per oral | 0.045, 0.45 g/kg of aqueous and 0.5, 5 g/kg EtOH extracts. 10 days | Negative control. | Increase in duration of estrous cycle and in diestrus phase and progesterone concentration in high dose extract treatment. | Monsefi et al., 2006. |

exacerbation of gastrointestinal tract disorders. The duration of the psoriasis condition before treatment with Chaga preparations was 1 year in 5 patients, up to 3 years in 7 patients, 7 to 5 years in 8 patients, up to 10 years in 13 patients, from 10 to 15 years in 7 patients, and more than 15 years in 10 patients. Among the patients, 3 were suffering from psoriatic erythroderma, 1 had psoriatic arthritis, 18 had extensive psoriasis with a massive infiltration of plaques, 20 had extensively spread small plaque rashes, and 8 had localized psoriatic plaques. Forty-three patients started the treatment with Chaga during the acute stage of psoriasis, and 7 started during the steady-state. Chaga extract was heated au-bain-marie, and 1 tablespoon of the extract was diluted in a glass of boiled water at room temperature. One tablespoon of this solution was taken orally, 3 times a day, 20–30 minutes before meals. Water solutions of Befungin® were prepared by mixing 1 dessertspoon of Befungin® in 100 mL of boiled water (after cooling to room temperature). The intake instructions were the same as those described above. Both Chaga preparations have no unpleasant odor or taste and were tolerated well by the patients even after several months of continuous intake. Most of the patients (42) only used a Chaga preparation for internal use, although 8 also used ointments and one of the preparations for internal use. Twenty-four patients used the Chaga preparations for 3–6 months, 18 patients used them for up to 12 months, and 8 patients used them for more than 2 years. The therapeutic effect of the Chaga manifested slowly, reaching a maximum at the 3rd month of regular intake. In most cases, the psoriatic rashes disappeared starting at the torso, then on the scalp, upper limbs and finally, on the hips and lower legs. The normalizing effect of Chaga treatment was observed on the nail plates after 2–3 months. Extensive psoriasis with massive plaques was completely cured in 14 patients, and improvements were mentioned for 2 patients. Extensive psoriasis with localized plaques was completely cured in 16 patients, and improvements were mentioned for 3 patients. Limited psoriasis lesions and erythrodermic lesions were completely cured in 5 and 3 patients, respectively. Psoriasis-therapy with Chaga was especially successful where psoriasis occurred in combination with chronic inflammatory diseases of the gastrointestinal tract, liver and biliary system. The maximum efficiency of treatment was noted after 9 to 12 weeks of continuous intake. Additionally, improvement in gastrointestinal functions, increased vitality and general tonus was noted in all patients after long and regular chaga intake, demonstrating the adaptogenic properties of *I. obliquus* (Dosychev, Bystrova, 1973).

Chaga and Befungin® are available in Russia in pharmacies without a prescription and are recommended for internal administration at the dose of 100 mL of the infusion (10 g in 100 mL of water), 6 times a day, or 20 mL of Befungin®, 3 times a day for 3–5 months as a regulator of metabolism and as part of the complex therapy of gastrointestinal diseases (Mashkovskii, 2002). Chaga is well known and popular in Russia, and its safety and some evidence for its efficacy is based on a long tradition of empirical use. However, there is a lack of information in the literature regarding its efficacy under controlled conditions. Further clinical studies are required to evaluate the claimed activity in patients, and more details on the drug's safety would be desirable. Given the recent findings of the importance of the GI-tract microbiome, studies of the effect of Chaga on this biome would be of great interest.

### 5.17. Tonics

#### 5.17.1. RADICES ARALIAE MANDSHURICAE

*Aralia elata* (Miq.) Seem. syn *A. mandshurica* Rupr. & Maxim, also known as Japanese angelica tree (*Araliaceae*), is an upright deciduous small tree or shrub growing up to 6 m in height, native to eastern Russia, China, Korea, and Japan. The stem and root barks

**Table 21**
Summary of Pharmacological Studies for *Rhizomata et radices Rubiae*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antidiarrhoeal | *in vivo*. Rats, castor oil-induced diarrhea. Mice, small intestinal transit. | Root | Aqueous extract, 12.5% yield. | Per oral | 300, 600, 800 mg/kg / single dose administration. | Negative control. Positive control: loperamide | Protected rats, in a dose-dependent fashion, against diarrhoeal dropping by 37-64%. Inhibited by 41% the gastrointestinal transit of charcoal in mice at 800 mg/kg . | Karim et al., 2010 |
| Antifungal | *in vitro*. Disc diffusion method. | Root | MeOH extract with 6.3% yield | *in vitro*. | No data | Negative control. Positive control: alizarin, emodin, parietin. | 43% inhibition of *Trichoderma viride*, 41% inhibition of *Doratomyces stemonitis* and 35% inhibition of *Penicillium verrucosum*. | Manojlovic et al., 2005 |
| Antileishmaniasis | *in vivo*. BALB/c mice infected with leishmania (L) major [MRHO/IR/75/ER]. | Root | EtOH (80%, 60, 40%) extracts | Per oral | No data. | Negative control. | The lesion of mice treated with 40, 60 and 80% extract in water were wet, without secondary infection and necrosis. | Bafghi et al., 2008 |
| Antilithiasis | *in vivo*. Rabbits, foreign-body bladder calculus model | Root | Hydroxy-anthraquinone derivatives | Per oral | No data | No data | Pronounced calcium-complex binding effect and reduction in the growth rate of the calculi | Berg et al., 1976. |
| Antilithiasis | *in vitro*. | Root | 5% aqueous solution of extract. | *in vitro* | Kidney stone 20 mg | No | After 15 days the weight of stone was decreased by 25% and the stone structure became friable | Vichkanova et al., 2009 |
| Antimicrobial | *in vitro*. Agar-disc diffusion method. | Root | Aqueous, EtOH, MeOH and EtOAc extracts | *in vitro*. | 10–100 µL in 6 mm disc. | Negative control. Positive control: erythromycin | Full inhibition of *Aspergillus flavus*, *Fusarium oxysporium*, and *Streptomyces murinus* at 100 µg/mL by EtOH and MeOH extracts. | Kalyoncu et al., 2006 |

**Table 22**
Summary of Pharmacological Studies for *S. aucuparia* fruits.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | in vitro. Mouse leukemia cells L1210, | Fruits | Methylene chloride extract, soxhlet | 96 well plate | 10 μg per well | Positive control Methotrexate Negative control | 98% growth inhibition | Goun et al., 2002 |
| Anti-inflammatory | *in vitro.* PPARα or PPARγ activation in human embryonic kidney (HEK) 293 cells. | Fruits | Detannified MeOH extract | 96 well plate | 10 μg/mL | Negative control. Positive control GW7647 and pioglitazone | Strong activation (75-100%) of PPARα and PPARγ | Vogl et al., 2013 |
| Antimicrobial | *in vitro.* Liquid culture. | Fruits | Polyphenol-rich fraction | *in vitro.* | 1 mg/mL | Negative control. | Strong growth inhibition of *Bacillus cereus.* Bacteriostatic effect against *Campylobacter jejuni* and *S. aureus.* | Nohynek et al., 2006 |
| Antimicrobial | *in vitro.* Liquid culture. Inhibition of bacterial hemag-glutination | Fruits | Polyphenol-rich fraction with anthocyanins, flavonols, 5-caffeoylquinic and 3-caffeoylquinic acids. | *in vitro.* | 1 mg/mL. 0.5-2.0 μg of total phenolics/mL for hemag-glutination | Negative control. | Weak inhibition of *Salmonella enterica*, and *E. coli*. Inhibitory effect on hemag-glutination of *E. coli* HB101 (pRR7), which expresses the M hemagglutinin. | Kylli et al., 2010 |
| Antioxidant | *in vitro.* Liposome and emulsion oxidation assays. | Fruits | Polyphenol-rich fraction with anthocyanins, flavnols, 5-caffeoylquinic and 3-caffeoylquinic acids. | *in vitro.* | 2.1, 4.2, 8.4 μg/mL of phenolics for liposomes. 25, 50, and 100 μg/g of phenolics for emulsion | Negative control. | In liposome model 90-97% inhibition of hexanal formation; 68-77% inhibition formation of conjugated diene hydroperoxides. In emulsion oxidation model 86-95% inhibition hexanal formation; 80-87% inhibition formationconjugated diene hydroperoxides. | Kylli et al., 2010 |
| | *in vitro.* Ferric reducing antioxidant power (FRAP). DPPH assay. | Fruits | Acetone (70%) extracts of fresh fruits | 96 well plate | 30 μL of 1/40 diluted samples for FRAP assay and 50 μL for DPPH assay | Negative control. | The FRAP value 61–105 μM $Fe^{2+}$/g of fresh weight and the DPPH radical scavenging activity: 9.7-21 g of berries/g of DPPH radical. | Hukkanen et al., 2006 |
| | *in vitro.* DPPH assay. | Fruits | Water soluble polysaccharides (yield 4.2%). | *in vitro.* | 0.5 mg/mL | Negative control. Positive control: trolox | 35-53% of the activity of trolox taken as100% | Zlobin et al., 2012 |
| Anti-proliferative | *in vitro.* HeLa cell viability assay | Fruits | Polyphenol-rich fraction | 96 well plate | 50 μg/mL | Negative control. | Reduced viability of HeLa cell to 50% of control | McDougall et al., 2008 |

of *Aralia elata* have been used as a traditional and local medicine in East Asian countries and in Russia to treat coughs, diabetes, gastric ulcers, hepatitis, and inflammatory diseases such as rheumatoid arthritis (Namba, 1980; Perry, 1980; Turova, Sapozhnikova, 1989; Ma et al., 2005). The Nanai ("nanaitsy"in Russian), a Tungusic people of the Russian Far East, have used the roots of *A. elata* for toothache and stomatitis, as a tonic, and to treat liver diseases (Vostrikova, 1973). The Ainu, aboriginal peoples who once dominated Hokkaido in Japan, have used the roots of *A. elata* (Ayus-ni or enenkeni in Japan) as a stomachic (Mitsuhashi, 1976). In Russian codified medicine, *Aralia* belongs to the group of classical adaptogens (Brekhman, Dardymov, 1969).

The toxic acute and subchronic effects of a *A. mandshurica* dried root extract (standardized to a minimum of 3% of aralosides) were studied in Sprague-Dawley rats of both sexes after per oral administration. In the acute toxicity experiment, an extract was administered twice a day at various concentrations. The $LD_{50}$ was estimated as 16.5 g/kg and 16.8 g/kg for male and female rats, respectively. Before death, the animals exhibited nervous depression, diminished motor activity, frequent micturition, respiratory difficulty, and diarrhea. In a subchronic toxicity assay, the extract was administered per oral at the doses of 0.2, 1.7, 3.4 g/kg over 90 days. Depression of the CNS response was not observed. An increase in the levels of aspartate aminotransferase (AST) and serum alkaline phosphatase (SAP) were observed at the dose of 3.4 g/kg in both sexes on day 90 of administration, but no changes were observed in urea and serum protein levels. A significant decrease in body weight was recorded in both sexes at the dose of 3.4 g/kg. Moreover, the animals treated with doses of 1.7 and 3.4 g/kg showed a diminished fecal consistence. An increase in liver weight was produced with all doses of *A. mandshurica*, but neither macroscopic nor histological alterations were observed in the liver or in other organs. The authors concluded that the extract of *Aralia* might accumulate, causing a toxic effect over the long term (Burgos et al., 1994). The hepatotoxic effect of a dried root extract of *A. mandshurica* (standardized to a minimum of 3% of aralosides) was studied over 60 days (0.16 g/kg, 1.5 g/kg and 3 g/kg) in Landrace pigs of both sexes. No changes in behavior, external appearance, food consumption, or body weight were observed. The levels of alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (gGT) were increased significantly at all concentrations of *A. mandshurica* at day 60. SAP levels did not significantly differ throughout the experiment. Subclinical hepatitis, which was characterized by the presence of lymphocytes and polymorphonuclears in the portal and periportal region, was observed (Burgos et al., 1997). The $LD_{50}$ for mice after per oral administration of a combination of aralosides (A, B, and C) was 0.47 g/kg (Brekhman, Dardymov, 1969). The acute toxicity of araloside A (chikusetsusaponin IV), as isolated from *A. elata*, was studied in ICR male mice. The $LD_{50}$ after 1 week of oral administration was 3.22 g/kg (Lee et al., 2005). Table 24 summarizes some pharmacological studies that have been undertaken on *Aralia* and that are reported in the literature.

In an open, single-arm study including 106 patients who were treated for various asthenic conditions, a success rate of approximately 90% was reported using *Aralia*. The administration (3 times per day for 30 days) of 2 mL of *A. mandshurica* tincture (1:15, EtOH 70%, standardized for aralosides) to patients aged 23 to 60 years with a diagnosis of long-term effects of traumatic brain injury with associated asthenic syndrome and neurotic reactions, depression, neurasthenia, and psychasthenia, significantly increased their working capacity, appetite, and sleep. A decrease in the number of complaints of fatigue, headache, and general weakness was observed. Some patients have reported increased sexual potency and libido (Gubina, 1988). Positive effects in patients with myasthenia syndrome accompanied by chronic post-influenza arachnoiditis were registered after 2 weeks of treatment with *Aralia* tincture (Gubina, 1959). Normalization of body function is one of the main attributes of adaptogens. There were no statistically significant effects of *Aralia* tincture on patients with normal blood pressure, although a normalization of blood pressure was observed in patients with hypotension (Turova, Sapozhnikova, 1989). *Aralia* exhibits a pronounced positive effect in clinical trials on introverts and on people with high levels of neuroticism. The maximal positive effect was observed during the first 4 months of treatment (Markin, Markina, 2007; Markina, Markin, 2008).

The effects of oral treatment with the phytopreparation Aralox (which contains *A. mandshurica* and *Engelhardtia chrysolepis* Hance (*Juglandaceae*) extracts) on some parameters of lipid metabolism were studied. A randomized placebo-controlled study was conducted over 15 weeks and included 32 women with nondiabetic obesity. The patients received Aralox (main group, $n=16$) or placebo (control group, $n=16$) 3 times daily, 30–45 min before meals. A single dose of Aralox included 150 mg of *A. mandshurica* extract containing at least 20% triterpene saponins (aralosides) and 150 mg of an extract of *Engelhardtia chrysolepis* leaves containing at least 20% flavonoid (dehydroquercetin-3-rhamnoside). Thirteen women from the main group and 14 controls completed the 15-week study. No appreciable differences were detected in the physical characteristics and nutrition of the examined patients between the two groups before Aralox/placebo treatment. The patients receiving Aralox 3 times daily lost $4.3 \pm 0.7$ kg ($p < 0.001$) over 15 weeks vs. $0.7 \pm 0.2$ kg for the placebo group. Body weight loss due to Aralox was almost exclusively (95%) due to fat loss. Perilipin content in the adipocytes of patients treated with Aralox decreased by 27%. A course of Aralox treatment promoted an increase in adipocyte HSL activity from $5.2 \pm 1.1$ to $8.1 \pm 1.4$ U/mg protein, whereas controls exhibited virtually no change in this parameter. Aralox decreased the plasma triglyceride content from $3.6 \pm 0.2$ to $1.8 \pm 0.7$ mmol/L; in the controls, the triglyceride level did not change (Abidov et al. 2006).

Since 1975, Saparal tablets containing a mixture of ammonium salts of aralosides A, B, and C (0.05 g) have been on the market in the USSR / Russia. Aralosides (A, B and C) stimulate the central nervous and immune systems, possess anti-stress properties, and protect against unfavorable environmental conditions, such as hypoxia or viral infections. After swimmers trained while taking Saparal at the dose of 50 mg/day for 35 days, a variety of effects was observed; the level of tissue hypoxia decreased after physical loading due to an increase in the level of oxidation-reduction processes in the tissue, the protective properties of an organism were promoted, and the cytophagous activity of leukocytes was increased. The decrease in work capacity during the first two-three days after high physical loading was also reduced (Sokolov et al., 1971). *Aralia* is a popular plant in the traditional medical systems in Russia and Asia and has the reputation of being an adaptogen. *Aralia* tincture and Saparal tablets are available in Russia in pharmacies by prescription and are recommended for internal administration at the dose of 30–40 drops, 2–3 times a day, or 1 tablet, 2–3 times a day, for 10–15 days for use as a CNS stimulant and as an adaptogen (Sokolov, 2000). However, it is important to reproduce and confirm the non-clinical studies and to perform clinical trials according to Good Clinical Practice (GCP).

### 5.17.2. RHIZOMATA ET RADICES RHODIOLAE ROSEAE

*Rhizomata et radices Rhodiolae roseae* consists of the dried roots and rhizomes of *Rhodiola rosea* L. (syn. *Sedum roseum* (L.) Scop.), (Crassulaceae), which is commonly known as golden root, rose root, roseroot, and arctic root, a perennial plant with shoots reaching 5-35 cm in height.

**Table 23**
Summary of Pharmacological Studies for *I. obliquus*.

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antiallergic | *in vivo.* Mice | Fruiting bodies | Aqueous extract | Intraperito-neally Per oral. | 0.1, 0.5, 2.5, 0.1, 1, 10 mg/mouse | Negative control | 100% inhibition anaphylactic shock induced by compound 48/80 at 2.5 mg Oral administration reduced total IgE levels and slightly affected production of IgG1. Spleen cell cultures from OVA-sensitized mice that had received extract orally showed an increase in IFN-γ | Yoon et al., 2013. |
| Anti-astmathic | *in vivo.* Asthmatic mice. | Sclerotium | EtOH extract | Intraperito-neally | No data. | Negative control. | Inhibition expression of phosphor-p38 MAPK, balancing IFN-γ/IL-4 ratio and decreasing number inflammatory cells | Yan et al., 2011 |
| Anticancer | *in vitro.* Mouse leukemia cells L1210 | Not specified | Methylene chloride and MeOH extracts, soxhlet | 96 well plate | 10 μg/well | Positive control: Methotrexate Negative control | 100% growth inhibition by Methylene chloride and 92% by MeOH extracts. | Goun et al., 2002 |
| Anticancer | *in vivo.* Mice with melanoma. *in vitro.* Melanoma B16-F10 cells. | Sclerotium | Aqueous extract | Intraperito-neally, per oral 48 well plates | Initial concentration 50 mg/mL 20 mg/kg/day (i.p) 200 mg/kg/day (p.o) during 10 days | Negative control. Positive control | Intraperitoneal administration reduced tumor growth to 33% of positive control. Inhibited growth of B16-F10 cells by causing cell cycle arrest at G0/G1 phase. | Youn et al., 2009 |
| Antidiabetic | *in vitro.* 3T3-L1 Preadipocytes. | Fruiting bodies | Aqueous extract with glucose-rich polysaccharides 149 kDa | 96 well plate | 10, 25, 50, 100 μg/mL | Negative control. Positive control: insulin | Extract enhanced differentiation of 3T3-L1 preadipocytes, and dose-dependent increased TG accumulation. It stimulated gene expression of CCAAT/enhancer-binding protein α and PPARγ during adipocyte differentiation, and induced the expression of PPARγ target genes such as aP2, LPL and CD36. | Joo et al., 2010 |
| Anti-inflammatory | *in vivo.* Acetic acid-induced abdominal constriction, hot plate tests in mice. Carrageenan-induced edema in rats. | Sporophores | MeOH extract (29.8% yield) | Per oral | 100, 200 mg/kg/ 7 consecutive days (in rats), 100, 200 mg/kg /single dose in mice | Negative control. Positive control: aspirin, ibuprofen. | Dose dependant reduction of paw edema in rats and analgesic activity in mice | Park et al., 2005 |
| | *in vivo.* Mice with dextran sulphate sodium (DSS)-induced colitis | Fruiting bodies | Aqueous extract | Per oral | 50, 100 mg/kg / twice a day, 7 days before and during DSS admini-stration, for 14 days. Twice a day 7 day concur-rent with DSS administration | Negative control, DSS | Diminishing colitis by suppressing expression of inflammatory mediators TNF-α, IFN-γ, IL-1β and IL-6, and iNOS in colonic tissues. | Mishra et al., 2012 |
| Anti-inflammatory | *in vitro.* Murine macrophage cell line (RAW 264.7), lipopolysac-charide-activated macrophages | Sporophores | MeOH extract (29.8% yield) | 96 well plate | 45, 90, 135 μg/mL | Negative control. Positive control: l-*N*6-(1-iminoethyl) lysine | Inhibition of iNOS and COX-2 expression via the down-regulation of NF-κB binding activity and reduction in nuclear p65 protein levels | Park et al., 2005 |
| Antimutagenic | *in vitro.* Ames test | Sclerotium | Subfractions from MeOH extract | Agar plates | 50 μg /plate | Negative control | Inhibition of mutagenesis induced in *Salmonella typhimurium* strain TA100 by the directly acting mutagen MNNG (0.4 μg /plate) by 77.3-80.0%. Inhibition of 0.15 μg /plate 4NQO-induced mutagenesis in TA98 and TA100 by 52.6–62.0%. Mutagenesis in TA100 by Trp-P-1 and B(α)P was reduced by 70.5–87.2%. | Ham et al., 2009 |

**Table 23** (*continued*)

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antioxidant | *in vitro.* DPPH assay | Sclerotium | Subfractions from MeOH extract | *in vitro.* | 5–500 μg/mL | Negative control. Positive control: ascorbic acid, tocopherol, BHA | $IC_{50}$=69 μg/mL for subfraction 1 | Ham et al., 2009 |
| | *in vitro.* DPPH, hydroxyl radicals, superoxide anion radicals, $H_2O_2$ assays | Sclerotium | Polysaccharide fractions IOP40, IOP60, IOP80 with yield 2.2%, 11.6%, 0.84%, | *in vitro.* | 62.5–1000 μg/mL | Negative control. Positive control: ascorbic acid | Order of reducing power in DPPH, $H_2O_2$, and hydroxyl-scavenging activity was IOP60 > IOP40 > IOP80 | Du et al., 2013 |
| | *in vitro.* ABTS, DPPH, superoxide anion radicals assays | Fruiting bodies | Isolated inonoblins A, B, and C, phelligridins D, E, and G. | *in vitro.* | No data | Negative control. Positive control: trolox, caffeic acid | Inonoblin C was most active in ABTS assay (0.65 TEAC), phelligridin D in superoxide anion radicals assay ($IC_{50}$=85.5 μM), Phelligridin E in DPPH assay (1.57 TEAC) | Lee et al., 2007 |
| Immunomodulatory | *in vivo.* Balb/c mice | Sclerotium | Aqueous extract | Per oral | 1–100 mg/kg/ up to 8 weeks | Negative control. | Increased in 1.5-3.5 fold the proliferative activity of splenocytes transformed *in vitro* by a polyclonal Con A mitogen or an alloantigen in a mixed culture of lymphocytes (MCL) from allogenic mice spleen. Induced formation of additional T-killers in the MCL. 8 weeks administration stimulated cytotoxic activity of peritoneal macrophages. | Shashkina et al., 2006 |
| Immunomodulatory | *in vivo.* Ovalbumin (OVA)-sensitized BALB/c mice. *ex vivo.* LPS-stimulated peritoneal macrophages. | Sclerotium | Aqueous extract | Per oral | Daily 50, 100, 200 mg/kg | Negative control. | $IgG_{2a}$ was suppressed after the second immunization with OVA. ConA stimulation in spleen cells isolated from OVA-sensitized mice treated with 100 mg/kg resulted in 5.2% decrease in IL-4 production and a 102.4% increase in IFN-γ, compared to controls. IL-4, IFN- γ, and IL-2 were reduced after ConA stimulation in isolated CD4+T cells. Extract inhibits the secretion of NO from LPS-stimulated peritoneal macrophages ex vivo. | Ko et al., 2011 |
| Radioprotective | *in vivo.* Rats irradiated with cesium (2.0 Gy) | Sclerotium | Chromogenic complex | Per oral. | 4.0 mg/kg /30 days | Negative control. | Between 3 and 10 days after exposure, recovery of hemopoietic tissue function and bone marrow cellularity. Stimulation of cells participating in the immune protection of neutrophils (microphages) and lymphocytes. | Gavrilov et al., 2003 |
| Radioprotective | *in vivo.* Wistar rats Balb/c mice γ-irradiated (0.025 sGr/min) 30 days. | Sclerotium | Aqueous, EtOH extracts, aqueous suspension | Per oral | Dose not indicated/ single administration in rats 2–3 min after the intravenous injection of $^{90}Sr$ isotope irradiation. 30 days administration of suspension in mice | Negative control. | Decrease in the extent of radionuclide deposition in the bone and soft tissues and increase of radionuclide elimination in 33-35% in rats. Extension of average lifespan of mice up to 305 days (against 186 days in the untreated control group) and prevented a sharp drop of leukocytes and lipid peroxidation. | Rasina, 2002 |

*Rhodiola rosea* is one of the most popular classical plant adaptogens utilized in Russia. In traditional and popular Russian medicine, *R. rosea* is used to increase physical endurance, work productivity, longevity, and resistance to altitude sickness and to treat fatigue, depression, anaemia, impotence, gastrointestinal ailments, and infections and disorders of the nervous system (Turova, Sapozhnikova, 1989). In Linne's Materia Medica (Linne, 1749), the root of *Rhodiola* is recommended for the treatment of headaches, "hysteria", hernias, and discharges and for use as an astringent. A monograph on the root is also found in the first Swedish national pharmacopoeia (Panossian et al., 2010). Alm (Alm, 2004) mentioned the use of *Rhodiola* in popular medicine against scurvy, and this root was also used medically as a stimulant and, in France, as an astringent (as described by Virey in a medical textbook published in 1811).

This plant was first recommended in 1969 by the Pharmacological Committee of the Ministry of Health of the USSR for use as a stimulant against fatigue by patients who suffered asthenic states and for healthy people with astheny during periods of high mental exertion or after intensive physical work. The drug can also be used to treat borderline nervous-mental diseases, neuroses, neurotic disorders, and psychopathies. In psychiatric practice, extracts of *R. rosea* are indicated for the correction of neurological side effects associated with psychopharmacological therapy, and for the intensification and stabilization of remissions in cases of asthenic and apathetical-aboulic type schizophrenia (Saratikov, Krasnov, 1987, 2004: Panossian et al., 2010). Since 1975, *Rhodiola* liquid extract (1:1, EtOH 40%) has been produced industrially in Russia on a large scale, and since 1985, *Rhodiola* tablets containing *R. rosea* SHR-5 extract have been on the market in Sweden. In April 2009, the first *R. rosea* product Vitano (based on the *R. rosea* extracts WS 1375, which was registered as a traditional herbal medicinal product), was introduced in the UK (Hung et al., 2011) for use as an adaptogen (Box 1) to treat decreased performance due to fatigue and the sensation of weakness (Panossian et al., 2010).

The safety of *R. rosea* extract was tested in rats, mice, dogs, and humans. *Rhodiola rosea* has a very low level of toxicity. The $LD_{50}$ after intraperitoneal injection of the liquid extract in mice was found to be 28.6 mL/kg, equivalent to approximately 3,360 mg/kg. The equivalent dosage in a 70 kg human would be approximately 235 g. Because the usual clinical dose is 200–600 mg/day, there is a very large safety margin (Brown et al., 2002). No toxic signs were observed after administration of the glycoside salidroside at the dose of 1,000 mg/kg (equivalent to 50 mL/kg of extract). Intragastric administration of the extract (1 mL/kg) or salidroside (20 mg/kg) for 14 days was found safe in rabbits. In a dose range of 10–40 mg/kg, salidroside does not affect arterial blood pressure in rabbits after intraperitoneal or intravenous injection. The values of $LD_{50}$ for p-tyrosol, another of the main compounds present in *R. rosea,* were found to be 2,700 mg/kg and 1,700 mg/kg in mice after intragastric and intraperitoneal injection, respectively, and 7,079 mg/kg in rats after intragastric administration. No toxicity was observed after 3 months of chronic intragastric administration of p-tyrosol at the doses of 200 mg/kg in male rats and 10 mg/kg in dogs (Saratikov, Krasnov, 2004). Salidroside did not exhibit genotoxicity in a reverse mutation assay (up to a maximal dose of 5,000 μg/plate), in a chromosomal aberration assay (at doses up to 2,000 μg/kg, and in a mouse micronucleus assay (at doses up to 1,500 mg/kg) (Zhu et al., 2010). No induction of mutations in the sexual and somatic cells of rats was observed after intragastric administration of p-tyrosol at the dose of 2,500 mg/kg (Saratikov, Krasnov, 2004). After the per oral administration of an EtOH extract from the roots of *R. rosea* in mice (10-316 mg/kg), significant reductions in exploratory behavior and in the number of rearings and head dippings were observed, but no changes were seen in the sedative-hypnotic and anticonvulsant response. Moreover, *R. rosea* reduced licking time in the formalin test. *Rhodiola rosea* extract (1,000 mg/mL) was not toxic for *Artemia salina.* These results all confirm the very low toxicity risk of *Rhodiola* (Montiel-Ruiz et al., 2012).

*Rhodiola rosea* extract WS® 1375 was safe and generally well tolerated at a dose of 200 mg twice daily for 4 weeks in subjects with life-stress symptoms. Two hundred milligrams of dry extract from *R. rosea* roots and rhizomes is equivalent to 300–1,000 mg of *R. rosea* roots and rhizomes (Edwards et al., 2012).

The results of several hundred pharmacological studies of *R. rosea* are assessed in several review articles and books (Saratikov, Krasnov, 1987, 2004; Kelly, 2001; Brown et al., 2002; Panossian, Wagner, 2005; Panossian, Wikman, 2009; Panossian et al., 2010, Hung et al., 2011; Ishaque et al., 2012). The main pharmacological effects summarized in these reviews include adaptogenic and stress-protective (neuro-cardio and hepato- protective) effects; stimulation of the CNS, including cognitive functions such as attention, memory, and learning; anti-fatigue, antidepressive and anxiolytic effects; increases in lifespan; cardioprotective effects; and the normalization of endocrine activity. It is interesting that the effect of *Rhodiola* on the CNS does not depend linearly on the dose. The dose-dependent activity curve is bell-shaped; in small doses, *Rhodiola* is inactive; at intermediate doses, *Rhodiola* is active; and at high doses, it becomes inactive again (Kurkin et al., 2003; Perfumi, Mattioli, 2007; Wiegant et al. 2009; Panossian et al., 2010). Table 25 summarizes some pharmacological studies that have been undertaken on *Rhodiolae roseae* and that are reported in the literature.

A systematic review of randomized clinical trials of *R. rosea* was published by Hung et al. (2011). Orally administered for 2–6 weeks, a dry SHR-5 extract prepared with EtOH 70% (v/v) and administered in daily doses of 288–680 mg (1–4 tablets) has been shown to improve mood (Darbinyan et al., 2007), cognitive performance and attention, and to relieve fatigue (Darbinyan et al., 2000; Spasov et al., 2000; Shevtsov et al., 2003; Olsson et al., 2009) in stress-related conditions. In an endurance exercise performance test, 24 healthy volunteers who were treated with 100 mg of *R. rosea* extract (containing 3% rosavin + 1% salidroside) exhibited significant ($p < 0.05$) increases in time to exhaustion, $VO_2$, $VCO_2$, peak $O_2$ output, and peak $CO_2$ output (De Bock et al., 2004). Recovery after exercise was facilitated after the treatment of untrained subjects with 340 mg RHODAX (a preparation containing 30 mg of the active substances of *R. rosea* extract) twice a day for 30 days before and 6 days after exhausting physical exercise (Abidov et al., 2004).

Based on the abovementioned studies and other data, the EMA's Community herbal monograph on *Rhodiola rosea* L. *rhizoma et radix* (EMA/HMPC/232091/2011) approved its use in 2011 for the temporary relief of symptoms associated with stress, such as fatigue, exhaustion and mild anxiety for traditional use only. *R. rosea* is a popular plant in traditional medical systems in the Nordic countries, Eastern Europe, and Asia, and has a very well-documented reputation as an adaptogen. No major risks have been associated with *R. rosea.* An extract of *Rhodiola* is available in Russia in pharmacies without a prescription and is recommended for internal administration at the dose of 5–10 drops, 2–3 times a day, for 20 days (1–2 months in psychiatric praxis) as a CNS stimulant and as an adaptogen (Sokolov, 2000). However, it is important to reproduce and confirm the pre-clinical studies and to perform large-scale clinical trials according to GCP.

### 5.18. No pharmacological group is stated in the Pharmacopoeia

#### 5.18.1. HERBA POLYGONI PERSICARIAE

*Persicaria maculosa* Gray (syn. *Polygonum persicaria* L.), Polygonaceae, also known as lady's thumb, is a perennial plant that grows up to 1 m high and has narrow, lancet-shaped leaves that are 8–10 cm long. A decoction and an infusion have been used in

**Table 24**
Summary of Pharmacological Studies for *Aralia.*

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Antiarrhythmic | *in vivo.* Rats, coronary occlusion and reperfusion | Roots | Aqueous extract | Intragastric | 16 mg/kg, 5 days | Negative control | Improvement heart resistance to arrhythmogenic effect of ischemia and reperfusion. 86% of animals receiving extract before coronary occlusion developed no arrhythmias, *vs.* 19% in controls. Severity of arrhythmia in treated rats was 74% lower during ischemia and coronary blood flow recovery than controls. | Maslov et al., 2009 |
| Anticancer | *in vitro.* Human kidney cancer cell lines GRC-1 and 786-O | Roots | Isolated araloside A | in vitro | 1, 3, 10, 30, 100 μM | Negative control | Reduction of cellular viability of booth cells in a dose- and time-dependent manner. Number of Tunnel-positive cancer cells was higher in cells treated with Araloside A than untreated cells. Araloside A increased expression of bax mRNA and inhibited expression of bcl-2 mRNA. | Yu et al., 2011 |
| Anticataract | *ex vivo.* Rat lenses from male Sprague-Dawley rats. Sugar cataract was induced by adding of (+)-xylose to media | Bark | Aqueous extract with 7% yield | 24 well plate | 0.5, 1 mg/mL | Negative control | After treatment at 1 mg/mL lens opacity was lowered by 36.4 and 31.3% after 24 and 48 h, respectively | Chung et al., 2005 |
| Anticataract | *in vivo.* STZ-induced diabetic rats | Bark | Aqueous extract with 7% yield | Per oral | 300, 600 mg/kg daily, 11 weeks after STZ administration | Negative control | After treatment with 300 or 600 mg/kg extract the opacities of lenses decreased by 15% and 12% respectively. | Chung et al., 2005 |
| Anti-inflammatory | *in vitro.* Murine macrophage cell line (RAW 264.7), lipopolysac-charide-activated macrophages | Roots | Isolated saponin elatoside F | 96-well plates 24-well plates | 0.96, 9.6, 48, 96 μM | Negative, Positive control: tosyl phenylalanyl chloromethyl ketone, | Inhibition of LPS-induced NO production in 28.8, 43.2, 67.9, and 81.2% at 0.96, 9.6, 48, and 96 μM. Inhibition of NF-κB activity in 20.4, and 33.7% at 48 μM, and 96 μM respectively. | Lee et al., 2009 |
| Antiulcer | *in vivo.* Aspirin-induced ulcer. HCl-EtOH induced gastric lesions. | Root bark | Isolated araloside A | Per oral | 50, 100 mg/kg | Negative control. Positive control: cimetidine. | Reduction of HCl-EtOH-induced gastric lesions and aspirin-induced gastric ulcers. Antiulcer action may be due to the inhibition of gastric acid secretion | Lee et al., 2005 |
| Cardioprotective | *in vivo.* Cardiac dysfunction in STZ induced diabetes rats. | Roots | Total aralosides, no details about isolation. | Per oral | 4.9, 9.8, 19.6 mg/kg, for 8 weeks | | Prevents diabetes-induced cardiac dysfunction by increased absolute value of left ventricular systolic pressure and maximum rates of pressure development, and enhanced amplitude of $I_{Ca}^{2+}$ in cardiac cells and decreasing connective tissue growth factor expression. High dose, but not low prevented cardiac ultrastructural changes in diabetic rats, indicated by closely lining up of myofilaments and almost normal structure of mitochondria | Xi et al., 2009 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cardioprotective | *In vitro*. Injury induced by $H_2O_2$, in H9c2 cells | Root bark | Water-soluble polysaccharide AEP-w1 (Mr $4.5 \times 10^4$ Da). Monosaccharide components: arabinogalactan, consisting of arabinose, galactose and trace glucose with molar ratios of 6.3:3.5:0.2. | 96-well plates | 100, 200, 400 μg/mL | Negative control | AEP-w1 suppressed cardiomyocyte apoptosis, the mitochondrial membrane potential change and cytochrome C release in $H_2O_2$-treated H9c2 cells. Intracellular reduced glutathione (GSH) reduction caused by $H_2O_2$ in H9c2 cells was restored by AEP-w1 pretreatment. | Zhang et al., 2013 |
| Gastroprotective | *in vivo*. Rats, cold-restraint stress (CRS), pylorus ligation | Roots | EtOH (50%) extracts | Intraperitoneal | 50 mg/kg, 30 min pretreatment | Negative control. | Pretreatment reduced incidence and severity of CRS-induced gastric glandular lesions. Gastric secretory volume was reduced, increased intraluminal gastric pH and decreased acid output. | Hernandez et al., 1988 |
| Hypoglycemic | *in vivo*. Rats, glucose tolerance test (GTT) | Root bark | Isolated oleanolic acid and 9 oligoglyosides | Per oral | 100 mg/kg, single administration | Negative control. | 3-O-monodesmo-sides elatosides A and E, stipuleano-side $R_1$ and oleanolic acid 3-O-glycosides showed potent inhibitory activity in GTT | Yoshikawa et al., 1996 |
| Hypoglycemic | *in vivo*. Rats, rabbits with high cholesterol diet. | Root | Saparal (mixture of ammonium salts of aralosides A, B, C) | Per oral | 10, 23, 58 mg/kg, 3 days (rats), 58 mg/kg (rabbits) | Negative control. | Blood serum cholesterol in rats was reduced by 29.8% comparing to control at 58 mg/kg. Level of cholesterol in the aorta was reduced by 31.7%. In rabbits blood cholesterol was reduced by 61.4%. | Voskanyan et al., 1983 |

Russian traditional medicine for the treatment of hemorrhoidal bleeding and as a laxative and a diuretic (Vereschagin et al., 1959). The infusion of *P. persicaria* is recommended to treat patients with atonic constipation (Sokolov, 2000). The infusion and an EtOH 70% extract of the aerial parts increase gastrointestinal motility, induce vasoconstriction in blood vessels, increase blood viscosity and activate blood coagulation in rabbits (Samarina, 1950). Antihypertensive properties were demonstrated in frogs and guinea pigs (Samarina, 1948). A laxative effect and increased diuresis were observed in mice after administration of an EtOH (70%) extract of *P. persicaria* (Belikova, 1944).

Reportedly, the aerial parts of *P. persicaria* have very low toxicity (Sokolov, 2000); however, no details are available. A limited number of pharmacological studies regarding *Herba polygoni persicariae* are available (Table 26).

A single-arm, uncontrolled, non-blinded study was performed on a group of 34 patients suffering from hemorrhoids. The patients were treated with an infusion of *P. persicaria* three times a day before meals for 7–21 days at doses 20-100 mL. Positive results were observed in 27 patients. Subjective complaints decreased, bowel movements became regular, bleeding stopped completely or decreased, and a diuretic effect was observed (Turova, Sapozhnikova, 1989).

Aerial parts of *P. persicaria* are available in pharmacies without a prescription and are recommended at the dose of 20 mL of infusion (20 g in 200 mL of water) taken 3 times per day to treat chronic atonic constipation and hemorrhoids (Sokolov, 2000). However, the chemical and pharmacological evidence to support these medical applications, especially as a antihypertensive, dates from the early 1940s and needs further confirmation.

### 5.18.2. HERBA THERMOPSIDIS LANCEOLATAE

*Thermopsis lanceolata* R. Br. (bush pea, Leguminosae) is a perennial plant attaining 40 cm in height. The aerial part is harvested before flowering. Decoctions are used in Russia to treat respiratory catarrh, flu, bronchitis, pneumonia and headaches (Akopov, 1990; Mamedov, Craker, 2001). In China, *T. lanceolata* is used to stimulate breathing and prevent coughs (Li et al., 2007). The dry extract of *Thermopsis* (using 25% EtOH as an extragent) was proposed in USSR in 1933 as an expectorant and to promote the thinning and removal of secretions (Vereschagin et al., 1959). The standardized extract Cytiton (containing 0.15% cytosine and obtained from the seeds of *T. lanceolata*) has been prescribed to stimulate respiratory function, improve blood circulation and treat asphyxia (Khalmatov et al., 1984; Gammerman et al., 1984).

Various extracts of *T. lanceolata* have all shown to be toxic. The toxicity of a MeOH extract was studied in mice after per oral administration. All mice died within 2–2.5 min after the single acute administration of 300 mg/kg of extract. After 60 days of chronic administration at the dose of 50 mg/kg, this material was found to be toxic (Zhu et al., 2003). Toxicity resulted in paroxysmal supraventricular and ventricular tachycardia and extrasystoles (Chatval, 2009). In low doses, dry extracts of *T. lanceolata* excite the respiratory center; in high doses, these extracts can cause vomiting and paralyze the centers of the brain and the medulla oblongata. The maximal single dose of the aerial part for adults is 0.1 g, and the maximal daily dose is 0.3 g (Sokolov, 2000). The acute toxicity of cytisine (the main quinolizidine alkaloid in *T. lanceolata*) was studied in rats and mice. The $LD_{50}$ was estimated at 5–50 mg/kg body weight in rats after per oral administration. In repeated dose toxicity studies, cytisine was administered to the rats for 30 and 90 days at the doses of 7.6 mg/kg and up to 1.35 mg/kg, respectively. No changes were observed in clinical laboratory parameters or histomorphology in experimental animals. When applied chronically in mice (3.3 mg/kg) for 45 days

**Table 25**
Summary of Pharmacological Studies for *R. roseae.*

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Adaptogenic and CNS | *in vivo.* Mice, forced-swimming test, swimming to exhaustion, light/dark exploration, open field, tail-flick | Roots | Commercial EtOH extract (containing 3% rosavin and 1% salidroside) | Intragastric | 10, 15, 20 mg/kg / single dose | Negative control | Induction antidepressant-like, adaptogenic, anxiolytic-like and stimulating effects. Bell shaped dose-activity curve | Perfumi, Mattioli, 2007 |
| Adaptogenic | *in vivo.* Rats, exhaustive swimming | Rhizome and roots | EtOH (60% v/v) extract with 3.02% rosavines and 0.89% salidroside | Intragastric | 50 mg/kg/ single dose | Negative control | Prolonged duration of swimming (by 24.6%). Activated the synthesis or resynthesis of ATP in mitochondria. | Abidov et al., 2003 |
| Anticancer | *in vitro.* Human lymphoblastoid Raji cells | Roots | Crude EtOH (40%) extract | *in vitro* | 10, 50, 200 μg/mL | Positive control: methotrexate fluorouracil, cyclophosphamide, vinblastine. Negative control | 99% growth inhibition at 200 μg/mL; 75% inhibition at 50 μg/mL with formation of giant polyploid cells. | Spiridonov et al., 2005 |
| Antiarrhythmic | *in vivo.* Rats, isolated heart. | Roots | EtOH (40%) extract | Per oral | 3.5 mL/kg, 8 days | Negative control, Positive control: Naloxone, ICI 174,864 | Prevention reperfusion arrhythmias and elicitation protective effect in experiments on isolated heart in interrupting the perfusion with Krebs–Henseleit solution followed by reperfusion. Antiarrhythmic effect was mediated through activation of μ-opiate receptors in myocardium. | Maslov et al., 1997 |
| Antiviral | *in vitro.* Plaque reduction assay *in vivo.* BALB/c mice, Sprague-Dawley (SD) rats Coxsackievirus B3 (CVB3) | Roots | Salidroside (purity 99%) | Per oral | 20, 60, 80 mg/kg / 7 days | Negative control. Positive control: ribavirin | Antiviral effects both *in vitro and in vivo*. Salidroside modulate the mRNA expression of interferon-γ, interleukin-10 (IL-10), TNF-α, and interleukin-2 (IL-2). | Wang et al., 2009 |
| Antiviral | *in vitro.*Virus-induced cytopathic effect (CPE) in Madin-Darby canine kidney (MDCK) cells Viruses: H1N1 (A/PR/8/34) and H9N2 (A/Chicken/ Korea/ MS96/96). | Roots | Aqueous, EtOAc extracts. Isolated kaempferol, herbacetin, rhodiolinin, rhodionin, and rhodiosin | in vitro. | Initial concentration 5 mM | Negative control. Positive control: oseltamivir (Tamiflu) | EtOAc extract $EC_{50}$= 102.1 μg/mL against H1N1 and 145.4 μg/mL against H9N2. Aqueous extract $EC_{50}$=78.5 μg/mL against H1N1 and 139.7 μg/mL against H9N2. For kaempferol, herbacetin, and rhodiolinin $EC_{50}$= 30.2, 35.0, and 41.7 μM against H1N1- and 18.5, 23.0, and 29.3 μM against H9N2. | Jeong et al., 2009 |
| Antiviral | *in vitro.* HIV-1 protease inhibition | Roots | MeOH extract | in vitro. | 100 μg/mL | Negative control. Positive control: acetyl pepstatin | 70.4% inhibition of HIV-1 protease | Min et al., 1999 |
| Hypotensive | *in vivo.* SHR rats. | Roots | Aqueous extract with salidroside (8.4 mg/g) and p-tyrosol (1.9 mg/g). | Per oral | 35, 50, 75 mg/kg | Negative control | Dose-dependent decrease systolic blood pressure and increase β-endorphin release. | Lee, et al., 2013. |
| Neurotropic | *in vivo.* Mice, thiopental-induced sleep | Roots | EtOH extract | Per oral | 10–500 mg/kg | Negative control | Stimulation at 10 mg/kg (sleep period reduced by 12.5 times), sedation at 500 mg/kg (sleep period was increased 3-fold) | Kurkin et al., 2003 |

**Table 26**
Summary of Pharmacological Studies for *Herba polygoni persicariae*

| Activity tested | Model used | Plant part used | Extract type | Admin | Dosage/ duration | Control | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Anticancer | *in vitro*. Cervical carcinoma HeLa, acute monocytic leukemia THP-1 cell lines. Sulphorhodamine B cell growth inhibition assay | Aerial part | Isolated cardamomin, pinostrobin | 96 well plate | 1, 10, 30, 50, 100 μg/mL | Negative control. Positive control: paclitaxel | For cardamomin $IC_{50}$=1.8 μg/mL against THP-1 and 17 μg/mL against HeLa. For pinostrobin $IC_{50}$=9 μg/mL against THP-1 | Dzoyem et al., 2012 |
| Antifungal | *in vitro*. Microbroth dilution assay. *C. albicans, S. cerevisiae, Cryptococcus neoformans, Aspergillus flavus, As. fumigatus, As. niger, Trichophyton rubrum, Tr. mentagrophytes, Microsporum gypseum.* | Aerial part | Dichlormethane extract. Isolated polygodial, isopolygodial, and cardamonin. | in vitro. | Initial concentration 100 μL | Negative control. Positive control: retoconazole, amphotericin, terbinafine | MIC (μg/mL ) for dichloro-methane extract was 31.2 against *Tr. Mentagrophytes;* polygodial 3.9 against *C. albicans*, 7.8 against *C. neoformans*, *Tr. rubrum*, *Tr. Mentagrophytes, and* 15.6 against *S. cerevisiae;* cardamonin 15.6 against *Tr. rubrum*, and *Tr. mentagrophytes* | Derita, Zacchino, 2011 |
| Anti-inflammatory | *in vivo*. Carrageenan-induced edema in rats | Aerial part | EtOH extract | Intraperito-neal | Not provided | Negative control. | Anti-inflammatory activity. | Yano et al., 2011 |

and in rats (0.45 and 0.9 mg/kg) and dogs (0.45 mg/kg) for 6 months, cytisine was not found to cause any changes in clinical laboratory and histomorphological parameters in the animals; however, some light liver dystrophic changes were observed (Tzankova and Danchev, 2007). Overall, very limited pharmacodynamics data are available.

No clinical data on *T. lanceolata* were found. Currently, the aerial parts of *T. lanceolata* are not available in pharmacies. "Cough tablets" (containing 0.0067 g of powdered aerial parts of *T. lanceolata* and 0.25 g of $NaHCO_3$) are available in Russia in pharmacies without a prescription and are recommended for use as an expectorant at the dose of 3 tablets per day taken for 3–5 days. Tablets containing 0.05 g of a standardized dry extract of *T. lanceolata* (1% of alkaloids) are recommended for adults as an expectorant at the dose of 2–3 tablets per day (Sokolov, 2000). The dry cough mixture, containing 0.045 g of a standardized dry extract of *T. lanceolata* per dose, is recommended for use by adults as an expectorant at 1 dose dissolved in a tablespoon of water, to be taken 3–4 times per day (Mashkovskii, 2002). The information available regarding the chemical and pharmacological effects of this material is insufficient, and use of the drug use cannot be recommended until more detailed studies (especially on its safety) become available.

## 6. Conclusions

This review article examines the data on medicinal plants included in the Russian Pharmacopoeia, which have been used for many years in the officinal Russian medicine; these plants are not very well known as medicines outside of their region of origin. Only 83 medicinal plants are referenced in the State Pharmacopoeia of the USSR ($11^{th}$ ed.), which provides the results of sophisticated scientific investigations and practical evaluation. All medicinal plants were evaluated by professionals involved in drug regulatory affairs based on state standards. The *in vivo* and *in vivo* effects and, in some cases, the effectiveness and safety of HMPs have been studied in considerable detail. However, our analysis is limited, for example, by the fact that many unpublished documents are deposited in the regulatory archive that are not available to the public.

During most of the Soviet period, the country was closed not only from a political point of view, but also scientifically. Many scientific articles were never translated into English, and much information collected by scientists was not made available for the international community. In this review, we summarize and critically assess data that were published in Russia and other countries on medicinal plants that have a long history of often well-studied application in the Russian Federation; the review highlights the potential for further developing these herbal medicines.

Most importantly, Soviet / Russian scientists contributed significantly to the development of plant-derived adaptogens – tonics that play an important role in the regulation of metabolism. *Aralia*, *Rhodiola*, and Chaga are good examples of adaptogens that have been studied extensively (especially in the USSR / Russia). Modern research on the molecular mechanisms of action of these drugs are essential to improving our understanding of the effects of adaptogens and their potential to improve many aspects of neuropsychiatric disorders, including perceived energy levels, cognitive function, memory, attention, and mental and physical performance, particularly under stress.

Great potential is exhibited by the group of plants with expectorant effects. However, further studies are required to develop the potential of these plants to yield more efficient

treatments. In this and other cases, the risks of adulteration must be monitored carefully.

Four plants mentioned in the Pharmacopoeia of the USSR are diuretics and three are astringents. It is interesting that the rhizomes of *Bergenia crassifolia* are known as astringents but the leaves appear to meet the criteria required for being an adaptogen. A number of positive effects, especial antihypertensive effects, are attributed to *G. uliginosum. However,* publications regarding the chemistry and pharmacological effects of this material are fragmentary.

We hope that this analysis will foster more detailed research and development on some of these medicinal plants. It is important to reproduce and confirm the non-clinical studies and to perform clinical trials of the mentioned medicinal plants according to GCP.

## References


Abad, M.J., Bermejo, P., Villar, A., 1995. An approach to the genus Tanacetum L. Compositae): phytochemical and pharmacological review. Phytotherapy Research 9, 79–92.

Abbet, C., Mayor, R., Roguet, D., Spichiger, R., Hamburger, M., Potterat, O., 2014. Ethnobotanical survey on wild alpine food plants in Lower and Central Valais (Switzerland). Journal of Ethnopharmacology 160 (1), 624–634.

Abderhalden, E., 1935. Handbuch der biologischen Arbeitsmethoden, 4. Urban & Schwarzenberg, Leipzig p. 1289.

Abidov, M., Crendal, F., Grachev, S., Seifulla, R., Ziegenfuss, T., 2003. Effect of extracts from Rhodiola rosea and Rhodiola crenulata (Crassulaceae) roots on ATP content in mitochondria of skeletal muscles. Bulletin of Experimental Biology and Medicine 136 (6), 585–587.

Abidov, M., Grachev, S., Seifulla, R.D., Ziegenfuss, T.N., 2004. Extract of Rhodiola rosea radix reduces the level of C-reactive protein and creatinine kinase in the blood. Bulletin of Experimental Biology and Medicine 138, 63–64.

Abidov, M., Rio, M., Ramazanov, T., 2006. Effects of Aralia mandshurica and Engelhardtia chrysolepis extracts on some parameters of lipid metabolism in women with nondiabetic obesity. Bulletin of Experimental Biology and Medicine 141, 343–346.

Akopov, I.E., 1990. The most important native medicinal plants and their uses. Meditsina, Tashkent.

Albayrak, S., Aksoy, A., Sagdiç, O., Budak, U., 2010. Phenolic compounds and antioxidant and antimicrobial properties of helichrysum species collected from eastern Anatolia, Turkey. Turkish Journal of Biology 34, 463–473.

Alm, T., 2004. Ethnobotany of Rhodiola rosea (Crassulaceae) in Norway. SIDA Contributions to Botany 21, 321–344.

Alm, T., Iversen, M., 2010. Norway's Rosmarin (Rhododendron tomentosum) in past and present tradition. In: Pardo-de-Santayana, M, Pieroni, A, Puri, RK (Eds.), Ethnobotany in the New Europe: people, health and wild plant resources. Berghahn Books, pp. 263–270.

Alvarez, A.L., Habtemariam, S., Juan-Badaturuge, M., Jackson, C., Parra, F., 2011. in vitro anti HSV-1 and HSV-2 activity of Tanacetum vulgare extracts and isolated compounds: An approach to their mechanism of action. Phytotherapy Research 25, 263–301.

Appleby, J.H., 1983. Ivan the Terrible to Peter the Great: British formative influence on Russia's medico-apothecary system. Medical History 27 (3), 289–304.

Arif, R., Kupeli, E., Ergun, F., 2004. The biological activity of Centaurea L. species. Gazi University Journal of Science 17, 149–164.

Aronson, J.K., 2009. Meyler's Side Effects of Herbal Medicines. Elsevier p. 118.

Artemova, A., 2001. Birch for Healing and Rejuvenating. Dilya, Moscow – St, Petersburg, pp. 29–32.

Bafghi, A.F., Noorbala, M.T., Hejazian, S.H., 2008. The effect of Rubia tinctorium extract on cutaneous leishmaniasis in BALB/c mice. World Journal of Zoology 3, 25–29.

Barceloux, D.G., 2008. Coltsfoot (Tussilago farfara L.), in Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals. John Wiley & Sons, Inc., Hoboken, NJ, USA, pp. 447–448.

Barnaulov, O.D., Manicheva, O.A., Shelyuto, V.L., Konopleva, M.M., Glyzin, V.I., 1984. Effect of flavonoids on development of experimental gastric dystrophies in mice. Pharmaceutical Chemistry Journal 18, 544–549.

Bashmurin, A.F., 1951. About diuretic and choleretic effects of preparations from blue cornflower. Pharmacology and toxicology 14, 53–55.

Basova, E.V., 2004. Chemical and pharmacological study of wild rosemary. PhD dissertation. Tomsk. ⟨http://medlib.tomsk.ru/fulltext/130278.pdf⟩.

Bekhterev, V.M., 1898. The importance of a mixture of Adonis vernalis or Digitalis with bromides or codeine in the treatment of epilepsy. Review of Psychiatry (in Russian) 9, 679.

Belikova, A.P., 1944. About laxative effect of plants of Polygonaceae family. Pharmakologia I toxicologia 7, 59.

Belousov, M.V., Belousova, N.I., Berezovskaya, T.P., Dmitruk, S.E., Klokova, M.V., Komissarenko, N.F., Kulpina, T.G., Serykh, E.A., 1998. New pharmacological properties of the raw material of Ledum palustre L. of siberian flora and the possibilities of its complex usage. Rastitelnye Resursy 30, 74–82.

Belousov, M.V., Saratikov, A.S., Akhmedzhanov, R.R., Berezovskaya, T.A., Yusubov, M. S., Dmitruk, S.E., Basova, E.V., 2006. Pharmacological properties of Ledum palustre (Ericaceae) from Tomsk region. Rastitelnye Resursy 42, 130–140.

Belousov, M.V., Saratikov, A.S., Tshichalin, V.S., Akhmedganov, R.R., Berezovskaya, T. P., Basova, E.V., Yusubov, M.S., 2007. Hepatoprotective properties of Ledum palustre (Ericaceae) shoots dry extract. Rastitelnye Resursy 43, 126–129.

Berg, W, Hesse, A, Hensel, K, Unger, G., Hartmann, U., Schneider, H.J., 1976. Einfluss von Anthrachinonderivaten auf die tierexperimentelle Harnsteinbildung. Urologe A 15, 188–191.

Bhakuni, D.S., Dhar, M.L., Dhar, M.M., Dhawan, B.N., Gupta, B., Srim, R.C., 1971. Screening of Indian plants for biological activity. Part III. Indian Journal of Experimental Biology 9, 91–102.

Blinova, K.F., Yakovlev, G.P. (Eds.), 1990. Botanical Pharmacognostic Dictionary. Vysshaya shkola, Moscow.

Bokova, T.I., Vasil'tsova, I.V., 2011. Evaluation of the biological activity of birch buds and leaves in model investigations. Contemporary Problems of Ecology 4, 647–650.

Borisova, N.A., Stankevich, N.B., Davydov, V.V., 1984. Biological activity of the raw material of Convallaria majalis L. stocked in the Leningrad region. Farmatsiya-Moscow 33, 9–11.

Boyeva, S.A., Brezhneva, T.A., Maltseva, A.A., Buzlama, A.V., Slivkin, A.I., 2007. Saponins of the Polemonium caeruleum L. and Beta vulgaris L. plants. The features of obtaining, the comparative assessment of the hypoglycemic activity. Proceedings of Voronezh State University: Chemistry, Biology, Pharmacy 1, 139-141.

Brekhman, I.I., Dardymov, I.V., 1969. New substances of plant origin which increase nonspecific resistance. Annual Review of Pharmacology 9, 419–430.

Brown, R.P., Gerbarg, P.L., Ramazanov, Z., 2002. Rhodiola rosea: a phytomedicinal overview. Herbal Gram 56, 40–52.

Bruneton, J., 1995. Pharmacognosy, Phytochemistry, Medicinal Plants. Tec-Doc Lavoisier, Paris, New York, pp. 310–311.

Bulatov, P.K., Berezina, M.P., Yakimov, P.A., 1959. Chaga and its use for the treatment of stage IV cancer. Medgiz, Leningrad, pp. 261–312.

Bundesgesundheitsamt, 1992. Abwehr von Arzneimittelrisiken. Stufe II. (Defence against medicine risks. stage II.) BAnz no. 111, vom 17.6.1992. Pharmazeutische Industrie 54, 177–181.

Buniatian, N.D., Chikitkina, V.V., Iakovleva, L.V., 1998. The hepatoprotective action of ellagotannins. Eksperimental'naia i Klinicheskaia Farmakologiia 61 (5), 53–55.

Burgos, R., Hancke, J., Wikman, G., Cubillos, V., Caballero, E., Oyarzo, M., Sanchez, N., 1994. Toxicological assessment of Aralia mandshurica (Araliaceae) root extract after subchronic administration in rats. A biochemical and histological study. Phytotherapy Research 8 (1), 1–9.

Burgos, R.A., Hancke, J.L., Cáceres, D.D., Wilkman, G., Fuenzalida, H., 1997. Hepatotoxic effect of Aralia mandshurica dried root extract in pigs. Phytotherapy Research 11 (1), 59–61.

Buturlin, V.V., 1953. Results of application of Gnaphalium uliginosum in hypertension. Sovetskaia meditsina 17, 40–42.

Cam, M., Hisil, Y., Kuscu, A., 2007. Organic acid, phenolic content, and antioxidant capacity of fruit flesh and seed of Viburnum opulus. Chemistry of Natural Compounds 43 (4), 460–461.

Campbell, A., Chapman, M., 2000. Handbook of poisoning in dogs and cats. Chapter 59. Rowan/*Sorbus aucuparia*. Blackwell Science, MA p. 234.

Cantrell, C.L., Abate, L., Fronczek, F.R., Franzblau, S.G., Quijano, L., Fischer, N.H., 1999. Antimycobacterial eudesmanolides from Inula helenium and Rudbeckia subtomentosa. Planta Medica 65, 351–355.

Česoniene, L., Daubaras, R., Viškelis, P., Šarkinas, A., 2012. Determination of the total phenolic and anthocyanin contents and antimicrobial activity of Viburnum opulus fruit juice. Plant Foods for Human Nutrition 67 (3), 256–261.

Chatval, N.A., 2009. Cardiac arrhythmia caused by herbal remedies. Fundamental research 7, 65–66.

Chen, K.K., Anderson, R.C., 1947. Digitalis-like action of some new glycosides and esters of strophanthidin. Journal of Pharmacology and Experimental Therapeutics 90, 271–275.

Chen, K.K., Brown Robbins, E., Bliss, C.I., 1942. The digitalis-like principles of Calotropis compared with other cardiac substances. Journal of Pharmacology and Experimental Therapeutics 74, 223–234.

Cheng, H.-Y., Lin, T.-C., Yang, C.-M., Shieh, D.-E., Lin, C.-C., 2005. in vitro anti-HSV-2 activity and mechanism of action of proanthocyanidin A-1 from Vaccinium vitis-idaea. Journal of the Science of Food and Agriculture 85 (1), 10–15.

Chernetsova, E.S., Crawford, E.A., Shikov, A.N., Pozharitskaya, O.N., Makarov, V.G., Morlock, G.E., 2012. ID-CUBE direct analysis in real time high-resolution mass spectrometry and its capabilities in the identification of phenolic components from the green leaves of Bergenia crassifolia L. Rapid Communications in Mass Spectrometry 26 (11), 1329–1337.

Chernetsova, E.S., Shikov, A.N., Crawford, E.A., Grashorn, S., Laakso, I., Pozharitskaya, O.N., Makarov, V.G., Hiltunen, R., Galambosi, B., Morlock, G.E., 2014. Characterization of volatile and semi-volatile compounds in green and fermented leaves of Bergenia crassifolia L. by gas chromatography-mass spectrometry and ID-CUBE direct analysis in real time-highresolution mass spectrometry. European Journal of Mass Spectrometry 20 (2), 199–205.

Cho, J., Kim, H.M., Ryu, J.H., Jeong, Y.S., Lee, Y.S., Jin, C., 2005. Neuroprotective and antioxidant effects of the ethyl acetate fraction prepared from Tussilago farfara L. Biological and Pharmaceutical Bulletin 28, 455–460.

Choi, D.H, Kang, D.G., Cui, X., Cho, K.W., Sohn, E.J., Kim, J.S., Lee, H.S., 2006. The positive inotropic effect of the aqueous extract of Convallaria keiskei in beating rabbit atria. Life Science 79, 1178–1185.
Chung, Y.S., Choi, Y.H., Lee, S.J., Choi, S.A., Lee, J.H., Kim, H., Hong, E.K., 2005. Water extract of Aralia elata prevents cataractogenesis in vitro and in vivo. Journal of Ethnopharmacology 101, 49–54.
Churin, A.A., Masnaya, N.V., Sherstoboev, E.Yu., Suslov, N.I., 2005. Effect of Bergenia crassifolia extract on specific immune response parameters under extremal conditions. Eksperimental'naya i Klinicheskaya Farmakologiya 68 (5), 51–54.
Committee for the Pharmacopoeia of People's Republic of China, 2010. Pharmacopoeia of People's Republic of China, Part 1. Chemical Industry Publishing House, Beijing, China p. 312.
Czinner, E., Hagymási, K., Blázovics, A., Kéry, Á., Szoke, É., Lemberkovics, É., 2001. The in vitro effect of Helichrysi flos on microsomal lipid peroxidation. Journal of Ethnopharmacology 77, 31–35.
Czinner, E., Hagymási, K., Blázovics, A., Kéry, Á., Szőke, É., Lemberkovics, É., 2000. in vitro antioxidant properties of Helichrysum arenarium (L.) Moench. Journal of Ethnopharmacology 73, 437–443.
Dampc, A., Luczkiewicz, M., 2013. Rhododendron tomentosum (Ledum palustre). A review of traditional use based on current research. Fitoterapia 85, 130–143.
Darbinyan, V., Aslanyan, G., Amroyan, E., Gabrielyan, E., Malmstrom, C., Panossian, A., 2007. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nordic Journal of Psychiatry 61, 2343–2348.
Darbinyan, V., Kteyan, A., Panossian, A., Gabrielian, E., Wikman, G., Wagner, H., 2000. Rhodiola rosea in stress induced fatigue - a double blind cross-overstudy of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine 7, 365–371.
Das, H., Raghav, S., Gupta, B., Das, R.H., 2007. Anti-inflammatory compounds from medicinal plant Ruta graveolens. Acta Horticulturae 756, 389–398.
De Bock, K., Eijnde, B.O., Ramaekers, M., Hespel, P., 2004. Acute Rhodiola rosea intake can improve endurance exercise performance. International Journal of Sport Nutrition and Exercise Metabolism 14, 298–307.
Delaquis, P.J., Stanich, K., Girard, B., Mazza, G., 2002. Antimicrobial activity of individual and mixed fractions of dill, cilantro, coriander and eucalyptus essential oils. International Journal of Food Microbiology 74, 101–109.
Derita, M., Zacchino, S., 2011. Validation of the ethnopharmacological use of Polygonum persicaria for its antifungal properties. Natural Product Communications 6, 931–933.
Deriu, A., Zanetti, S., Sechi, L.A., Marongiu, B., Piras, A., Porcedda, S., Tuveri, E., 2008. Antimicrobial activity of Inula helenium L. essential oil against Gram-positive and Gram-negative bacteria and Candida spp. International Journal of Antimicrobial Agents 31 (6), 588–590.
Dorn, D.C., Alexenizer, M., Hengstler, J.G., Dorn, A., 2006. Tumor cell specific toxicity of Inula helenium extracts. Phytotherapy Research 20, 970–980.
Dosychev, E.A., Bystrova, V.N., 1973. Treatment of psoriasis using chaga fungus preparations. Vestnik Dermatologii i Venerologii 5, 79–83.
Dragendorff, G.G., 1879. Relationship between the chemical constituents and botanical features of plants. Pharmaceutical journal, 14–17.
Du, X., Mu, H., Zhou, S., Zhang, Y., Zhu, X., 2013. Chemical analysis and antioxidant activity of polysaccharides extracted from Inonotus obliquus sclerotia. International Journal of Biological Macromolecules 62, 691–696.
Duraipandiyan, V., Indwar, F., Ignacimuthu, S., 2010. Antimicrobial activity of confertifolin from Polygonum hydropiper. Pharmaceutical Biology 48 (2), 187–190.
Duric, K., Kovac-Besovic, E., Niksic, H., Sofic, E., 2013. Antibacterial activity of methanolic extracts, decoction and isolated triterpene products from different parts of birch, Betula pendula, Roth. Journal of Plant Studies 2 (2), 61–70.
Dzoyem, J.P., Nkuete, A.H.L., Kuete, V., Tala, M.F., Wabo, H.K., Guru, S.K., Rajput, V.S., Sharma, A., Tane, P., Khan, I.A., Saxena, A.K., Laatsch, H., Tan, N.-H., 2012. Cytotoxicity and antimicrobial activity of the methanol extract and compounds from Polygonum limbatum. Planta Medica 78 (8), 787–792.
Edwards, D., Heufelder, A., Zimmermann, A., 2012. Therapeutic effects and safety of Rhodiola rosea extract WS® 1375 in subjects with life-stress symptoms - Results of an open-label study. Phytotherapy Research 26, 1220–1225.
Ehrlen, J., Eriksson, O., 1993. Toxicity in fleshy fruits - a non-adaptive trait? Oikos 66, 107–113.
Erdoğan Orhan, I., Özçelik, B., Kartal, M., Kan, Y., 2012. Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. Turkish Journal of Biology 36 (3), 239–246.
Faraschuk, E.F., 1972. Application of Bidens tripartita extract for the treatment of patients with psoriasis. In Proceedings of All-Union Scientific Conference in pharmacological and clinical investigation of herbal medicinal preparations. Moscow, p. 165.
Fedukovich, N.N., 1960. Experience in the utilization of a new preparation from Polygonum hydropiper - hydropiperin in prevention of obstetrical and gynecological hemorrhages. Sovetskaia meditsina 24, 123–126.
Felter, H.W., 1922. Eclectic Materia Medica, Pharmacology and Therapeutics. Eclectic Medical Publications, Sandy, OR ([reprinted 1998]).
Franz, G., 1969. Untersuchungen über die Schleimpolysaccharide von Tussilago farfara L., Symphytum officinalis L., Borago officinalis L. und Viola tricolor L. Planta Medica 17, 217–220.
Fraunfelder, F.W., 2004. Ocular side effects from herbal medicines and nutritional supplements. American Journal of Ophthalmology 138 (4), 639–647.
Fukuyama, Y., Sato, T., Asakawa, Y., Takemoto, T., 1980. A potent cytotoxic warburganal and related drimane-type sesquiterpenoids from Polygonum hydropiper. Phytochemistry 21, 2895–2898.
Gammerman, A.F., Kadaev, G.N., Yacenko-Khmelevsky, A.A., 1984. Medicinal plants (Herbs-healers). High School, Moscow.
Garbacki, N., Gloaguen, V., Damas, J., Bodart, P., Tits, M., Angenot, L., 1999. Anti-inflammatory and immunological effects of Centaurea cyanus flower- heads. Journal of Ethnopharmacology 68, 235–241.
Gavrilov, A.S., Shchegolev, A.A., Gusel'nikova, E.V., Larionov, L.P., Bredneva, N.D., 2003. Adaptogen action of preparations from Inonutus obliquus. Pharmaceutical Chemistry Journal 37, 95–98.
Gharib Naseri, M.K., Heidari, A., 2007. Antispasmodic effect of Anethum graveolens fruit extract on rat ileum. International Journal of Pharmacology 3, 260–264.
Golubenko, B.G., 1967. Capillary resistance in patients with myocardial infarct and angina pectoris and the effect on it by anticoagulants and a preparation of Sorbus aucuparia -Vitamin CP. Sovetskaia Meditsina 30, 98–101.
Gordienko, A.D., Yakovleva, L.V., 1999. The effect of althan on the functional activity of mitochondria and microsomes in the rat liver in toxic hepatitis. Eksperimental'naya i Klinicheskaya Farmakologiya 62, 59–61.
Goun, E.A., Petrichenko, V.M., Solodnikov, S.U., Suhinina, T.V., Kline, M.A., Cunningham, G., Nguyen, C., Miles, H., 2002. Anticancer and antithrombin activity of Russian plants. Journal of Ethnopharmacology 81, 337–342.
Gubina, G., 1988. Clinical Applications of Aralia mandshurica Tincture. In: Turova., A (Ed.), Medicinal Preparations from Plants. Science Press, Moscow, pp. 263–269.
Gubina, G.P., 1959. On the treatment of post-influenzal asthenia. Zhurnal Nevropatologii i Psikhiatrii im S.S. Korsakova 59, 1239–1242.
Gurskaya, I.V., Tolkach, N.G., Gurskij, P.D., Buzuk, G.N., 2009a. Acute and subacute toxicity of preparative forms of elecampane. Proceedings of the Educational Institution Vitebsk State Academy of Veterinary Medicine: academic and research journal 45, 59–62.
Gurskaya, I.V., Tolkach, N.G., Gurskij, P.D., Buzuk, G.N., 2009b. Topical-product-induced irritation properties of preparative forms of elecampane. Proceedings of the Educational Institution Vitebsk State Academy of Veterinary Medicine: academic and research journal 45, 57–59.
Habermehl, G.G., 1998. Secondary and tertiary metabolites as plant toxins. Toxicon 36, 1707–1719.
Hachiya, N., Takizawa, Y., Kawamura, T., Tateno, T., Sakabe, Y., Asanoma, M., Noda, M., Ishizaki, M., Ishibashi, T., Kuroda, K., 1985. A review of acute toxicity and genotoxicity data on natural food additives. Toxicology Forum 8, 91–105 (in Japanese).
Hajhashemi, V., Abbasi, N., 2008. Hypolipidemic activity of Anethum graveolens in rats. Phytotherapy Research 22, 372–375.
Häkkinen, S.H., Kärenlampi, S.O., Heinonen, I.M., Mykkänen, H.M., Torronen, A.R., 1999. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. Journal of Agricultural and Food Chemistry 47, 2274–2279.
Ham, S.-S., Kim, S.-H., Moon, S.-Y., Chung, M.J., Cui, C.-B., Han, E.-K., Chung, C.-K., Choe, M., 2009. Antimutagenic effects of subfractions of chaga mushroom (Inonotus obliquus) extract. Mutation Research - Genetic Toxicology and Environmental Mutagenesis 672 (1), 55–59.
Hansel, R., Keller, K., Rimpler, H., Schneider, G. (Eds.), 1992. Hagers Handbuch der Pharmazeutischen Praxis, 4. Band. Springer-Verlag, Berlin–Heidelberg.
Haraguchi, H., 1992. Antioxidative substances in leaves of Polygonum hydropiper. Journal of Agricultural and Food Chemistry 40, 1349–1351.
Harbilas, D., Martineau, L.C., Harris, C.S., Adeyiwola-Spoor, D.C., Saleem, A., Lambert, J., Caves, D., Johns, T., Prentki, M., Cuerrier, A., Arnason, J.T., Bennett, S.A.L., Haddad, P.S., 2009. Evaluation of the antidiabetic potential of selected medicinal plant extracts from the Canadian boreal forest used to treat symptoms of diabetes: part II. Canadian Journal of Physiology and Pharmacology 87, 479–492.
Hazarika, A., Sarma, H.N., 2006. The estrogenic effects of Polygonum hydropiper root extract induce follicular recruitment and endometrial hyperplasia in female albino rats. Contraception 74, 426–434.
Heamalatha, S., Swarnalatha, S., Divya, M., Gandhi Lakshmi, R., Ganga Devi, A., Gomathi, E., 2011. Pharmacognostical, pharmacological, investigation on Anethum graveolens Linn: A review. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2, 564–574.
Heinrich, M., Barnes, J., Gibbons, S., Williamson, E.M., 2012. Fundamentals of Pharmacognosy and Phytotherapy, 2nd edition Churchill Livingston (Elsevier), Edinburgh & London.
Hernandez, D.E., Haneke, J.L., Wikman, G.J., 1988. Evaluation of the anti-ulcer and antisecretory activity of extracts of Aralia elata root and Schizahdra chinensis fruit in the rat. Journal of Ethnopharmacology 23, 109–114.
Heyl, F.W., Hart, M.C., Schmidt, J.M., 1918. An examination of the leaves of Adonis vernalis. Journal of the American Chemical Society 40, 436–453.
Heywood, V., 2011. Ethnopharmacology, food production, nutrition and biodiversity conservation: towards a sustainable future for indigenous peoples. Journal of Ethnopharmacology 137, 1–15.
Hirono, I., Mori, H., Culvenor, C.C., 1976. Carcinogenic activity of coltsfoot, Tussilago farfara L. Gann 67, 125–129.
Ho, K.Y., Huang, J.S., Tsai, C.C., Lin, T.C., Hsu, Y.F., Lin, C.C., 1999. Antioxidant activity of tannin components from Vaccinium vitis-idaea L. Journal of Pharmacy and Pharmacology 51, 1075–1078.
Ho, K.Y., Tsai, C.C., Huang, J.S., Chen, C.P., Lin, T.C., Lin, C.C., 2001. Antimicrobial activity of tannin components from Vaccinium vitis-idaea L. Journal of Pharmacy and Pharmacology 53, 187–191.

Hosseinzadeh, H., Karimi, G.-R., Ameri, M., 2002. Effects of Anethum graveolens L. seed extracts on experimental gastric irritation models in mice. BMC Pharmacology 2 (art. 21)⟨http://www.biomedcentral.com/1471-2210/2/21⟩.
Hukkanen, A.T., Polonen, S.S., Kärenlampi, S.O., Kokko, H.I., 2006. Antioxidant capacity and phenolic content of sweet rowanberries. Journal of Agricultural and Food Chemistry. 54, 112–119.
Hung, S.K., Perry, R., Ernst, E., 2011. The effectiveness and efficacy of Rhodiola rosea L.: A systematic review of randomized clinical trials. Phytomedicine 18, 235–244.
Huo, Y., Shi, H.M., Wang, M.Y., Li, X.B., 2008. Chemical constituents and pharmacological properties of Radix Inulae. Pharmazie 63, 699–703.
Hwangbo, C., Lee, H.S., Park, J., Choe, J., Lee, J.-H., 2009. The anti-inflammatory effect of tussilagone, from Tussilago farfara, is mediated by the induction of heme oxygenase-1 in murine macrophages. International Immunopharmacology 9, 1578–1584.
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2002. Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene, and Styrene, Vol. 82. IARC press, Lyon, pp. 129–151.
Ino, N., Tanaka, T., Okumura, A., Morishita, Y., Makita, H., Kato, Y., Nakamura, M., Mori, H., 1995. Active and subacute toxicity tests of madder root, natural colorant extracted from madder (Rubia tinctorium), in (C57BL/6 × C3H)F1 mice. Toxicolology and Industrial Health 11, 449–458.
Inoue, K., Yoshida, M., Takahashi, M., Shibutani, M., Takagi, H., Hirose, M., Nishikawa, A., 2009. Induction of kidney and liver cancers by the natural food additive madder color in a two-year rat carcinogenicity study. Food and Chemical Toxicology 47, 184–191.
Ishaque, S., Shamseer, L., Bukutu, C., Vohra, S., 2012. Rhodiola rosea for physical and mental fatigue: A systematic review. BMC Complementary and Alternative Medicine 12, 70.
Ishchenko, M.M., Nechaĭ, Ie.O, Korol'kov, O.S., 1996. The pentoxifylline and corglycon treatment of patients with circulatory encephalopathy against a background of atherosclerotic lesions of the major cerebral arteries. Likars'ka Sprava 1-2, 143–145.
Ivancheva, S., Stantcheva, B., 2000. Ethnobotanical inventory of medicinal plants in Bulgaria. Journal of Ethnopharmacology 69, 165–172.
Ivanov, S.A., Nomura, K., Malfanov, I.L., Ptitsyn, L.R., 2012. Glutinoin, a novel antioxidative ellagitannin from Alnus glutinosa cones with glutinoic acid dilactone moiety. Natural Product Research 26, 1806–1816.
Ivanov, S.A., Nomura, K., Malfanov, I.L., Sklyar, I.V., Ptitsyn, L.R., 2011. Isolation of a novel catechin from Bergenia rhizomes that has pronounced lipase-inhibiting and antioxidative properties. Fitoterapia 82, 212–218.
Jarboe, C.H., Schmidt, C.M., Nicholson, J.A., Zirvi, K.A., 1966. Uterine Relaxant Properties of Viburnum. Nature 212, 837.
Jarboe, C.H., Zirvi, K.A., Nicholson, J.A., Schmidt, C.M., 1967. Scopoletin, an antispasmodic component of Viburnum opulus and Viburnum prunifolium. Journal of Medicinal Chemistry 10, 488–489.
Jeong, H.J., Ryu, Y.B., Park, S.-J., Kim, J.H., Kwon, H.-J., Kim, J.H., Park, K.H., Rho, M.-C., Lee, W.S., 2009. Neuraminidase inhibitory activities of flavonols isolated from Rhodiola rosea roots and their in vitro anti-influenza viral activities. Bioorganic and Medicinal Chemistry 17 (19), 6816–6823.
Jiang, Z., Liu, F., Goh, J.J.L., Yu, L., Li, S.F.Y., Ong, E.S., Ong, C.N., 2009. Determination of senkirkine and senecionine in Tussilago farfara using microwave-assisted extraction and pressurized hot water extraction with liquid chromatography tandem mass spectrometry. Talanta 79, 539–546.
Jin, C., Strembiski, W., Kulchytska, Y., Micetich, R.G., Daneshtalab, M., 1999. Flavonoid glycosides from Ledum palustre subsp. decumbens. Daru 7, 5–8.
Jing, L., Shuang, G., Jingbo, L., 2009. Acute and genetic toxicity of ursolic acid extract from Ledum palustre L. Shipin Kexue 30, 250–252.
Jing, L., Shuang, G., Jingbo, L., Na, G., Xue, S., Wenhui, Q., Xuming, D., 2011. in vivo genotoxicity evaluation of crude extract from Ledum palustre and protective effects on cyclophosphamide-induced genotoxicity in mice. Latin American Journal of Pharmacy 30, 112–118.
Joo, J.I., Kim, D.H., Yun, J.W., 2010. Extract of chaga mushroom (Inonotus obliquus) stimulates 3T3-L1 adipocyte differentiation. Phytotherapy Research 24, 1592–1599.
Juan-Badaturuge, M., Habtemariam, S., Jackson, C., Thomas, M.J.K., 2009. Antioxidant principles of Tanacetum vulgare L. aerial parts. Natural Product Communications 4, 1561–1564.
Kalyoncu, F., Cetin, B., Saglam, H., 2006. Antimicrobial activity of common madder (Rubia tinctorum L.). Phytotherapy Research 20, 490–492.
Karamova, N.S., Fatykhova, D.G., Abdrakhimova, J.R., Ilinskaya, O.N., 2010. Evaluation of antigenotoxic effects of juices of plants Chelidonium majus L., Plantago major L. and Tussilago farfara L. Ecological genetics 8, 56–65.
Karim, A., Mekhfi, H., Ziyyat, A., Legssyer, A., Bnouham, M., Amrani, S., Atmani, F., Melhaoui, A., Aziz, M., 2010. Anti-diarrhoeal activity of crude aqueous extract of Rubia tinctorum L. roots in rodents. Journal of Smooth Muscle Research 46, 119–123.
Kaukin, A.V., 2002. Healing via trees [in Russian]. Sovetsky Sport, Moscow, pp. 175–180.
Kaur, G.J., Arora, D.S., 2009. Antibacterial and phytochemical screening of Anethum graveolens, Foeniculum vulgare and Trachyspermum ammi. BMC Complementary and Alternative Medicine 9 (art. 30).
Kawasaki, Y., Goda, Y., Yoshihira, K., 1992. The mutagenic constituents of Rubia tinctorum. Chemical and Pharmaceutical Bulletin 40, 1504–1509.
Kelly, G.S., 2001. Rhodiola rosea: apossible plant adaptogen. Alternative Medicine Review 6, 293–302.
Kern, W., Roth, H.J., Schmid, W., List, P.H., Horhammer, L. (Eds.), 1972. Hagers Handbuch der Pharmazeutischen Praxis, 3. Band. Springer-Verlag, Berlin/Heidelberg/New York.
Khalmatov, Kh.Kh., Kharlamov, I.A., Alimbayeva, P.K., Karriev, M.O., Khaetov, I.H., 1984. Osnovnuiye Lekarstvennuiye Rasteniya Srednei Azii (The main medicinal plants of Central Asia). Meditsina, Tashkent.
Khazanov, V.A., Smirnova, N.B., 2000. Kinetic characteristics of the energy production system in rat brain under conditions of posthypoxic encephalopathy and its correction with Bergeniae crassifoliae extracts. Bulletin of Experimental Biology and Medicine 1, 63–65.
Khishova, O.M, Shcherbinin, I.Yu., Dubashinskaya, N.V., 2013. Sedative effect of a combination of the powders of Greek valerian (Polemonium caeruleum) and common valerian (Valeriana officinalis) rhizomes and roots. Farmatsiya-Moscow 1, 43–44.
Kiem, P.V., Nhiem, N.X., Cuong, N.X., Hoa, T.Q., Huong, H.T., Le, Huong, Minh, M., Kim, Y.H., C.V., 2008. New phenylpropanoid esters of sucrose from Polygonum hydropiper and their antioxidant activity. Archives of Pharmacal Research 31, 1477–1482.
Kim, D., Nam, B., 2006. Extracts and essential oil of Ledum palustre L. leaves and their antioxidant and antimicrobial activities. Journal of Food Science and Nutrition 11, 100–104.
Kirichenko, E.E., Sychev, I.A., Chekulaeva, G.Y., 2012. The study of antiinflammatory activity of polysaccarides isolated from Tanacetum vulgare. Russian Journal of Medicine and Biology named after academician I.P. Pavlov 3, 53–57.
Ko, S.-K., Jin, M., Pyo, M.-Y., 2011. Inonotus obliquus extracts suppress antigen-specific IgE production through the modulation of Th1/Th2 cytokines in ovalbumin-sensitized mice. Journal of Ethnopharmacology 137 (3), 1077–1082.
Kokoska, L., Polesny, Z., Rada, V., Nepovim, A., Vanek, T., 2002. Screening of some Siberian medicinal plants for antimicrobial activity. Journal of Ethnopharmacology 82, 51–53.
Konishi, Z., Shimada, Y., Nagao, T., Okabe, H., Konoshima, T., 2002. Antiproliferative sesquiterpene lactones from the roots of Inula helenium. Biological and Pharmaceutical Bulletin 25, 1370–1372.
Kowalewski, Z., Kedzia, W., Koniar, H., 1976. Action of helenin on microorganisms. Archivum Immunologiae et Therapia Experimentalis 24, 121–125.
Kravkov, N.P., 1912. About application of water pepper (Polygonum hydropiperis) at internal bleeding. Russky vrach 7, 217.
Krivenko, V.V., Potebnia, G.P., Loiko, V.V., 1989. Experience in treating digestive organ diseases with medicinal plants. Vrachebnoe Delo 3, 76–78.
Kroeber, L., 1951. Cat's Foot, Gnaphalium dioecum L., Antennaria dioeca, Gnaphalium arenarium, Helichrysum arenarium DC as cholagogues and choleretics. Pharmazie 6, 615–617.
Kurkin, V.A., Dubishchev, A.V., Titova, I.N., Volotsueva, A.V., Petrova, E.S., Zhestkova, N.V., Klimova, I.Yu, 2003. Neurotropic properties of some phytopreparations containing phenylpropanoids. Rastitelnye Resursy 3, 115–122.
Kuroiwa, K., Shibutani, M., Inoue, K., Lee, K.-Y., Woo, G.-H., Hirose, M., 2006. Subchronic toxicity study of water pepper extract in F344 rats. Food and Chemical Toxicology 44, 1236–1244.
Kylli, P., Nohynek, L., Puupponen-Pimiä, R., Westerlund-Wikstro m, B., McDougall, G., Stewart, D., Heinonen, M., 2010. Rowanberry phenolics: compositional analysis and bioactivities. Journal of Agricultural and Food Chemistry 58, 11985–11992.
Lahlou, S., Israili, Z.H., Lyoussi, B., 2008a. Acute and chronic toxicity of a lyophilised aqueous extract of Tanacetum vulgare leaves in rodents. Journal of Ethnopharmacology 117, 221–227.
Lahlou, S., Tangi, K.C., Lyoussi, B., Morel, N., 2008b. Vascular effects of Tanacetum vulgare L. leaf extract: in vitro pharmacological study. Journal of Ethnopharmacology 120, 98–102.
Lavrenov, V.K., Lavrenova, G.V., Lobinzev V.G., 1988. Experience in the use of medicinal plants for combined respiratory diseases in miners. 2 Republican Conference on Medical Botany. –Kiev, p. 368.
Lavrenova, G.V., Lavrenov, V.K., 1997. Encyclopaedia of medicinal plants. Part 1. Donechchina Publ, Donetsk (p.78-78).
Lazarev, N.V., Liublina, E.I., Rozin, M.A., 1959. States of non-specific increased resistance. Patologicheskaya Fiziologia i Eksperimantalnaya Terapia 3 (4), 16–21.
Lazovskaya, A.V., 1959. Chaga and its use for the treatment of stage IV cancer. Medgiz, Leningrad, pp. 96–104.
Lebada, R., Schreier, A., Scherz, S., Resch, C., Krenn, L., Kopp, B., 2000. Quantitative analysis of the pyrrolizidine alkaloids senkirkine and senecionine in Tussilago farfara L. by capillary electrophoresis. Phytotherapy research 6, 366–369.
Lee, E.B., Kim, O.J., Kang, S.S., Jeong, C., 2005. Araloside A, an antiulcer constituent from the root bark of Aralia elata. Biological and Pharmaceutical Bulletin 28 (3), 523–526.
Lee, I.-K., Kim, Y.-S., Jang, Y.-W., Jung, J.-Y., Yun, B.-S., 2007. New antioxidant polyphenols from the medicinal mushroom Inonotus obliquus. Bioorganic and Medicinal Chemistry Letters 17 (24), 6678–6681.
Lee, J.H., Ha, Y.W., Jeong, C.S., Kim, Y.S., Park, Y., 2009. Isolation and tandem mass fragmentations of an anti-inflammatory compound from Aralia elata. Archives of pharmacal research 32, 831–840.
Lee, W.-J., Chung, H.-H., Cheng, Y.-Z., Lin, H.J., Cheng, J.-T., 2013. Rhodiola-water extract induces β-endorphin secretion to lower blood pressure in spontaneously hypertensive rats. Phytotherapy Research 27 (10), 1543–1547.
Lehmann, H.D., 1984. Zur Wirkung pflanzlicher Glykoside auf Widerstandsgefäße und Kapazitätsgefäße. Arzneimittel-Forschung 34, 423–429.
Levin, M.M., Yasnetsov, V.S., Sul'shenko, A.I., Faraschuk, N.A., 1974. Experience in the treatment of alopecia baldness with galenic preparations of Bidens tripartita. Sovetskaya medicina 10, 135.

Li, C.-T., Liu, Y.-P., He, F.-C., Li, Y., 2012a. in vitro antioxidant activities of Tussilago farfara, a new record species to Changbai Mountain. Chinese Journal of Natural Medicines 10, 260–262.
Li, T.S.C., 2002. Chinese and related North American herbs: phytopharmacology and therapeutic values. CRC press Inc., Boca Raton p. 598.
Li, Y., Chao, X., Zhang, Y., 2007. Research progress of Thermopsis lanceolate. Journal of Ningxia Agricultural College 1, 80–84.
Li, Z.-Y., Zhi, H.-J., Xue, S.-Y., Sun, H.-F., Zhang, F.-S., Jia, J.-P., Xing, J., Zhang, L.-Z., Qin, X.-M., 2012b. Metabolomic profiling of the flower bud and rachis of Tussilago farfara with antitussive and expectorant effects on mice. Journal of Ethnopharmacology 140 (1), 83–90.
Linne, C., 1749. Materia Medica. Liber I. de Plantis, Stockholm p. 168.
List, P.H., Horhammer, L. (Eds.), 1976. Hagers Handbuch der pharmazeutischen Praxis, vierte Neuausgabe, fünfter Band: Chemikalien und Drogen. Springer-Verlag, Berlin.
Litvinenko, V.I., Popova, T.P., Popova, N.V., Bubenchikova, V.N., 1992. Medicinal plants and preparations derived from them. Farmacevtichnyi Zhurnal 3, 83–84.
Lorenz, D., Lucker, P.W., Krumbiegel, G., Mennicke, W.H., Wetzelsberger, N., 1985. Pharmacokinetic studies of alizarin in man. Methods and Findings in Experimental and Clinical Pharmacology 7, 637–643.
Luchkova, M.M., 1978. Treatment of peptic ulcer with alanton. Vrachebnoe Delo 6, 69–71.
Lukomsky, I.G., 1955. Preventive dentistry Medgiz.
Ma, Z.Q., Song, S.J., Li, W., Xu, S.X., 2005. Two new saponins from the bud of Aralia elata (Miq.) Seem. Journal of Asian Natural Products Research 7, 817–821.
Mahran, G.H., Kadry, H.A., Isaac, Z.G., Thabet, C.K., Al-Azizi, M.M., El-Olemy, M.M., 1991. Investigation of diuretic drug plants. 1. Phytochemical screening and pharmacological evaluation of Anethum graveolens L., Apium graveolens L., Daucus carota L. and Eruca sativa Mill. Phytotherapy Research 5, 169–172.
Makarova, M.N., Makarov, V.G., 2010. Molecular biology of flavonoids (chemistry, biochemistry? pharmacology): Manula for doctors. Lema publishing, St-Petersburg, pp. 272–290.
Maloshtan, L.N., Serbina, N.A., 1999. Toxicological studies of anti-inflammatory phytopreparation – Altan. Provisor (Ukraine) 4 ⟨http://provisor.com.ua/archive/1999/N4/altan.php?part_code=8&art_code=1472⟩.
Maltseva, A.A., Sorokina, A.A., 2010. Great Valerian (Polemonium caeruleum): chemical composition, pharmacological properties. Farmatsiya-Moscow 5, 54–56.
Mamedov, N., Craker, L.E., 2001. Medicinal plants used for the treatment of bronchial asthma in Russia and Central Asia. Journal of Herbs, Spices & Medicinal Plants 8, 91–118.
Manojlovic, N.T., Solujic, S., Sukdolak, S., Milosev, M., 2005. Antifungal activity of Rubia tinctorum, Rhamnus frangula and Caloplaca cerina. Fitoterapia 76, 244–246.
Marhold, J., 1986. Prehled Prumyslove Toxikologie, Organicke Latky. Avicenum, Prague, Czechoslovakia p. 1376 (in Czechoslovakian).
Markin, V.V., Markina, L.D., 2007. Use of natural adaptogens for students. Siberian Medical Review 45, 54–58.
Markina, L.D., Markin, V.V., 2008. Forecasting of the development of dysadaptable conditions and algorithm of their effective correction. Pacific Medical Journal 3, 30–36.
Marles, R.J., Kaminski, J., Arnason, J.T., Pazos-Sanou, L., Heptinstall, S., Fischer, N.H., Crompton, C.W., Kindack, D.G., Awang, D.V.C., 1992. A bioassay for inhibition of serotonin release from bovine platelets. Journal of Natatural Products 55, 1044–1056.
Mashentseva, A.A., Dehaen, W., Seitembetov, T.S., Seitembetova, A.J., 2011. Comparison of the antioxidant activity of the different Betula pendula Roth. extracts from northern Kazakhstan. Journal of Phytology 3, 18–25.
Mashkovskii, M.D., 2002. Medicinal Agents [in Russian], Vol. 1. Novaya Volna, Moscow.
Maslov, L.N., Lishmanov, Yu.B., Arbuzov, A.G., Krylatov, A.V., Budankova, E.V., Konkovskaya, Yu.N., Burkova, V.N., Severova, E.A., 2009. Antiarrhythmic Activity of Phytoadaptogens in Short-Term Ischemia-Reperfusion of the Heart and Postinfarction Cardiosclerosis. Bulletin of Experimental Biology and Medicine 147, 331–334.
Maslov, L.N., Lishmanov, Yu.B., Naumova, A.V., Lasukova, T.V., 1997. Do endogenous ligands of peripheral μ- and δ-opiate receptors mediate antiarrhythmic and cardioprotective effects of Rhodiola rosea? Bulletin of Experimental Biology and Medicine 124 (8), 754–756.
Matsumoto, T., Tokuda, H., 1990. Antitumor-promoting activity of sesquiterpene isolated from an herbal spice. In: Kuroda, Y., Shankel, D.M., Waters, M.D. (Eds.), Antimutagenesis and Anticarcinogenesis Mechanisms II. Plenum Press, New York, pp. 423–427.
May, G., Willuhn, G., 1978. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. Arzneimittel-Forschung 28, 1–7.
McDougall, G.J., Ross, H.A., Ikeji, M., Stewart, D., 2008. Berry extracts exert different antiproliferative effects against cervical and colon cancer cells grown in vitro. Journal of Agricultural and Food Chemistry 56, 3016–3023.
Mikaelian, A.S., Oganesian, E.T., Stepanova, E.F., Krikova, A.V., 2006. The study of pharrnaceutical activity of total complexes of three part Bur marigold. Kuban Research Medical Journal 10, 62–66.
Min, B.S., Bae, K.H., Kim, Y.H., Miyashiro, H., Hattori, M., Shimotohno, K., 1999. Screening of Korean plants against human immunodeficiency virus type 1 protease. Phytotherapy Research 13 (8), 680–682.
Mishra, S.K. Kang, Kim, J.H., Oh, D.K., Kim, M.K., S.H., 2012. Orally administered aqueous extract of Inonotus obliquus ameliorates acute inflammation in dextransulfatesodium (DSS)-induced colitis in mice. Journal of Ethnopharmacology 143, 524–532.
Mitsuhashi, H., 1976. Medicinal plants of the Ainu. Economic Botany 30 (3), 209–217.
Moiseyev, I.N., Voskresensky, O.N., Tkatchenko, Ye.K., Skiba, O.I., Kalabin, Yu.V., Pykhtyeyev, D.M., 2008. Induction of inflammatory-destructive changes in the oral epithelium by delagil, emotional-painful stress and their inhibition by combinatiun of the ellagic and gallic acids. Dosyagnenny biologii ta mediciny 2, 20–24.
Molokovskii, D.S., Davydov, V.V., Khegai, M.D., 2002. Antidiabetic activities of adaptogenic formulations and extractions from medicinal plants. Rastitelnye Resursy 38, 15–28.
Monsefi, M., Ghasemi, M., Bahaoddini, A., 2006. The effects of Anethum graveolens L. on female reproductive system. Phytotherapy Research 20 (10), 865–868.
Montiel-Ruiz, R.M., Roa-Coria, J.E., Patiño-Camacho, S.I., Flores-Murrieta, F.J., Déciga-Campos, M., 2012. Neuropharmacological and toxicity evaluations of ethanol extract from Rhodiola rosea. Drug Development Research 73, 106–113.
Morikawa, T., Wang, L-B., Nakamura, S., Ninomiya, K., Yokoyama, E., Matsuda, H., Muraoka, O., Wu, L-J., Yoshikawa, M., 2009. Medicinal Flowers. XXVII. New flavanone and chalcone glycosides, arenariumosides I, II, III, and IV, and tumor necrosis factor-α inhibitors from everlasting, flowers of Helichrysum arenarium. Chemical and Pharmaceutical Bulletin 5, 361–367.
Muraviova, D.A., 1991. Pharmacognosy. Medicine, Moscow.
Muto, Y., Ichikawa, H., Kitagawa, O., Kumagai, K., Watanabe, M., Ogawa, E., Seiki, M., Shirataki, Y., Yokoe, I., Komatsu, M., 1994. Studies on antiulcer agents. I. The effects of various methanol and aqueous extracts of crude drugs on antiulcer activity. Yakugaku Zasshi 114, 980–994.
Myronchenko, S.I., Zvyagintseva, T.V., 2008. Effect of altan preparation on lipid peroxidation after local irradiation. Fundamental research 6, 83–84.
Namba, T., 1980. The Encyclopedia of Wakan-Yaku with Color Pictures. Vol. II. Hoikusha Publ. Co., Ltd., Osaka p. 180.
Narimanov, A.A., 1992. Reproductive capacity of male mice protected from supralethal effect of gamma-radiation by the administration of a mixture of extracts from Archangelica officinalis and Ledum palustre. Radiobiologia 32, 271–275.
Narimanov, A.A., Myakisheva, S.N., Kuznetsova, S.M., 1991. The radioprotective effect of Archangelica officinalis Hoffm. and Ledum palustre L. extracts on mice. Radiobiologia 31, 391–393.
Nartowska, J., Sommer, E., Pastewka, K., Sommer, S., Skopinska-Rozewska, E., 2004. Anti-angiogenic activity of convallamaroside, the steroidal saponin isolated from the rhizomes and roots of Convallaria majalis. Acta Poloniae Pharmaceutica 61, 279–282.
Naseri, M., Mojab, F., Khodadoost, M., Kamalinejad, M., Davati, A., Choopani, R., Hasheminejad, A., Bararpoor, Z., Shariatpanahi, S., Emtiazy, M., 2012. The study of anti-inflammatory activity of oil-based dill (Anethum graveolens L.) extract used topically in formalin-induced inflammation male rat paw. Iranian Journal of Pharmaceutical Research 11, 1169–1174.
Nazir, N., Koul, S., Qurishi, M.A., Taneja, S.C., Ahmad, S.F., Bani, S., Qazi, G.N., 2007. Immunomodulatory effect of bergenin and norbergenin against adjuvantinduced arthritis - a flow cytometric study. Journal of Ethnopharmacology 112, 401–405.
Nicholson, J.A., Darby, T.D., Jarboe, C.H., 1972. Viopudial, a hypotensive and smooth muscle antispasmodic from Viburnum opulus. Experimental Biology and Medicine. 140 (2), 457–461.
Nikolaeva, V.G., Khokhlova, A.A., 1981. Effect of tincture of buds of Betula verrucosa on Staphylococc. Rastitelnye Resursy 17 (3), 410–413.
Nistor Baldea, L.A., Martineau, L.C., Benhaddou-Andaloussi, A., Arnason, J.T., Lévy, É., Haddad, P.S., 2010. Inhibition of intestinal glucose absorption by anti-diabetic medicinal plants derived from the James Bay Cree traditional pharmacopeia. Journal of Ethnopharmacology 132 (2), 473–482.
Nohynek, L.J., Alakomi, H., Kähkonen, M.P., Heinonen, M., Helander, I.M., Oksman-Caldentey, K., Puupponen-Pimiä, R., 2006. Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. Nutrition and Cancer 54, 18–32.
Nosal, M.A., Nosal, I.M., 1960. Lekarstvennuiye Rasteniya i Sposobui ikh Primrniya v Narodye (Medicinal plants and the ways that they are used by people). State medical publishing, Kiev p. 256.
Olsson, E.M.G., von Scheele, B., Panossian, A.G., 2009. A randomized double-blind placebo controlled parallell group study of SHR-5 extract of Rhodiola rosea roots as treatment for patients with stress related fatigue. Planta Medica 75, 105–112.
Onitsev, P.I., 1962. Biological evaluation of preparations from Polygonum hydropiper. Aptechnoe Delo 11, 49–52.
Ovodova, R.G., Golovchenko, V.V., Popov, S.V., Shashkov, A.S., Ovodov, Yu.S., 2000. The isolation, preliminary structural studies, and physiological activity of water-soluble polysaccharides from the squeezed berries of the snowball tree Viburnum opulus. Russian Journal of Bioorganic Chemistry 26, 54–59.
Ozaki, H., Nagase, H., Urakawa, N., 1985. Interaction of palytoxin and cardiac glycosides on erythrocyte membranes and Na++K+ ATPase. European Journal of Biochemistry 152, 475–480.
Panchenkov, M.M, 1950. Combined treatment of peptic ulcer disease with Gnaphalium uliginosum and Polemonium caeruleum. Clinical Medicine 3, 86–87.
Panossian, A, Wikman, G., 2008. Pharmacology of Schisandra chinensis Bail.: An overview of Russian research and uses in medicine. Journal of Ethnopharmacology 118, 183–212.

Panossian, A., 2003. Adaptogens: Tonic herbs for fatigue and stress. Alternative and Complementary Therapies 9, 327–332.
Panossian, A., Wagner, H., 2005. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytotherapy Research 19, 819–838.
Panossian, A., Wikman, G., Wagner, H., 1999. Plant adaptogens III. Earlier and more recent aspects and concepts on their mode of action. Phytomedicine 6 (4), 287–300.
Panossian, A., Wikman, G., 2009. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Current Clinical Pharmacology 4, 198–219.
Panossian, A., Wikman, G., Sarris, J., 2010. Rosenroot (Rhodiola rosea): Traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine 17, 481–493.
Pardo, E.G., Garcia-Tellez, D., del Pozo, E.C., 1951. The action of several principles anid extracts of the digitalis group on ischemic skeletal muscle. Journal of Pharmacology and Experimental Therapeutics 101, 63–67.
Park, Y.M., Won, J.H., Kim, Y.H., Choi, J.W., Park, H.J., Lee, K.T., 2005. in vivo and in vitro anti-inflammatory and anti-nociceptive effects of the methanol extract of Inonotus obliquus. Journal of Ethnopharmacology 101, 120–128.
Pawlaczyk, I., Czerchawski, L., Pilecki, W., Lamer-Zarawska, E., Gancarz, R., 2009. Polyphenolic-polysaccharide compounds from selected medicinal plants of Asteraceae and Rosaceae families: Chemical characterization and blood antic-oagulant activity. Carbohydrate Polymers 77 (3), 568–575.
Peev, C., Dehelean, C., Mogosanu, C., Feflea, S., Tiulea, C., 2010. Spring drugs of betula pendula Roth.: Biologic and pharmacognostic evaluation. Studia Uni-versitatis "Vasile Goldis" Arad. Seria Stiintele Vietii (Life Sciences Series) 3, 41–43.
Perfumi, M., Mattioli, L., 2007. Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside Rhodiola rosea L. extract in mice. Phytotherapy Research 21, 37–43.
Perry, L.M., 1980. Medicinal Plants of East and Southern Asia. The MIT Press, Cambridge p. 41.
Petrovsky, Yu.A., Skakun, N.P., Turko, I.P., 1953. Flamin Helichrysum arenarium as cholagogic preparation. Pharmacology and toxicology 5, 50.
Pevzner, E.S., Raitsina, M.Z., 1954. Experience in birch buds treating of patients with eczema. In: Collection of scientific works of Belorussian skin and venereal diseases institute 4, 368.
Pieroni, A., Quave, C.L., Villanelli, M.L., Mangino, P., Sabbatini, G., Santini, L., Boccetti, T., Profili, M., Ciccioli, T., Rampa, L.G., Antonini, G., Girolamini, C., Cecchi, M., Tomasi, M., 2004. Ethnopharmacognostic survey on the natural ingredients used in folk cosmetics, cosmeceuticals and remedies for healing skin diseases in the inland Marches, Central-Eastern Italy. Journal of Ethnopharmacology 91, 331–344.
Pirvu, L., Dragomir, C., Schiopu, S., Mihul, S.C., 2012. Vegetal extracts with gastroprotective activity. Part. I. Extracts obtained from Centaurea cyanus L. raw material. Romanian Biotechnological Letters 17 (2), 7169–7176.
Popov, S.V., Popova, G.Y., Nikolaeva, S.Y., Golovchenko, V.V., Ovodova, R.G., 2005. Immunostimulating activity of pectic polysaccharide from Bergenia crassifolia (L) Fritsch. Phytotherapy Research 19, 1052–1056.
Popova, T.M., 2002. Study of lipid peroxidation and altan antioxidant activity in case of salmonellosis. Visnik of Kharkiv National University 546, 74–75.
Pozharitskaya, O.N., Ivanova, S.A., Shikov, A.N., Makarov, V.G., Galambosi, B., 2007. Separation and evaluation of free radical-scavenging activity of phenol compo-nents of green, brown, and black leaves of Bergenia crassifolia by using HPTLC-DPPH method. Journal of Separation Science 30, 2447–2451.
Pozharitskaya, O.N., Shikov, A.N., Makarova, M.N., Kosman, V.M., Faustova, N.M., Tesakova, S.V., Makarov, V.G., Galambosi, B., 2010. Anti-inflammatory activity of a HPLC-fingerprinted aqueous infusion of aerial part of Bidens tripartita L. Phytomedicine 17, 463–468.
Prakash, A.O., 1985. Biological evaluation of some medicinal plant extracts for contraceptive efficacy in females. In: Runnebaum, B., Rabe, T., Kiesel, L. (Eds.), Future Aspects in Contraception. MTP Press Limited, pp. 115–128.
Pyaskovskii, S., Rikhter, S., 1961. Complex investigation of physiologically active substances of lower plants. Academy of Science USSR, Moscow - Leningrad, pp. 258–263.
Qiu, J., Luo, M., Wang, J., Dong, J., Li, H., Leng, B., Zhang, Q., Dai, X., Zhang, Y., Niu, X., Deng, X., 2011. Isoalantolactone protects against Staphylococcus aureus pneu-monia. FEMS Microbiology Letters 324 (2), 147–155.
Rahman, E., Goni, S.A., Rahman, M.T., Ahmed, M., 2002. Antinociceptive activity of Polygonum hydropiper. Fitoterapia 73, 704–706.
Rahman, I., Gogoi, I., Dolui, A.K., Handique, R., 2005. Toxicological study of plant extracts on termite and laboratory animals. Journal of Environmental Biology 26, 239–241.
Rasina, L.N., 2002. The criopreparation chaga (Inonotus obliquus) effect both on deposition or decorporation of 90Sr and on influence of external prolonged γ-irradiation. Radiatsionnaya Biologiya. Radioekologiya 42, 399–403.
Register Russia, 2012. On line State Register of Medicinal preparations by the Ministry of Public Health and Social Development of the Russian Federation., ⟨http://grls.rosminzdrav.ru/GRLS.aspx⟩ (accessed 2012).
Rezaee-Asl, M., Bakhtiarian, A., Nikoui, V., Sabour, M., Ostadhadi, S., Yadavar-Nikravesh, M-S., Giorgi, M., 2013. Antinociceptive properties of hydro alcoholic extracts of Anethum graveolens L. (dill) seed and aerial parts in mice. Clinical and Experimental Pharmacology 3 (2), 122, http://dx.doi.org/10.4172/2161-1459.1000122.
Rhee, J.K., Baek, B.K., Ahn, B.Z., 1985. Structural investigation on the effects of the herbs on Clonorchis sinensis in rabbits. The American Journal of Chinese Medicine 13, 119–125.
Rifat-uz-Zaman, M.S, Akhtar, M.S., Khan, M.S., 2004. Preliminary eva-luation of Anethum graveolens fruit in indomethacin-ulcer induced rats. Journal of Biological Sciences 4, 151–156.
Rikalo, N.A., 2005. Efficacy of phytoremedy altanum on experimental klebsiellosis. Teoretichna i experimentalna medicina (Ukraine) 2, 41–44.
Roder, E., 1988. Wie gef∼ihrlich ist Huflattich als Hustentee? Deutsche Apotheker-Zeitung 128 (43), 2321–2322.
Rop, O., Reznicek, V., Valsikova, M., Jurikova, Mlcek, T.J., Kramarova, D., 2010. Antioxidant properties of European cranberrybush fruit (Viburnum opulus var. edule). Molecules 15, 4467–4477.
Rossijsky, D.M., 1934. Water pepper (Polygonum hydropiperi) as bleeding stop medicine. Kazansky medicinsky zhurnal 5, 448.
Rossijsky, D.M., 1942. About therapeutical use of preparations from alder (Alnus incana). Farmatsiya-Moscow 5, 27.
Roulet, M., Laurini, R., Rivier, L., Calame, A., 1988. Hepatic veno-occlusive disease in newborn infant of a woman drinking herbal tea. Journal of Pediatrics 112, 433–436.
Ryu, J.H., Jeong, Y.S., Sohn, D.H., 1999. A new bisabolene epoxide from Tussilago farfara, and inhibition of nitric oxide synthesis in LPS-activated macrophages. Journal of Natural Products 62, 1437–1438.
Saar, M., 1991. Fungi in Khanty folk medicine. Journal of Ethnopharmacology 31, 175–179.
Safonova, E.A., Razina, T.G., Lopatina, K.A., Fedorova, E.P., Zueva, E.P., 2010. Reduc-tion in paclitaxel toxic effect on blood system with the help of water-soluble polysaccharides from Tussilago farfara and Acorus calamus. Siberian Journal of Oncology 2, 42–46.
Sagdic, O., Aksoy, A., Ozkan, G., 2006. Evaluation of the antibacterial and antiox-idant potentials of cranberry (gilaburu, Viburnum opulus L.) fruit extract. Acta Alimentaria 35, 487–492.
Sahib, A.S., Mohammad, I.H., Al-Gareeb, A.I., 2012. Effects of Anethum graveolens leave powder on lipid profile in hyperlipidemic patients. Spatula DD 2, 153–158.
Samarina, G.I., 1948. About pharmacology of Polygonum persicaria. Farmakologiya i Toksikologiya 5 (2), 32–36.
Samarina, G.I., 1950. About pharmacology of preparations from Polygonum persi-caria herb. Izvestia Academy of sciences Kazakhstan SSR. Seria Phyziologiches-kaya 92 (3), 61.
Saratikov, A.S., Krasnov, E.A., 2004. Rhodiola rosea (Golden root) Fourth edition, Revised and Enlarged. Tomsk State University Publishing House p. 292.
Saratikov, A.S., Krasnow, E.A., 1987. Rhodiola rosea is aValuable Medicinal Plant. Medical Institute Tomsk, Tomsk, 252.
Schinella, G.R., Giner, R.-M., Del Carmen Recio, M., De Buschiazzo, P.M., Ríos, J.-L., Máñez, S., 1998. Anti-inflammatory effects of South American Tanacetum vulgare. Journal of Pharmacy and Pharmacology 50 (9), 1069–1074.
Sezik, E., Yesilada, E., Shadidoyatov, H., Kulivey, Z., Nigmatullaev, A.M., Aripov, H.N., Takaishi, Y., Takeda, Y., Honda, G., 2004. Folk medicine in Uzbekistan I. Toshkent, Djizzax, and Samarqand provinces. Journal of Ethnopharmacology 92 (197-07).
Shashkina, M.Ya., Shashkin, P.N., Sergeev, A.V., 2006. Chemical and medicobiologi-cal properties of chaga. Pharmaceutical Chemistry Journal 40, 560–568.
Shass, E.Yu., 1952. Phytotherapy. Academy of Medicinal science of USSR, Moscow.
Shchepotin, B.M., Shchulipenko, I.M., Prisiazhniuk, M.S., 1984. Use of infusions of medicinal plants in patients with hypertensive disease. Vrachebnoe Delo 6, 18–22.
Shevtsov, V.A., Zholus, B.I., Shervarly, V.I., Vol'skij, V.B., Korovin, Y.P., Khristich, M.P., Roslyakova, N.A., Wikman, G., 2003. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mentalwork. Phytomedicine 10, 95–105.
Shikov, A.N., Kundracikova, M., Palama, T.L., Pozharitskaya, O.N., Kosman, V.M., Makarov, V.G., Galambosi, B., Kim, H.J., Jang, Y.P., Choi, Y.H, Verpoorte, R., 2010a. Phenolic constituents of Gnaphalium uliginosum L. Phytochemistry Letters 3, 45–47.
Shikov, A.N., Pozharitskaya, O.N., Kamenev, I.Yu., Makarov, V.G., 2011. Arznei und Gewurzpflanzen in Russland. Zeitschrift fur Arznei & Gewurzpflanzen 16, 135–137.
Shikov, A.N., Pozharitskaya, O.N., Makarova, M.N., Dorman, H.J.D., Makarov, V.G., Hiltunen, R., Galambosi, B., 2010b. Adaptogenic effect of black and fermented leaves of Bergenia crassifolia L. in mice. Journal of Functional Foods 2, 71–76.
Shikov, A.N., Pozharitskaya, O.N., Makarova, M.N., Kovaleva, M.A., Laakso, I., Dorman, H.J.D., Hiltunen, R., Makarov, V.G., Galambosi, B., 2012. Effect of Bergenia crassifolia L. extracts on weight gain and feeding behavior of rats with high-caloric diet-induced obesity. Phytomedicine 19, 1250–1255.
Skakun, N.P., Stepanov, N.Yu., 1988. Comparative evaluation of the hepatoprotec-tive, antioxidant and choleretic activity of flavonoid drugs. Vrachebnoe Delo 12, 52–54.
Smirnova, A.S., Iadrova, V.M., 1968. Comparative study of the astringent effect of liquid extracts from Viburnum opulus L. Farmatsiya-Moscow 17, 42–45.
Sokolov, P.D., 1990. Plant resources of USSR. Flowering plants, its chemical composition, application. Families Caprifoliaceae - Plantaginaceae. Nauka, Leningrad.
Sokolov, S., Monogarov, V.D., Sobolev, V.L., 1971. The influence of the saponins of the Aralia mandshurica on the processes of recovery on athletes after intensive physical work loads, Biologically Active Substances of Flora and Fauna of the Far

East and Pacific Ocean. Far East Scientific Center of the Academy of Science of the USSR, Vladivostok, pp. 113–114.
Sokolov, S.Ya., 2000. Phytotherapy and Phytopharmacology: The Manual for Doctors. Medical News Agency, Moscow.
Solovieva, V.A., 2005. Traditional methods of health promotion [Narodnye metody ukreplenija zdorovja]. Izdatelsky dom "Neva", St-Petersburg p. 352.
Sorokina, A.A., Maltseva, A.A., Brezhneva, T.A., Slivkin, A.I., 2010. Evaluation of the hypoglycemic activity of great valerian (Polemonium caeruleum) preparation. Farmatsiya-Moscow 2, 18–20.
Soylak, M., Elci, L., Saracoglu, S., Divrikli, U., 2002. Chemical analysis of fruit juice of European cranberrybush (Viburnum opulus) from Kayseri – Turkey. Asian Journal of Chemistry 14, 135–138.
Spang, R., 1989. Toxicity of tea containing pyrrolizidine alkaloids. Journal of Pediatrics 115, 1025.
Spasov, A.A., Wikman, G.K., Mandrikov, V.B., Mironova, I.A., Neumoin, V.V., 2000. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine 7, 85–89.
Sperl, W., Stuppner, H., Gassner, I., 1995. Reversible hepatic veno-occlusive disease in an infant after consumption of pyrrolizidine-containing herbal tea. European Journal of Pediatrics 154, 112–116.
Spiridonov, N.A., Konovalov, D.A., Arkhipov, V.V., 2005. Cytotoxicity of some Russian ethnomedicinal plants and plant compounds. Phytotherapy Research 19, 428–432.
Stepanova, E.F., Krikova, A.V., Mikaelian, A.S., Goncharova, V.V., Korochinsky, A.V., 2006. Effect of complex fractions of Bidens tripartita on circulatory dynamics of normotensive rats. Modern problems of education and science 2, 105–107.
Stević, T., Šavikin, K., Zdunić, G., Stanojković, T., Juranić, Z., Janković, T., Menković, N., 2010. Antioxidant, cytotoxic, and antimicrobial activity of Alnus incana (L.) ssp. incana Moench and A. viridis (Chaix) DC ssp. viridis extracts. Journal of Medicinal Food 13 (3), 700–704.
Suslov, N.I., Churin, A.A., Skurikhin, E.G., Provalova, N.V., Stal'bovskii, A.O., Litvinenko, V.I., Dygai, A.M., 2002. Effect of the natural nootrope and adaptogen preparations on the bioelectric cortex activity in rats. Eksperimental'naya i Klinicheskaya Farmakologiya 65, 7–10.
Szadowska, A., 1962. Pharmacology of galenic preparations and flavonoids from Helichrysum arenarium. Acta Poloniae Pharmaceutica 19, 465–479.
The State Pharmacopoeia of the USSR, 11th ed., part 2, 1990. Medizina, Moscow.
Tomczykowa, M., Tomczyk, M., Jakoniuk, P., Tryniszewska, E., 2008. Antimicrobial and antifungal activities of the extracts and essential oils of Bidens tripartita. Folia Histochemica et Cytobiologica 46, 389–393.
Tournier, H., Schinella, G., De Balsa, E.M., Buschiazzo, H., Mañez, S., De Buschiazzo, P. M., 1999. Effect of the chloroform extract of Tanacetum vulgare and one of its active principles, parthenolide, on experimental gastric ulcer in rats. Journal of Pharmacy and Pharmacology 51, 215–219.
Tshibilaev, Ch.S., Severtsev, V.A., Tshibilaev, T.Ch., 2006. History of development of pharmaceutical production in Russia. Russian Academy of natural history, Moscow.
Tunón, H., Olavsdotter, C., Bohlin, L., 1995. Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. Journal of Ethnopharmacology 48, 61–76.
Turischev, S., 2008. Medicinal plants with sedative effects. Vrach 3, 69–71.
Turova, A.D., 1955. Pharmacological study and clinical application of Polemonium caeruleum. In: Polemonium caeruleum [in Russian], Moscow.
Turova, A.D., Sapozhnikova, E.N., 1989. Medicinal Plants of USSR and their applications. Medizina, Moscow ([in Russian]).
Tzankova, V., Danchev, N., 2007. Cytisine - from ethomedical use to the development as a natural alternative for smoking cessation. Biotechnology & Biotechnological Equipment 21 (2), 151–160.
Ulger, H., Ertekin, T., Karaca, O., Canoz, O., Nisari, M., Unur, E., Elmali, F., 2012. Influence of gilaburu (Viburnum opulus) juice on 1,2-dimethylhydrazine (DMH)-induced colon cancer. Toxicology and Industrial Health , http://dx.doi.org/10.1177/0748233712445049.
Urban, J., Kokoska, L., Langrova, I., Matejkova, J., 2008. in vitro anthelmintic effects of medicinal plants used in Czech Republic. Pharmaceutical Biology 46 (10–11), 808–813.
Utkin, L.A., 1931. Traditional Medicinal plants of Siberia. Proceedings of scientific research institutes of industry 434, 24.
Varlakov, M.N., 1943. Substitution of imported senega with the roots of Polemonium caeruleum. Farmatsiya-Moscow, 1.
Velioglu, Y.S., Ekici, L., Poyrazoglu, E.S., 2006. Phenolic composition of European cranberrybush (Viburnum opulus L.) berries and astringency removal of its commercial juice. International Journal of Food Science and Technology 41, 1011–1015.
Vereschagin, V.I., Sobolevskaya, K.A., Yakubova, A.I., 1959. Useful plants of West Siberia. Publishing of Academy of Science of USSR, Moscow-Leningrad.
Vichkanova, S.A., Adgina, V.V., Fateeva, T.V., Trumpe, T.E., 1992. Brusniver – new herbal mixture with antimicrobial, anti-inflammatory and diuretic activity. Proceedings of the II Russian National Congress Man and health. Moscow, p. 195.
Vichkanova, S.A., Derevjanko, I.I., Adgina, V.V., Fateeva, T.V., 2004. Experimental-clinical study of plyherbal mixture Brusniver. In: Genetical resources of medicinal and aromatic plants. Moscow, VILAR, 262-265.
Vichkanova, S.A., Kolkhir, V.K., Sokolskaya, T.A., Voskoboinikova, I.V., Bykov, V.A., 2009. Medicinal preparations from plants (experience of VILAR). Ardis, Moscow p. 432.
Vityazev, F.V., Paderin, N.M., Golovchenko, V.V., 2012. in vitro Binding of Human Serum Low Density Lipoproteins by Sulfated Pectin Derivatives. Russian Journal of Bioorganic Chemistry 38, 319–323.
Vogel, V.G., Kluge, E., 1961. Comparative studies on the diuretic action of some steroids with cardiac action. Arzneimittelforschung 11, 848–850.
Vogl, S., Picker, P., Mihaly-Bison, J., Fakhrudin, N., Atanasov, A.G., Heiss, E.H., Wawrosch, C., Reznicek, G., Dirsch, V.M., Saukel, J., Kopp, B., 2013. Ethnopharmacological in vitro studies on Austria's folk medicine - An unexplored lore in vitro anti-inflammatory activities of 71 Austrian traditional herbal drugs. Journal of Ethnopharmacology 149 (3), 750–771.
Voronina, K.V., 1952. Results of study of South-East traditional medicinal plants. Uchenie zapiski SGU, Vol. 35. USSR, Saratov.
Voskanyan, V.L., Vasilenko, Yu.K., Ponomarev, V.D., 1983. Hypolipidemic properties of saparal and oleanolic acid. Pharmaceutical Chemistry Journal 17 (2), 123–126.
Vostrikova, G.G., 1973. K izucheniju lekarstvennych sredstv narodnoi meditsiny nanaitsev. Voprosy pharmatsii na Dalnem Vostoke. Khabarovsk 1, 60–69.
Vučić, D., Čomić, L., Petković, M., Stefanović, O., 2009. Antibacterial effects of leaves of Vaccinium vitis-idaea L. Planta medica 75, 1044.
Wagner, H., 1993. Pharmazeutische Biologie. Drogen und ihre Inhaltsstoffe. Gustav Fischer Verlag, Stuttgart, New York.
Wagner, H., Wierer, M., Bauer, R., 1986. in vitro Hemmung der Prostaglandin-Biosynthese durch etherische Ole und phenolische Verbindungen. Planta Medica 3, 184–187.
Wang, H., Ding, Y., Zhou, J., Sun, X., Wang, S., 2009. The in vitro and in vivo antiviral effects of salidroside from Rhodiola rosea L. against coxsackievirus B3. Phytomedicine 16 (2–3), 146–155.
Wang, X., Sun, H., Fan, Y., Li, L., Makino, T., Kano, Y., 2005. Analysis and bioactive evaluation of the compounds absorbed into blood after oral administration of the extracts of Vaccinium vitis-idaea in rat. Biological and Pharmaceutical Bulletin 28 (6), 1106–1108.
Wang, Y.M., 1979. Pharmacological studies of extracts of Tussilago farfara L. (II) Effects on the cardiao-vascular system. Yao Xue Xue Bao 14, 268–276.
Weeks, J.R., Holck, H.G.O., 1943. The potency of a new extract of convallaria majalis leaves: III. Assays by the papillary muscle procedure and the U.S.P. XII cat method. Journal of Pharmacology and Experimental Therapeutics 78, 180–186.
Weiss, R.F., 1988. Herbal Medicine. Beaconsfield Publishers, Beaconsfield, UK p. 146.
Westendorf, J., Marquardt, H., Poginsky, B., Dominiak, M., Schmidt, J., Marquardt, H., 1990. Genotoxicity of naturally occurring hydroxyanthraquinones. Mutation Research 240, 1–12.
Westendorf, J., Pfau, W., Schulte, A., 1998. Carcinogenicity and DNA adduct formation observed in ACI rats after long-term treatment with madder root. Rubia tinctorum L. Carcinogenesis 19, 2163–2168.
Wiegant, F.A., Surinova, S., Ytsma, E., Langelaar-Makkinje, M., Wikman, G., Post, J.A., 2009. Plant adaptogens increase life span and stress resistance in C. elegans. Biogerontology 10, 27–42.
Wolniak, M., Tomczykowa, M., Tomczyk, M., Gudej, J., Wawer, I., 2007. Antioxidant activity of extracts and flavonoids from Bidens tripartita. Acta Poloniae Pharmaceutica - Drug Research 63, 441–447.
Xi, S., Zhou, G., Zhang, X., Zhang, W., Cai, L., Zhao, C., 2009. Protective effect of total aralosides of Aralia elata (Miq) Seem (TASAES) against diabetic cardiomyopathy in rats during the early stage, and possible mechanisms. Experimental and molecular medicine 41, 538–547.
Xie, G., Schepetkin, I.A., Quinn, M.T., 2007. Immunomodulatory activity of acidic polysaccharides isolated from Tanacetum vulgare L. International Immunopharmacology 7, 1639–1650.
Yan, G., Jin, G., Li, L., Qin, X., Zheng, C., Li, G., 2011. Protective effects and mechanism of Inonotus obliquus on asthmatic mice. Zhongguo Zhong Yao Za Zhi 36 (8), 1067–1070.
Yang, Y., Yu, T., Jang, H.J., Byeon, S.E., Song, S.Y., Lee, B.H., Rhee, M.H., Kim, T.W., Lee, J., Hong, S., Cho, J.Y., 2012. in vitro and in vivo anti-inflammatory activities of Polygonum hydropiper methanol extract. Journal of Ethnopharmacology 139, 616–625.
Yano, H.M., Bacchi, E.M., Hayashi, L.S.S., de Lucia, R., 2011. Anti-inflammatory activity and effect on locomotion of Polygonum persicaria L. (Polygonaceae) extract in rats. Latin American Journal of Pharmacy 30, 1635–1638.
Yarnell, E., 2000. The botanical roots of pharmaceutical discovery. Alternative & Complementary Therapies. June 2000, p. 125-128.
Yarnell, E., Abascal, K., 2003. Botanicals for regulating heart rhythms. Alternative and Complementary Therapies 9, 125–129.
Yelina, G.A., 1993. Pharmacy on the bog. Nauka, Saint-Petersburg, pp. 236–239.
Yoon, T.J., Lee, S.J., Kim, E.Y., Cho, E.H., Kang, T.B., Yu, K.-W., Suh, H.J., 2013. Inhibitory effect of chaga mushroom extract on compound 48/80-induced anaphylactic shock and IgE production in mice. International Immunopharmacology 15 (4), 666–670.
Yoshikawa, M., Murakami, T., Harada, E., Murakami, N., Yamahara, J., Matsuda, H., 1996. Bioactive saponins and glycosides. VII. On the hypoglycemic principles from the root cortex of Aralia elata Seem.: structure related hypoglycemic activity of oleanolic acid oligoglycoside. Chemical Pharmaceutical Bulletin 44, 1923–1927.
Youn, M.-J., Kim, J.-K., Park, S.-Y., Kim, Y., Park, C., Kim, E.S., Park, K.-I., So, H.S., Park, R., 2009. Potential anticancer properties of the water extract of Inontus

obliquus by induction of apoptosis in melanoma B16-F10 cells. Journal of Ethnopharmacology 121 (2), 221–228.
Yu, L., Jinfeng, L., Zhenhong, L., Yanju, L., Mingna, L., Jing, J., Wanhai, Xu., 2011. The antitumor effects of Araloside A extracted from the root bark of Aralia elata on human kidney cancer cell lines. African Journal of Pharmacy and Pharmacology 5, 462–467.
Zakharov, N.A., Pridantseva, N.M., Khokhlova, A.A., Nikolaeva, V.G., 1980. Use of a tincture of birch buds for treating suppurative wounds. Vestnik Khirurgii Imeni I.I.Grekova 124, 82–85.
Zayachkivska, O.S., Gzhegotsky, M.R., Terletska, O.I., Lutsyk, D.A., Yaschenko, A.M., Dzhura, O.R., 2006. Influence of Viburnum opulus proanthocyanidins on stress-induced gastrointestinal mucosal damage. Journal of Physiology and Pharmacology 57 (SUPPL. 5), 155–167.
Zelenskaya, K.L., Povet'eva, T.N., Pashinskii, V.G., Fomina, T.N., Timina, E.A., Perova, A.V., 2005. Stress-inducing effect of hypoxia of different origin and its correction with Inula helenium L. tincture. Bulletin of Experimental Biology and Medicine 139, 414–417.
Zemlinsky, S.E., 1949. Medicinal plants of USSR.
Zevin, I., Altman, N., Zevin, L., 1997. A Russian herbal: traditional remedies for health and healing. Healing Arts Press, Vermont p. 250.
Zhang, J., Wang, H., Xue, Y., Zheng, Q., 2013. Cardioprotective and antioxidant activities of a polysaccharide from the root bark of Aralia elata (Miq.) Seem. Carbohydrate Polymers 93 (2), 442–448.
Zhang, S., 1989. Treatment of 500 cases of dysentery with Bidens tripartita. Shandong Journal of Traditional Chinese Medicine 8, 11–12.
Zhu, J., Wan, X., Zhu, Y., Ma, X., Zheng, Y., Zhang, T., 2010. Evaluation of salidroside in vitro and in vivo genotoxicity. Drug and Chemical Toxicology 33, 220–226.
Zhu, Z., Zhao, B., He, S., Zhou, Y., Cao, G., 2003. A toxicity experiment of general alkaloid of Thermopsis lanceolate on mice. Journal of Northwest Sci-Tech University of Agriculture and Forestry 31 (2), 25–28.
Zlobin, A.A., Martinson, E.A., Litvinets, S.G., Ovechkina, I.A., Durnev, E.A., Ovodova, R.G., 2012. Pectin polysaccharides of rowan Sorbus aucuparia L. Russian Journal of Bioorganic Chemistry 38, 702–706.
Zofina, A.A., 1946. Greek valerian as a sedative medicine. Pharmakologia i toxicologia 6.
Zvyagintseva, T.V., Myronchenko, S.I., Zhelnin, Ye.V., 2009. Photoprotective action of altan and thiotriazoline ointment in experiment. Experimentalna i klinichna medicina (Ukraine) 2, 63–67.