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Review

Medicinal Plants of the Russian Pharmacopoeia; their history and applications

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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.

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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 official 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 15th to the 16th 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. (*Schisandra draceae*) 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 medications. A herbal medicinal preparation is the finished product, and this term 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 “Allokolhol” (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](#) (11th edition). Last issued in 1987 (part 1) and 1990 (part 2), this Pharmacopoeia 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 leaves, 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 choleric agents, 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	<i>Ledum palustre</i> L., <i>Ericaceae</i>	Expectorant
2. CORTEX FRANGULAE ALNI	<i>Frangula alnus</i> Mill., <i>Rhamnaceae</i>	Laxative
3. CORTEX QUERCUS	<i>Quercus robur</i> L., <i>Quercus petrae</i> Liebl., <i>Fagaceae</i>	Astringent
4. CORTEX VIBURNI	<i>Viburnum opulus</i> L., <i>Caprifoliaceae</i>	Diuretic
5. FLORES CALENDULAE	<i>Calendula officinalis</i> L., <i>Asteraceae</i>	Antiseptic and anti-inflammatory
6. FLORES CENTAUREAE CYANI	<i>Centaurea cyanus</i> L., <i>Asteraceae</i>	Diuretic
7. FLORES CHAMOMILLAE	<i>Chamomilla recutita</i> (L.) Rauschert (<i>Matricaria recutita</i> L., <i>M. chamomilla</i> L.), <i>Asteraceae</i>	Anti-inflammatory, spasmolytic
8. FLORES CRATAEGI	<i>Crataegus sanguinea</i> Pall.; <i>C. laevigata</i> (Poir.) DC. [syn. <i>C. oxyacantha sensu</i> Pojark.] <i>C. korolkowii</i> L. Henry <i>C. altaica</i> (Loud.) Lange <i>C. chlorocarpa</i> Lenne et C. Koch <i>C. dahurica</i> Koehne ex Schneid. <i>C. monogyna</i> Jacq. <i>C. alemanniensis</i> Cin. <i>C. orientobaltica</i> Cin. <i>C. curvisepala</i> Lindm. <i>C. X curonica</i> Cin. <i>C. X dunensis</i> Cin. <i>C. pentagyna</i> Waldst. et Kit., <i>Rosaceae</i>	Cardiovascular
9. FLORES HELICHRYSI ARENARI	<i>Helichrysum arenarium</i> (L.) Moench, <i>Asteraceae</i>	Choleretic
10. FLORES SAMBUCI NIGRAE	<i>Sambucus nigra</i> L., <i>Caprifoliaceae</i>	Diaphoretic (sudorific)
11. FLORES TANACETI	<i>Tanacetum vulgare</i> L., <i>Asteraceae</i>	Anthelmintic and choleretic
12. FLORES TILIAE	<i>Tilia cordata</i> Mill. <i>T. platyphyllos</i> Scop., <i>Tiliaceae</i>	Diaphoretic (sudorific)
13. FOLIA BELLADONNAE	<i>Atropa bella-donna</i> L., <i>Solanaceae</i>	Cholinolytic (spasmolytic)
14. FOLIA DIGITALIS	<i>Digitalis purpurea</i> L., <i>D. grandiflora</i> Mill. (syn. <i>D. ambigua</i> Murr.), <i>Scrophulariaceae</i>	Cardiotonic
15. FOLIA EUCALYPTI VIMINALIS	<i>Eucalyptus viminalis</i> Labill., <i>Myrtaceae</i>	Anti-inflammatory
16. FOLIA FARFARAE	<i>Tussilago farfara</i> L., <i>Asteraceae</i>	Expectorant
17. FOLIA HYOSCYAMI	<i>Hyoscyamus niger</i> L., <i>Solanaceae</i>	Cholinolytic (spasmolytic)
18. FOLIA MENTHAE PIPERITAE	<i>Mentha piperita</i> L., <i>Lamiaceae</i>	Spasmolytic and choleretic
19. FOLIA MENYANTHIDIS TRIFOLIATAE	<i>Menyanthes trifoliata</i> L., <i>Menyanthaceae</i>	Bitterness (appetite stimulant) and choleretic
20. FOLIA PLANTAGINIS MAJORIS	<i>Plantago major</i> L., <i>Plantaginaceae</i>	Expectorant
21. FOLIA ORTHOSIPHONIS STAMINEI	<i>Orthosiphon stamineus</i> Benth., <i>Lamiaceae</i>	Diuretic
22. FOLIA SALVIAE	<i>Salvia officinalis</i> L., <i>Lamiaceae</i>	Anti-inflammatory
23. FOLIA SENNAE	<i>Cassia acutifolia</i> Del., <i>Fabaceae</i>	Laxative
24. FOLIA STRAMONII	<i>Datura stramonium</i> L., <i>Solanaceae</i>	Cholinolytic (spasmolytic)
25. FOLIA URTICAE	<i>Urtica dioica</i> L., <i>Urticaceae</i>	Haemostatic
26. FOLIA UVAE URSI	<i>Arctostaphylos uva-ursi</i> (L.) Spreng., <i>Ericaceae</i>	Diuretic

Table 1 (continued)

Monograph title	Latin name of plant, family (as in the State Pharmacopoeia of the USSR)	Pharmacological group
27. FOLIA VITIS-IDAEA	<i>Vaccinium vitis-idaea</i> L., <i>Ericaceae</i>	Diuretic
28. FRUCTUS ALNI	<i>Alnus incana</i> (L.) Moench <i>A. glutinosa</i> (L.) Gaertn., <i>Betulaceae</i>	Astringent
29. FRUCTUS ANETHI GRAVEOLENTIS	<i>Anethum graveolens</i> L., <i>Apiaceae</i>	Not claimed, Spasmolytic*
30. FRUCTUS ANISI VULGARIS	<i>Pimpinella anisum</i> L. (<i>Anisum vulgare</i> Gaertn.), <i>Apiaceae</i>	Not claimed, Expectorant*
31. FRUCTUS CARVI	<i>Carum carvi</i> L. <i>Apiaceae</i>	Not claimed, Spasmolytic*
32. FRUCTUS CRATAEGI	<i>Crataegus laevigata</i> (Poir.) DC. (<i>C. oxyacantha sensu</i> Pojark.) <i>C. korolkowii</i> L., Henry <i>C. altaica</i> (Lond.) Lange <i>C. chlorocarpa</i> Lenne <i>C. dahurica</i> Koehne ex Schneid. <i>C. monogyna</i> Jacq. <i>C. alemanniensis</i> Cin. <i>C. pentagyna</i> Waldst. et Kit. <i>C. orientobaltica</i> Cin. <i>C. curvisepala</i> Lindm. <i>C. X curonica</i> Cin. <i>C. X dunensis</i> Cin., <i>Rosaceae</i>	Cardiovascular
33. FRUCTUS FOENICULI	<i>Foeniculum vulgare</i> Mill., <i>Apiaceae</i>	Not claimed, Spasmolytic*
34. FRUCTUS JUNIPERI	<i>Juniperus communis</i> L., <i>Cupressaceae</i>	Diuretic
35. FRUCTUS MYRTILLI	<i>Vaccinium myrtillus</i> L., <i>Ericaceae</i>	Astringent
36. FRUCTUS PADI	<i>Padus avium</i> Mill. <i>P. asiatica</i> Kom., <i>Rosaceae</i>	Astringent
37. FRUCTUS RHAMNI CATHARTICAE	<i>Rhamnus cathartica</i> L., <i>Rhamnaceae</i>	Laxative
38. FRUCTUS ROSAE	<i>Rosa majalis</i> Herrm. (<i>R. cinnamomea</i> L.) <i>R. acicularis</i> Lindl. <i>R. davurica</i> Pall. <i>R. beggeriana</i> Schrenk <i>R. fedtschenkoana</i> Regel <i>R. canina</i> L. <i>R. corymbifera</i> Borkh. <i>R. micrantha</i> Smith, <i>R. kokanica</i> (Regel) Regel ex Juz., <i>R. psammophila</i> Chrshan., <i>R. tomentosa</i> Smith, <i>R. zangezura</i> P. Jarosch., <i>R. rugosa</i> Thunb., <i>Rosaceae</i>	Polyvitamin
39. FRUCTUS SORBI	<i>Sorbus aucuparia</i> L., <i>Rosaceae</i>	Polyvitamin
40. FRUCTUS VIBURNI	<i>Viburnum opulus</i> L., <i>Caprifoliaceae</i>	Diaphoretic, anti-inflammatory
41. GEMMAE BETULAE	<i>Betula pendula</i> Roth <i>B. pubescens</i> Ehrh., <i>Betulaceae</i>	Diuretic
42. GEMMAE PINI	<i>Pinus silvestris</i> L., <i>Pinaceae</i>	Expectorant
43. HERBA ADONIDIS VERNALIS	<i>Adonis vernalis</i> L., <i>Ranunculaceae</i>	Cardiotonic
44. HERBA ARTEMISIAE ABSINTHII, FOLIA ARTEMISIAE ABSINTHII	<i>Artemisia absinthium</i> L., <i>Asteraceae</i>	Bitterness (appetite stimulant) and choleretic
45. HERBA BIDENTIS	<i>Bidens tripartita</i> L., <i>Asteraceae</i>	Anti-inflammatory for external use
46. HERBA BURSARUM PASTORIS	<i>Capsella bursa-pastoris</i> (L.) Medik., <i>Brassicaceae</i>	Not claimed, Haemostatic*
47. HERBA CHELIDONII	<i>Chelidonium majus</i> L., <i>Papaveraceae</i>	Anti-inflammatory for external use
48. HERBA CENTAURII	<i>Centaurium erythraea</i> Rafn [syn.: <i>C. minus</i> 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
	<i>umbellatum</i> Gilib., <i>Erythraea Centaurium</i> (L.) Borkh] <i>C. pulchellum</i> (Sw.) Druce [syn.: <i>Erythraea pulchella</i> (Sw.) Hornem], <i>Centianaceae</i>	
49. HERBA CONVALLARIAE, FOLIA CONVALLARIAE, FLORES CONVALLARIAE	<i>Convallaria majalis</i> L., <i>C. transcaucasica</i> Utkin ex Grossh. <i>C. keiskei</i> Mig. <i>Liliaceae</i>	Cardiotonic
50. HERBA EQUISETI ARVENSIS	<i>Equisetum arvense</i> L., <i>Equisetaceae</i>	Diuretic
51. HERBA GNAPHALII ULIGINOSI	<i>Gnaphalium uliginosum</i> L., <i>Asteraceae</i>	Not claimed, Hypotensive, anti-inflammatory, choleric* [*]
52. HERBA HYPERICI	<i>Hypericum perforatum</i> L. <i>H. maculatum</i> Crantz (<i>H. quadrangulum</i> L.), <i>Hypericaceae</i>	Astringent, antiseptic
53. HERBA MILLEFOLII	<i>Achillea millefolium</i> L., <i>Asteraceae</i>	Not claimed, Haemostatic, anti-inflammatory
54. HERBA LEONURI	<i>Leonurus cardiaca</i> L. (<i>L. cardiaca</i> L. subsp. <i>villosus</i> (Desf.) Jav. <i>Leonurus quinquelobatus</i> Gilib., <i>Lamiaceae</i> .	Sedative
55. HERBA ORIGANI	<i>Origanum vulgare</i> L., <i>Lamiaceae</i>	Expectorant
56. HERBA POLYGONI AVICULARIS	<i>Polygonum aviculare</i> L., <i>Polygonaceae</i>	Not claimed, Diuretic*
57. HERBA POLYGONI HYDROPIPERIS	<i>Polygonum hydropiper</i> L., <i>Polygonaceae</i>	Haemostatic
58. HERBA POLYGONI PERSICARIAE	<i>Polygonum persicaria</i> L., <i>Polygonaceae</i> .	Not claimed, medicine of natural origin
59. HERBA THERMOPSIDIS LANCEOLATAE	<i>Thermopsis lanceolata</i> R. Br., <i>Fabaceae</i>	Not claimed, medicine of natural origin
60. HERBA SERPYLLI	<i>Thymus serpyllum</i> L., <i>Lamiaceae</i> .	Expectorant
61. HERBA THYMI VULGARIS	<i>Thymus vulgaris</i> L., <i>Lamiaceae</i>	Expectorant
62. HERBA VIOLAE	<i>Viola tricolor</i> L. <i>V. arvensis</i> Murr., <i>Violaceae</i>	Expectorant
63. INONOTUS OBLIQUUS	<i>Inonotus obliquus</i> (Pers.) Pil., <i>Hymenochaetaceae</i>	Not claimed, Regulation of metabolism, anti-inflammatory*
64. RADICES ALTHAEAE	<i>Althaea officinalis</i> L. <i>A. armeniaca</i> Ten., <i>Malvaceae</i> .	Expectorant
65. RADICES ARALIAE MANDSHURICAE	<i>Aralia elata</i> (Miq.) Seem. (<i>A. mandshurica</i> Rupr. et maxim.), <i>Araliaceae</i> .	Not claimed, Tonic*
66. RADICES GINSENG	<i>Panax ginseng</i> C. A. Mey., <i>Araliaceae</i>	Tonic
67. RADICUS ONONIDIS	<i>Ononis arvensis</i> L., <i>Fabaceae</i>	Not claimed, medicine of natural origin
68. RADICES RHEI	<i>Rheum palmatum</i> L. var <i>tanguticum</i> Maxim., <i>Polygonaceae</i>	Laxative
69. RADICES TARAXACI	<i>Taraxacum officinale</i> Wigg., <i>Asteraceae</i>	Bitterness (appetite stimulant) and choleric
70. RHIZOMATA BERGENIAE	<i>Bergenia crassifolia</i> (L.) Fritsch, <i>Saxifragaceae</i> .	Astringent, for external use
71. RHIZOMATA BISTORTAE	<i>Polygonum bistorta</i> L.	Astringent

Table 1 (continued)

Monograph title	Latin name of plant, family (as in the State Pharmacopoeia of the USSR)	Pharmacological group
72. RHIZOMATA CALAMI	<i>Acorus calamus</i> L., <i>Araceae</i>	Bitterness (appetite stimulant) and choleric
73. RHIZOMATA ET RADICES INULAE	<i>Inula helenium</i> L., <i>Asteraceae</i>	Expectorant
74. RHIZOMATA CUM RADICIBUS POLEMONII	<i>Polemonium caeruleum</i> L., <i>Polemoniaceae</i> .	Expectorant
75. RHIZOMATA ET RADICES RHODIOLAE ROSEAE	<i>Rhodiola rosea</i> L., <i>Crassulaceae</i>	Tonic
76. RHIZOMATA ET RADICES RUBIAE	<i>Rubia tinctorum</i> L. <i>R. iberica</i> (Fish. ex DC). <i>C. Koch</i> , <i>Rubiaceae</i>	Not claimed, Spasmolytic*
77. RHIZOMATA CUM RADICIBUS VALERIANAE	<i>Valeriana officinalis</i> L., <i>Valerianaceae</i>	Sedative
78. SEMINA CUCURBITAE	<i>Cucurbita pepo</i> L., <i>C. maxima</i> Duch. <i>C. moschata</i> (Duch.) Poir., <i>Cucurbitaceae</i>	Antihelminthic
79. SEMINA LINI	<i>Linum usitatissimum</i> L., <i>Linaceae</i>	Ambient
80. SEMINA SCHISANDRAE	<i>Schisandra chinensis</i> (Turcz.) Baill., <i>Schisandraceae</i>	Tonic
81. STROBILI PICEAE ABIETIS	<i>Picea abies</i> (L.) Karst., <i>Pinaceae</i>	Anti-inflammatory
82. STYLI CUM STIGMATIS ZEAE MAYDIS	<i>Zea mays</i> L., <i>Poaceae</i>	Choleric
83. THALLI LAMINARIAE	<i>Laminaria saccharina</i> (L.) Lam., <i>Laminariaceae</i>	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	<i>in vitro</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . Broth microdilution method <i>in vitro</i> . 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 – flavanomorein Essential oils by hydrodistillation	<i>in vitro</i> .	No data	Gram-positive: <i>Bacillus subtilis</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> . Gram-negative: <i>Escherichia coli</i> , <i>E. coli</i> (β-lactamase +), <i>Klebsiella pneumoniae</i> (ESBL+), <i>Pseudomonas aeruginosa</i> , Fungi: <i>Candida albicans</i> , <i>C. parapsilosis</i> , <i>Aspergillus fumigatus</i> , <i>A. terreus</i>	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 <i>C. albicans</i> and <i>C. parapsilosis</i>	Tomczykowa et al., 2008
Antioxidant	<i>in vitro</i> . DPPH assay	Dry flowers and herb	Aqueous, MeOH/water, acetone/water and MeOH crude extracts	<i>in vitro</i> .			Radical scavenging for MeOH/water extract of flowers - 68% ; for acetone/ water extract of herb -66%	Wolniak et al. 2007
	<i>in vitro</i> . DPPH assay	Aerial part	Isoookanin 7-O-glucoside, luteolin 7-O glucoside, luteolin	<i>in vitro</i> .			Radical scavenging : 25% for luteolin 7-O glucoside, 41% for luteolin	Wolniak et al. 2007
Antithrombin	<i>in vitro</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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, choleric, 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 choleric 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 hypotensive 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 *Centaureum erythraea* Rafn [syn.: *C. minus* Moench, *Erythraea Centaureum* (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	<i>in vivo</i> . 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	<i>in vitro</i> . Agar well diffusion method	Fruit	Fresh juice, standardized by phenolics and anthocyanins.	<i>in vitro</i> .	Wells with 50 µL of juice	Gram-positive: <i>S. aureus</i> , <i>S. epidermidis</i> , <i>B. subtilis</i> , <i>Listeria monocytogenes</i> , <i>Enterococcus faecalis</i> , <i>Micrococcus luteus</i> . Gram-negative: <i>P. aeruginosa</i> , <i>E. coli</i> , <i>Salmonella typhimurium</i> , <i>S. agona</i> Yeast: <i>Debaryomyces hansenii</i> , <i>Trichosporon cutaneum</i> , <i>Kluyveromyces marxianus var. lactis</i> , <i>Torulaspota delbrueckii</i> , <i>Saccharomyces cerevisiae</i> , <i>Candida parapsilosis</i>	Strong inhibition of <i>S.typhimurium</i> (inhibition zone 25.3-30.3 mm), <i>S. agona</i> (23.3-27.7 mm), <i>L. monocytogenes</i> (26.5 ± 0.35 mm), <i>E. faecalis</i> (25.7 mm), and <i>S. aureus</i> (24.1 mm). Most resistant: <i>P. aeruginosa</i> , <i>M. luteus</i> , <i>S. epidermidis</i> . No or little antifungal activity was observed	Česonienė et al., 2012
Antimicrobial	<i>in vitro</i> . Agar well diffusion method	Fruits	MeOH extract (10 and 15%)	<i>in vitro</i> .	No data	Negative control.	Most sensitive: <i>Aeromonas hydrophila</i> , most resistant <i>Yersinia enterocolitica</i> EC ₅₀ =24.56 mg/mg	Sagdic et al., 2006
Antioxidant	<i>in vitro</i> . DPPH assay	Fruit	Flesh, standardized by malic, oxalic, citric acids, total phenolic, total flavonoid, and total anthocyanin contents	<i>in vitro</i> .	No data	Negative control.	EC ₅₀ =2.35 mg/mg	Cam et al. 2007
	<i>in vitro</i> . DPPH assay	Fruit	Seeds, standardized by malic, oxalic, citric acids, total phenolic, total flavonoid, and total anthocyanin contents	<i>in vitro</i> .	No data	Negative control.	EC ₅₀ =2.35 mg/mg	Cam et al. 2007
	<i>in vitro</i> . 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	<i>in vitro</i> .	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	<i>in vivo</i> . 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	<i>in vitro</i> . Peritoneal cells of rats.	Fruit	Water-soluble polysaccharide fractions from the squeezed fruits. Acidic polysaccharides with α-1,4-linked 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	Polisaccharides, 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	<i>in vitro</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . 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	<i>in vivo</i> . Experimental gastric dystrophy by stomach alteration in reserpined or immobilized mice	Not specified	Isolated gnaphalosite 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 (1.7 fold) and large bandlike (2.3 fold) lesions compared with control (reserpined mice). Decrease of number of lesions of any type (by 2.6 to 3.1 fold) and number of animals with various gastric lesions (2.5 fold) compared with control (immobilized mice).	Barnaulov et al., 1984
Hypotensive	<i>in vivo</i> . SHR rats	Aerial part	Crude aqueous extract. gnaphalosite A; 6''-caffeyl-7-β-D-glucopyranosyloxy-4',5-dihydroxy-3',6'-dimethoxyflavone; 3',4',5,7-tetrahydroxy-6-methoxyflavone 7-O-(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 <i>Klebsiella pneumoniae</i>	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	<i>E. coli</i> , <i>Salmonella typhimurium</i> , <i>Enterobacter cloacae</i> , <i>P. aeruginosa</i> , <i>P. tolaasii</i> , <i>Proteus mirabilis</i> , Gram-positive <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Streptococcus faecalis</i> , <i>B. subtilis</i> <i>Micrococcus luteus</i> , <i>M. flavus</i> , <i>Sarcina lutea</i> , <i>Listeria monocytogenes</i> ; yeast: <i>C. albicans</i> . 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
	<i>in vitro</i> . 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	<i>in vivo</i> . Rats, CCl ₄ induced hepatitis	Catkins	Polyphenolic extract (ellagic and gallic acid)	Intragastric	1 mg/kg	Negative control. Positive control: Carsil.	It limits cholepoiesis disorder, has an anti-inflammatory and membrane stabilizing effect, recovers physiological antioxidant system, increase of bile secretion and cholesterol content in bile. Repaired functional activity of mitochondria to the intact level in EtOH-induced hepatitis and increased microsomal hydroxylase activity in CCl ₄ induced hepatitis	Buniatian et al., 1998
Hepatoprotective	<i>in vivo</i> . Rats CCl ₄ induced hepatitis, EtOH-induced hepatitis	Catkins	Polyphenolic extract (ellagic and gallic acid)	Intragastric	1 mg/kg	Negative control		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 LD₅₀ 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 chagirsy 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 LD₅₀ 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. Choleric 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 choleric, 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 choleric, 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 choleric 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 choleric. "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. Antihelminthic and choleric 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	<i>in vivo</i> . 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: <i>Rhodiola rosea</i> 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	<i>in vitro</i> . Human lymphoblastoid Raji cells	Rhizomes, green leaves	Crude EtOH (40%) extract	<i>in vitro</i>	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	<i>in vitro</i> . Liquid dilution method	Rhizomes, leaves	EtOH (80%) extract	<i>in vitro</i> .	No data	<i>B. cereus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>C. albicans</i> . Positive control: erythromycin, gentamicin, amphotericin B	MIC (mg/mL) for leaves/rhizomes: <i>B. cereus</i> : 62.50 / 15.63; <i>E. coli</i> : 62.50/15.63; <i>P. aeruginosa</i> , 15.63/ 62.50; <i>S. aureus</i> : 62.50/62.50; <i>C. albicans</i> : 250.00/ 15.63	Kokoska et al., 2002
Anti-inflammatory	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in situ</i> . DPPH assay after HPTLC separation.	Leaves, green, brown, black.	MeOH extract, with arbutin, bergenin, ellagic, gallic acids, hydroquinone.	<i>in vitro</i> .	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
	<i>in vitro</i> . DPPH assay.	Rhizomes	EtOH (70%) extract, (+)-catechin 3,5-di-O-gallate, (+)-catechin 3-O-gallate	<i>in vitro</i> .	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	<i>in vitro</i> . Human pancreatic lipase inhibition	Rhizomes	EtOH (70%) extract, (+)-catechin 3,5-di-O-gallate, (+)-catechin 3-O-gallate	96-well plate	25 μ L	Negative control. Positive control: (-)-Catechin 3-O-gallate, (-)-Epicatechin 3-O-gallate	IC ₅₀ (μ g/mL), 3.4 \pm 0.2 for extract, 0.42 \pm 0.04 for (+)-catechin 3,5-di-O-gallate, 2.02 \pm 0.11 for (+)-catechin 3-O-gallate.	Ivanov et al., 2011
Cerebro-protective	<i>in vivo</i> . 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 oxidase system.	Khazanov, Smirnova 2000
Immuno-stimulating	<i>in vivo</i> . Mice, delayed type hypersensitivity (DTH) reaction to aggregated ovalbumin on footpad swelling. <i>in vitro</i> . phagocytic activity of human blood neutrophils. <i>in vitro</i> . 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 <i>ad libitum</i> (6 mg/day) 3 weeks. 10 μ L for phagocytic activity. 50 μ L for peritoneal cells assay.	Negative control. Positive control: apple pectin	Increase of DTH reaction <i>in vivo</i> . Bergen enhanced uptake capacity of human neutrophils at 10 μ g/mL and stimulated generation of oxygen radicals by mouse peritoneal macrophages <i>in vitro</i> . Bergen increased spontaneous adhesion of peritoneal leukocytes but did not influence adhesion stimulated by PMA or adhesion of peritoneal leukocytes.	Popov et al. 2005
Hypotensive	<i>in vivo</i> . 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, Makarova 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 phenolcarboxylic acids extracted from tansy flowers (0.05 g/ tablet), is registered in Russia as a choleric 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 LD₅₀ values were 9.9 g/kg and 2.8 g/kg for the oral and intraperitoneal modes of administration, respectively. The LD₅₀ 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 LD₅₀ 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 choleric and an antihelminthic. Tanacechol[®] tablets containing 0.05 g of a purified complex extract of flavonoids and phenolcarboxylic 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	<i>in vitro</i> , agar-well diffusion method	Aerial part	MeOH extract, Soxhlet with gallic, <i>p</i> -hydroxybenzoic, chlorogenic, caffeic, syringic, <i>p</i> -coumaric, ferulic, rosmarinic acids, catechin, epicatechin, rutin, resveratrol, hesperidin, apigenin- 7-glucoside, eriodictyol, quercetin, naringenin, luteolin, apigenin, and acacetin.	<i>in vitro</i> .	100, 50, 25, 10 µg/mL	<i>Aeromonas hydrophila</i> , <i>Bacillus brevis</i> , <i>B. cereus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Morganella morganii</i> , <i>Mycobacterium smegmatis</i> , <i>Proteus mirabilis</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Yersinia enterocolitica</i> , <i>C. albicans</i> , <i>Saccharomyces cerevisiae</i> . Positive control: amoxicillin, and 11 other antibiotics.	No activity against <i>E. coli</i> , <i>B. subtilis</i> , <i>M. morganii</i> , <i>M. smegmatis</i> , <i>P. mirabilis</i> , <i>Y. enterocolitica</i> , <i>S. cerevisiae</i> . Inhibition diameter (mm at 100 µg/mL): <i>A. hydrophila</i> (28.0), <i>B. brevis</i> (22.5), <i>B. cereus</i> (22.5), <i>K. pneumoniae</i> (17.0), <i>P. aeruginosa</i> (28.0), <i>S. Aureus</i> (23.5).	Albayrak et al., 2010
Anticancer	<i>in vitro</i> . 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	<i>in vitro</i> . Clotting assays of activated partial thromboplastin time (APTT) and of prothrombin time (PT)	Flowers	Crude extract with polyphenolic-polysaccharide fraction	<i>in vitro</i> .	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	<i>in vitro</i> , 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- <i>O</i> -β-D-glucopyranoside, apigenin 7- <i>O</i> -β-D-glucopyranoside, apigenin 7- <i>O</i> -gentiobioside, apigenin 7,4'-di- <i>O</i> -β-D-glucopyranoside.	Morikawa et al., 2009
Antioxidant	<i>in vitro</i> . DPPH assay, reducing iron(III), H ₂ O ₂ : OH- luminol-microperoxidase 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- <i>O</i> -glucoside, luteolin-7- <i>O</i> -glucoside, quercetin-3- <i>O</i> -glucoside, chlorogenic acid)	<i>in vitro</i>	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 ₂ O ₂ /OH luminol-microperoxidase system)	Czinner et al., 2000
	<i>in vitro</i> . DPPH assay, phospho-molybdenum method	Aerial part	MeOH extract, Soxhlet with gallic, <i>p</i> -hydroxybenzoic, chlorogenic, caffeic, syringic, <i>p</i> -coumaric, ferulic, rosmarinic acids, catechin, epicatechin, rutin, resveratrol, hesperidin, apigenin- 7-glucoside, eriodictyol, quercetin, naringenin, luteolin, apigenin, and acacetin.	<i>in vitro</i>	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
	<i>in vitro</i> . Lipid peroxidation in rats liver microsomes	Inflorescences.	Lyophilized water extracts standardized by polyphenols and flavonoids	<i>in vitro</i>	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	<i>in vitro</i> . 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
Hypotensive	<i>in vivo</i> . Rats, dogs	Aerial part	Ether, EtOH, aqueous extracts	Intravenous	50 mg/kg (dogs), 500 mg/kg (rats)	Negative control	Hypotensive effect	Szadowska, 1962
Spasmodic	<i>in vivo</i> . Rats	Aerial part	Aqueous solutions of naringenin-5-glucoside, kaempferol-3-glucoside), apigenin dissolved in phosphate-buffered sodium hydroxide. EtOH extract containing all flavonoids and aqueous extract containing no flavonoids.	Intravenous	4 mg/100 g bw 50 mg/100 g bw	Negative control. Positive control: dehydrocholic acid	Spasmodic activity and choleric effects (approximately 33% of that of dehydrocholic acid) for individual compounds. The flavonoids extract demonstrated spasmodic 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 LD₅₀ 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 LD₅₀ values for the chloroform fraction were 350 mg/kg (intraperitoneal) and 2,600 mg/kg (intragastric), and the LD₅₀ 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 LD₅₀ 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 official 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 hemangio-endothelial 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	<i>in vitro</i> . Mouse leukemia cells L1210,	Aerial part	Methylene chloride and MeOH extracts, soxhlet	96 well plate	10 µg per well	Positive control: Methotrexate Negative control: albendazole	99% growth inhibition by methylene chloride extract, 95% growth inhibition by MeOH extract	Goun et al., 2002
Anthelmintic	<i>in vitro</i> . Egg hatching assay (<i>Ascaris suum</i>), larval migration inhibition (L3 larvae from <i>Trichostron-gylus colubriformis</i>)	Aerial part	EtOH (80%) extract.	96 well plate.	62.5–2000 µg/mL	Negative control: albendazole	46% ovicidal effect on <i>A. suum</i> eggs at 2000 µg/mL; 49.5% larval migration inhibition at 2000 µg/mL	Urban et al., 2008
Anti-inflammatory	<i>in vivo</i> , mouse-ear edema induced by 12-0-tetradecanoylphorbol 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: 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
	<i>in vivo</i> , Rats, formalin induced edema	Inflorescence	Polysaccharide complex (ammonium oxalate extract)	Intragastric	0.3 g/kg, 7 days	Negative 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	<i>in vitro</i> . DPPH assay,	Aerial part	MeOH crude extract, 3,5-O-dicaffeoylquinic acid, axillarin, luteolin	<i>in vitro</i> .	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	<i>in vitro</i> . 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	<i>in vitro</i> , 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-dicaffeoylquinic 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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

Immunomodulatory	<i>in vitro</i> . Activation of NF- κ B, NO, ROS, and TNF- α production.	Flowers	Polysaccharides with $M_r=326, 151, 64$ and 9 kDa	96 well plate	0–1600 μ g/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- κ B signaling in monocytic cells.	Xie et al., 2007
Spasmolytic	<i>in vitro</i> . Rats isolated aorta	Aerial part	Crude aqueous decoction, lyophilized.	<i>in vitro</i> .	50, 100, 200, 400, 800 μ g/mL	Negative control.	Biphasic concentration-dependent relaxation: a first rapid effect within 10 min after addition of extract (50 μ g/mL) and maximum at 200 μ g/mL, which relaxed contraction by about 30%	Lahlou et al., 2008b
	<i>in vitro</i> . Serotonin release inhibition.	Leaves	EtOH extract, parthenolide	<i>in vitro</i> .	1200–24000 μ g/mL for EtOH extract; 1.14–6.04 μ M for parthenolide	Negative control.	Serotonin release inhibition with $IC_{50}=9797$ μ g/mL fresh weight for EtOH extract and $IC_{50}=3.03$ μ mol 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 μ g/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 μ g.

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 efficacious 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 therapeutic 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 LD₅₀ 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 Polemonii* 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	<i>in vitro</i> . Broth dilution method.	Shoots	Aqueous extract and isolated polysaccharide complex	<i>in vitro</i>	1/20-1/160	Tested microbes <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Klebsiella pneumoniae</i>	Bacteriostatic effect at 1/160 dilution, excluding to <i>P. aeruginosa</i> (1/20 dilution) for polysaccharide complex.	Belousov et al., 2006
Anticancer	<i>in vitro</i> . 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	<i>in vitro</i> . Human lymphoblastoid Raji cells	Aerial part	Crude EtOH (40%) extract	<i>in vitro</i>	10, 50, 200 µg/mL	Positive control: methotrexate, fluorouracil, cyclophosphamide, vinblastine. Negative control	99% inhibition at 200 µg/mL	Spiridonov et al., 2005
Antidiabetic	<i>in vitro</i> . 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	<i>in vitro</i> .	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 by 10 mmol/L rosiglitazone	Harbilas et al., 2009
Antidiabetic	<i>in vitro</i> . Caco-2/15 cells; western blot analysis. <i>in vivo</i> . Rats, oral glucose tolerance test	Leaves	EtOH (80%, 1:10) extract with 153.5 µg/mg total phenolic		25–100 µg/mL (<i>in vitro</i>); 250 mg/kg (<i>in vivo</i>)	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. <i>in vivo</i> 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	<i>in vitro</i> . 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	<i>Cryptococcus neoformans</i> , <i>Saccharomyces Cerevisiae</i> , <i>Aspergillus niger</i> , <i>C. albicans</i> . Positive control amphotericin B, fluconazole	MIC = 16-63 µg/mL for <i>C. neoformans</i> , <i>S. cerevisiae</i> and <i>A. niger</i> . MIC = 0.16–10 µg/mL for amphotericin B and fluconazole. MIC = 250 µg/mL for <i>C. albicans</i> .	Jin et al., 1999

Table 9 (continued)

Activity tested	Model used	Plant part used	Extract type	Admin	Dosage/ duration	Control	Results	Reference
Anti-inflammatory	<i>in vitro</i> . Prostaglandin biosynthesis assay; PAF-induced exocytosis	Aerial part	Aqueous extract, lyophilized.	<i>in vitro</i>	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	<i>in vitro</i> . Prostaglandin-synthesizing cyclooxygenase system from sheep seminal vesicles and HPLC separation	Aerial part	Essential oil	<i>in vitro</i> .	37 µMol	Positive control: eugenol, carvacrol, thymol, guajazulen, urushiol, curcumin, piperin, capsaicin, apiol, cubebin, isoalantolacton, ledol	Ether oil inhibited cyclooxygenase <i>in vitro</i> 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	<i>in vivo</i> . 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 ± 4.6% inhibition of edema by EtOH 40% extract, comparable to butadione.	Belousov et al., 2006
Antioxidant	<i>in vitro</i> . DPPH assay, Fe ³⁺ -EDTA-H ₂ O 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-caryophyllene (2–6% range)	<i>in vitro</i> .	Not indicated	Negative control.	IC ₅₀ = 1.6 µg/mL in DPPH assay; IC ₅₀ = 2.7 µg/mL in Fe ³⁺ -EDTA-H ₂ O ₂ deoxyribose system; IC ₅₀ = 13.5 µg/mL in nonenzymatic lipid peroxidation of rat liver homogenate	Kim, Nam, 2006
Antithrombin	<i>in vitro</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . Mice irradiated with γ-irradiation	Aerial part	Combination of <i>Archangelica officinalis</i> and <i>L. palustre</i> 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
	<i>in vivo</i> . 30 days albino mongrel male mice irradiated with γ-irradiation (LD _{90/30})	Aerial part	Combination of <i>Archangelica officinalis</i> and <i>L. palustre</i> 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 ± 0.6 and 7.4 ± 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 times 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	<i>in vitro</i> . 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	<i>in vitro</i> . Murine macrophage cell line (RAW 264.7), lipopolysaccharide-activated macrophages	Flower buds	Isolated 1α,5α-bisacetoxy-8-angeloyloxy-3β,4β-epoxy-bisabol-7(14),-10-dien-2-one	96 well plate	No data	N ^G -monomethyl-L-arginine	Inhibition of arachidonic acid metabolism and i-NOS (71.1%) with IC ₅₀ = 8.9 µM.	Ryu et al., 1999
Anti-inflammatory	<i>in vitro</i> . Murine macrophage cell line (RAW 264.7), lipopolysaccharide-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 PGE ₂ as well as i-NOS and COX-2 LPS-stimulated RAW264.7 cells and murine peritoneal macrophages	Hwangbo et al., 2009
Antimicrobial	<i>in vitro</i> . Liquid dilution method	Aerial part, rhizome	EtOH (80%) extract	<i>in vitro</i> .	No data	<i>B. cereus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>C. albicans</i> . Positive control: erythromycin, gentamicin, amphotericin B	MIC (mg/mL) for aerial part/rhizome <i>B. cereus</i> : 16.63/62.5; <i>S. aureus</i> : 62.50/62.5	Kokoska et al., 2002
Antioxidant	<i>in vitro</i> . Lipid peroxidation in rat brain homogenates, DPPH assay.	Flower buds	EtOAc fraction from MeOH extract	<i>in vitro</i> .	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	<i>in vitro</i> . DPPH assay, pyrogallol autoxidation assay	Flower buds	EtOAc, BuOH, aqueous fractions from EtOH (70% extract). Main compounds: chlorogenic and 3, 5-O-dicaffeoylquinic acids.	<i>in vitro</i>	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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . Cortical cell cultures	Flower buds	EtOAc fraction from MeOH extract	<i>in vitro</i> .	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 _β (25–35)-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 Fe ²⁺ /ascorbic acid-induced damage at 30 µg/mL. H ₂ O 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 LD₅₀ 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 cavitory 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 LD₅₀ of cymarín (one of the active glycosides present) after intravenous injection in rats was found to be 24.8 ± 1.8 mg/kg (Vogel, Kluge, 1961) and the LD₅₀ after intravenous injection in cats was found to be 95.4 ± 3.0 µg/kg (Chen et al., 1942). The M.S.D. values for adonitoxin and cymarín are 0.621 ± 0.046 g/g and 0.880 ± 0.070 g/g frog, respectively (Chen, Anderson, 1947). The LD₅₀ for adonitoxin after intravenous injection in cats was found to be 191.3 ± 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 "Adonidid" (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	<i>in vitro</i> Human lymphoblastoid Raji cells	Root	Crude EtOH (40%) extract helenin (40% alantolactone and 60% isoalantolactone)	<i>in vitro</i>	10, 50, 200 µg/mL	Positive control: methotrexate fluorouracil, cyclophosphamide, 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
	<i>in vitro</i> . 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
Antihelminthic	<i>in vitro</i> . Egg hatching assay (eggs <i>Ascaris sum</i>) larval migration inhibition (LMI) (<i>Trichostron gylus colubriformis</i>)	Rhizomes and roots	EtOH (80%) extract	96 well plates	62.5–2000 µg/mL	Positive control: albendazole. Negative control.	Athelminthic 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
	<i>in vivo</i> . Rabbits infected with <i>Clonorchis sinensis</i>	Root	Boiled water extract	<i>in vivo</i> .	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	<i>in vivo</i> . 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	<i>in vitro</i> . Broth dilution assay	Root	Helenin (a crystalline mixture of eudesmanolides)	<i>in vitro</i> .	10–750 µg/mL	Negative control. Several strains of <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>C. albicans</i>	The MIC (µg/mL) against several strains of <i>S. aureus</i> was 10–400, <i>E. coli</i> and <i>P. aeruginosa</i> 200–750, <i>C. albicans</i> – 200–750.	Kowalewski et al., 1976
	<i>in vitro</i> . Broth microdilution method	Root	Stepwise supercritical fluid extract (SFE), hydrodistillate (HD). Main compounds: alantolactone, isoalantolactone and β -elemene	<i>in vitro</i> .	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 <i>Bacillus cereus</i> , <i>S. aureus</i> , <i>Enterococcus faecium</i> clinical strain resistant to ampicillin, erythromycin, penicillin and tetracycline (MIC > 0.03 mg/mL). <i>Candida</i> strains were most	Deriu et al., 2008

	<i>in vitro</i> . Radiorespirometric bioassay against <i>Mycobacterium tuberculosis</i>	Root	Isolated alantolactone, isoalantolactone, 11 α H, 13-dihydro- isoalanto-lactone	<i>in vitro</i> .		Negative control. Positive control: encelin from <i>Montanoa speciosa</i>	susceptible, with MIC = 0.009– 0.12 mg/mL. MIC for alantolactone and isoalantolactone was 32 μ g/mL.	Cantrell et al. 1999
	<i>in vivo</i> . Mice inoculated with <i>S. aureus</i> suspension in the left nare	Root	Isoalantolactone	Subcuta- neously	50 mg/kg, 2 h after infection with <i>S. aureus</i> 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	<i>in vitro</i> . MK-1, HeLa, B16F10 cell lines, MTT assay	Root	MeOH extract , isolated 1,3,11(13)- elematrien-8 β ,12- olide, igalan; 5 α - epoxyalantolac- tone; 4 β , 5 α -epoxy-1(10),11 (13)- germacradiene- 8,12-olide; alantolactone, isoalantolactone, 11 α ,13-dihyd- roalantolactone, 11 α ,13- dihydroisoalanto- lactone	<i>in vitro</i> .		Negative control. Positive control: 5-fluorouracil	GI ₅₀ (μ M) for 5 α -epoxyalan- tolactone was 3.6-6.9, for alantolactone – 4.7-6.9. 1,3,11(13)- elematrien-8 β ,12-olide, igalan exhibited almost the same potency, but GI ₅₀ against HeLa cells was 2 folds lower.	Konishi et al., 2002
Antithrombin	<i>in vitro</i> . Thrombin solution from bovine plasma	Not specified	Methylene chloride extract, soxhlet	96 well plate	50 μ L	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	<i>in vivo</i> . 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 <i>Beta vulgaris</i>	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.
	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . Rats, prolongation of soporific effect of sodium ethaminal	Roots with rhizome	Dry powder	Intragastric	30, 60, 120 mg/kg	Negative control. Positive control: <i>V. officinalis</i> powder	Combination of <i>P. caeruleum</i> and <i>V. officinalis</i> (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	<i>in vitro</i> . Single uterine horns from virgin Holtzman rats	Bark	MeOH extract with yield 4%.	<i>in vitro</i>	0.4 g/mL	No data	Complete relaxation of muscle at 1 mL	Jarboe et al., 1966
	<i>in vitro</i> . Single uterine horns from virgin Holtzman rats	Bark	Isolated scopoletin	<i>in vitro</i>	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
	<i>in vitro</i> . Barium stimulated rat uterus.	Bark	Isolated viopudial	<i>in vitro</i>	No data	No data	ED ₅₀ for spasmolytic effect 24 µg/ml	Nicholson et al., 1972
Hypotensive	<i>in vivo</i> . 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. "Adonisd" 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 "Adonisd" 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 LD₅₀ 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 LD₅₀ 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 discirculatory 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.) DC. (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.) Delarb. (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 LD₅₀ 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	<i>in vivo</i> . Rats, carrageenan-induced and Zymosan-induced edema. Mice, croton oil-induced inflammation of ear.	Flower-heads	Water-soluble EtOH-insoluble polysaccharides fraction	Intraperitoneal 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	<i>in vitro</i> . Haemolytic activity of complement. Anaphylatoxin activity in rat serum	Flower-heads	Water-soluble EtOH-insoluble polysaccharides fraction	<i>in vitro</i> .	10, 50, 250, 1000 µg/mL (haemolytic) 0.01, 0.1, 0.5, 1, 5, 10 mg/mL (anaphylatoxin)	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	<i>in vivo</i> . Rats with stress-induced ulcer (immersion and immobilization of rats into cold water, on dorsal position)	Herb, flowers	Vegetal product (combination of polysaccharides 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	<i>in vivo</i> . 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 LD₅₀ 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	<i>in vitro</i> . Caco-2/15 intestinal cells; western blot analysis. <i>in vivo</i> . Rats, oral glucose tolerance test (OGTT)	Not indicated	EtOH (80%, 1:10) extract	<i>in vitro</i> 96-well plate. <i>in vivo</i> per oral	25–100 µg/mL (<i>in vitro</i>); 250 mg/kg (<i>in vivo</i>)	Negative control. Positive control: cytochalasin B, phlorizin, phloretin.	100 µg/mL instantaneous inhibition glucose absorption in Caco2/15 cells. <i>in vivo</i> No effect in OGTT.	Nistor Baldea et al., 2010
Anti-inflammatory	<i>in vitro</i> . Prostaglandin biosynthesis assay; PAF-induced exocytosis	Leaves	Aqueous extract, lyophilized.	<i>in vitro</i>	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	<i>in vivo</i> . 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 to dexamethasone (1 g/kg).	Wang et al., 2005
Antimicrobial	<i>in vitro</i> . Agar dilution assay, <i>Porphyromonas gingivalis</i> , <i>Prevotella intermedia</i>	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.	<i>in vitro</i> .	0–100 µg/mL	Negative control. Positive control: tetracycline	Epicatechin-(4β-8)-epicatechin-(4β-8, 2β-O-7)-catechin, had strong antimicrobial activity against <i>Porphyromonas gingivalis</i> and <i>Prevotella intermedia</i> with MIC of 25 µg/ml.	Ho et al., 2001
Antimicrobial	<i>in vitro</i> . Tube dilution assay, eleven strains of <i>E. coli</i> .	Leaves	Aqueous, EtOAc, EtOH extracts	<i>in vitro</i> .	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	<i>in vitro</i> . 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.	<i>in vitro</i> .	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	<i>in vitro</i> . 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	<i>in vitro</i> . 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-suppressant	<i>in vivo</i> . Mice, in upset beaker saturated with 25% NH ₄ OH	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	<i>in vivo</i> . 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	<i>in vivo</i> . 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 ₄ Cl	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 ₄ Cl (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 × C3H)F₁ 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	<i>in vitro</i> . Human lympho-blastoid Raji cells	Buds	Crude EtOH (40%) extract	<i>in vitro</i>	10, 50, 200 µg/ mL	Positive control: methotrexate fluorouracil, cyclophosphamide, vinblastine. Negative control	63% inhibition at 50 µg/mL and 95% inhibition at 200 µg/ mL,	Spiridonov et al., 2005
Anticancer	<i>in vitro</i> . 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	<i>in vitro</i> . <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> . Agar diffusion assay, agar dilution assay.	Buds	Acetone extract (1:5), re-extracted with MeOH,	<i>in vitro</i> .	0.039- 5%	Negative control. Positive control: ciprofloxacin, gentamicin sulphate, penicillin	Inhibition zones for MeOH extract and decoction were against <i>S. aureus</i> : 11.2 and 10.2 mm, against <i>B. subtilis</i> : 11 and 8 mm, against <i>P. aeruginosa</i> : 11.6 and 0 mm. MIC for MeOH extract against <i>P. aeruginosa</i> : 1.25%, against <i>B. subtilis</i> : 2.5%, against <i>S. aureus</i> : 2.5%.	Duric et al., 2013
Antimicrobial	<i>in vitro</i> . Agar dilution assay, antibiotic-resistant forms of 144 strains of <i>Staphylococci</i> isolated from patients with mastitis, furunculosis, abscesses, peritonitis.	Buds	EtOH (70%) tincture (1:5)	<i>in vitro</i> .		Negative control.	Antibacterial activity was observed for all strains with MIC in dilution 1:90-1:100	Nikolaeva, Khokhlova, 1981
Antioxidant	<i>in vitro</i> . DPPH assay, ABTS ⁺ assay,	Buds	EtOH extract	<i>in vitro</i>	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 ⁺ assay.	Mashentseva et al., 2011
Antioxidant	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> , human whole blood cell culture system stimulated with lipopolysaccharide – activated macrophages. <i>in vitro</i> , Agar diffusion, method, HeLa cells	Aerial part	MeOH 50% extract.	96 well plate	500 µL/mL	Negative control.	35% inhibition TNF-α production	Das et al., 2007
Antiviral		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	<i>in vivo</i> , Cats	Not mentioned.	SCOA, a product which contains extracts from <i>Scilla</i> , <i>Convallaria</i> , <i>Oleander</i> and <i>Adonis</i>	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 <i>Adonis</i> extract on capacitance vessels twice as much as <i>Scilla</i> , <i>Oleander</i> and <i>Convallaria</i> extracts. Cymarin (main glycoside of <i>Adonis</i>), has stronger effect on veins than expected from its cardiotoxic effect.	Lehmann, 1984

significantly increased in the treated groups of both sexes. Histo-pathologically, 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-methylantraquinone, 2-ethoxymethyl-antraquinone, rubiadin, 1,3-dihydroxy-antraquinone, 7-hydroxy-2-methylantraquinone, lucidin, 1-methoxymethylantraquinone, and lucidin-3-O-primeveroside, which were isolated from the roots of *R. tinctorum*, exhibited mutagenicity with *Salmonella typhimurium* 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	<i>in vivo</i> , 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	<i>in vitro</i> . Agar diffusion, method. HeLa cells	Leaves	Aqueous extract (1:10)	<i>in vitro</i>	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	<i>in vivo</i> , beating rabbit atria	Aerial part	Aqueous extract (1:5), dry, convallatoxin	<i>ex vivo</i>	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	<i>in vitro</i> . Rabbit erythrocytes, (Na ⁺ + K ⁺)-ATPase, from hog cerebral cortex	Not specified	Convallatoxin.	<i>in vitro</i> .	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	<i>in vivo</i> . Cats	Not specified.	SCOA, a product which contains extracts from <i>Scilla</i> , <i>Convallaria</i> , <i>Oleander</i> and <i>Adonis</i>	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	<i>in vivo</i> . Cats wit modulated ischemia	Leaves	Tincture, no details about preparation	Intravenous	0.2 mL	Negative control. Positive control: tinctures of <i>A. vernalis</i> , <i>Digitalis purpurea</i> , <i>Narium oleander</i> .	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	<i>in vivo</i> . 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 ruberitric 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 antifatulent 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 12th 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 LD₅₀ 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 os* 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 hypoaacid 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	<i>in vivo</i> . 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	Transdermal	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	<i>in vivo</i> . 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	<i>in vitro</i> . Murine macrophage cell line (RAW 264.7), lipopolysaccharide-activated macrophages	Leaves	Commercial MeOH extract (99% purity)	96 well plate	0–200 μ g/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- κ B, 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	<i>in vivo</i> . 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	<i>in vitro</i> . Broth microdilution method.	Leaves	Confertifolin isolated from essential oil.	<i>in vitro</i> .	Initial concentration 0.5 mg/mL	Negative control. Positive control: fluconazole, ketoconazole, streptomycin	MIC (μ g/mL) was 1.56 against <i>Erwinia</i> sp, 6.25 against <i>S. aureus</i> and <i>K. pneumoniae</i> , 7.82 against <i>E. floccosum</i> , <i>C. Lunata</i> , and <i>Scopulariopsis</i> sp., and 16.62 against <i>T. mentagrophytes</i> and <i>T. rubrum</i>	Duraipandiyar et al., 2010
Antinociceptive	<i>in vivo</i> . 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	<i>in vitro</i> . DPPH assay	Aerial part	Hidropiperoside B and vanicosides A isolated from MeOH extract	96 well plate	No data	Negative control.	IC ₅₀ = 23.4 μ g/mL for hidropiperoside B, 26.7 μ g/mL, for vanicosides A.	Kiem et al., 2008
	<i>in vitro</i> . Ferric thiocyanate method	Leaves	Isolated 7,4'-dimethylquercetin, 3'-methylquercetin	<i>in vitro</i> .	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	<i>in vitro</i> . 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 μ g/mL.	Fukuyama et al., 1980
Estrogenic	<i>in vivo</i> . Ovary-intact and ovariectomized (OVX) rats	Roots	MeOH extract	Per oral	1000 mg/kg / 12 days	Negative control. Positive control: estradiol-17 β (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	<i>in vitro</i> Agar diffusion assay.	Seeds	Aqueous, hexane, EtOAc, acetone, EtOH extracts	<i>in vitro</i> .	0.1 mL	Negative control. Positive control: ampicillin, cefixime, chloramphenicol, co-trimoxazole, gentamicin, imipenem, piperacillin/tazobactam, tobramycin	Antibacterial activity against <i>E. faecalis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>S. typhimurium</i> , <i>S. flexneri</i> with MIC = 5–10 mg/mL for acetone extract and 20–50 mg/mL for aqueous extract.	Kaur, Arora, 2009
Antibacterial	<i>in vitro</i> . Microdilution assay. <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Proteus mirabilis</i> , <i>K. pneumoniae</i> , <i>Acinetobacter baumannii</i> <i>S. aureus</i> , <i>Enterococcus faecalis</i> , <i>B. subtilis</i> , and clinical isolates. <i>C. albicans</i> , <i>C. parapsilosis</i>	Aerial part	Essential oil by hydrodistillation	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.	Erdogan Orhan et al., 2012.
Antibacterial	<i>in vitro</i> . Broth dilution method. <i>S. aureus</i> , <i>E. coli</i>	Not specified	Commercial essential oil	96 well plate	0–0.5% (v/v)	Negative control.	MIC(v/v) = 0.37% against <i>S. aureus</i> and 0.47% against <i>E. coli</i>	Delaquis et al., 2002
Anticancer	<i>in vitro</i> . 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	<i>in vivo</i> . Mice, formalin induced inflammation <i>in vivo</i> . Rats, formalin induced edema	Aerial part, seeds Fresh aerial part	Hydroalcoholic extract Sesame oil extract (10:4)	Intraperitoneal Topical application on paw	300 mg/kg 100 mg/ 8 days	Negative control. Positive control: morphine. Negative control. Positive control: diclofenac gel 0.01%.	Analgesic effect 15–45 min after formaline injection by both extracts. Reducing of the paw inflammation even stronger than application of diclofenac.	Rezaee-Asl et al., 2013 Naseri et al., 2012
Antispasmodic	<i>in vitro</i> . 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	<i>in vitro</i> , antiviral	Aerial part	Essential oil by hydrodistillation	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.	Erdogan Orhan et al., 2012.
Diuretic	<i>in vivo</i> . Mongrel dogs.	Seeds	EtOH (70%) extract. Volatile oil by steam distillation.	Intravenous.	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	Mahrhan et al., 1991).

Gastroprotective	<i>in vivo</i> . Rats, EtOH and HCl-induced gastric ulcer	Seeds	Aqueous and EtOH (70%) extracts	Per oral, intraperitoneal.	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
	<i>in vivo</i> . Rats, indomethacin induced gastric ulcer after ligation of pylorus. <i>in vitro</i> 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . Disc diffusion method.	Root	MeOH extract with 6.3% yield	<i>in vitro</i> .	No data	Negative control. Positive control: alizarin, emodin, stemonitis and 35% inhibition of <i>Penicillium verrucosum</i> .	43% inhibition of <i>Trichoderma viride</i> . 41% inhibition of <i>Doratomyces</i> .	Manojlovic et al., 2005
Antileishmaniasis	<i>in vivo</i> . 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	<i>in vivo</i> . Rabbits, foreign-body bladder calculus model	Root	Hydroxy-antraquinone 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	<i>in vitro</i> .	Root	5% aqueous solution of extract.	<i>in vitro</i>	Kidney stone 20 mg	No	After 15 days the weight of stone was decreased by 25% and the stone structure became friable	Vichikanova et al., 2009
Antimicrobial	<i>in vitro</i> . Agar-disc diffusion method.	Root	Aqueous, EtOH, MeOH and EtOAc extracts	<i>in vitro</i> .	10–100 µL in 6 mm disc.	Negative control. Positive control: erythromycin	Full inhibition of <i>Aspergillus flavus</i> , <i>Fusarium oxysporium</i> , and <i>Sreptomyces murinus</i> 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. PPAR α or PPAR γ 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 PPAR α and PPAR γ	Vogl et al., 2013
Antimicrobial	in vitro. Liquid culture.	Fruits	Polyphenol-rich fraction	in vitro.	1 mg/mL	Negative control.	Strong growth inhibition of <i>Bacillus cereus</i> . Bacteriostatic effect against <i>Campylobacter jejuni</i> and <i>S. aureus</i> .	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 <i>Salmonella enterica</i> , and <i>E. coli</i> . Inhibitory effect on hemag-glutination of <i>E. coli</i> 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 (“nanaity” 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 ± 0.7 kg ($p < 0.001$) over 15 weeks vs. 0.7 ± 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 ± 1.1 to 8.1 ± 1.4 U/mg protein, whereas controls exhibited virtually no change in this parameter. Aralox decreased the plasma triglyceride content from 3.6 ± 0.2 to 1.8 ± 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 Rhodiola 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	<i>in vivo</i> . Mice	Fruiting bodies	Aqueous extract	Intraperitoneally 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-asthmatic	<i>in vivo</i> . Asthmatic mice.	Sclerotium	EtOH extract	Intraperitoneally	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	<i>in vitro</i> . Mouse leukemia cells L1210	Not specified	Methylene chloride and MeOH extracts, soxhlet	96 well plate	10 μ g/well	Positive control: Methotrexate Negative control	100% growth inhibition by Methylene chloride and 92% by MeOH extracts.	Goun et al., 2002
Anticancer	<i>in vivo</i> . Mice with melanoma. <i>in vitro</i> . Melanoma B16-F10 cells.	Sclerotium	Aqueous extract	Intraperitoneally, 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	<i>in vitro</i> . 3T3-L1 Preadipocytes.	Fruiting bodies	Aqueous extract with glucose-rich polysaccharides 149 kDa	96 well plate	10, 25, 50, 100 μ g/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 PPAR γ during adipocyte differentiation, and induced the expression of PPAR γ target genes such as aP2, LPL and CD36.	Joo et al., 2010
Anti-inflammatory	<i>in vivo</i> . Acetic acid-induced abdominal constriction, hot plate tests in mice. Carrageenan-induced edema in rats. <i>in vivo</i> . Mice with dextran sulphate sodium (DSS)-induced colitis	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
		Fruiting bodies	Aqueous extract	Per oral	50, 100 mg/kg / twice a day, 7 days before and during DSS administration, for 14 days. Twice a day 7 day concurrent with DSS administration	Negative control, DSS	Diminishing colitis by suppressing expression of inflammatory mediators TNF- α , IFN- γ , IL-1 β and IL-6, and iNOS in colonic tissues.	Mishra et al., 2012
Anti-inflammatory	<i>in vitro</i> . Murine macrophage cell line (RAW 264.7), lipopolysaccharide-activated macrophages	Sporophores	MeOH extract (29.8% yield)	96 well plate	45, 90, 135 μ g/mL	Negative control. Positive control: 1-N6-(1-iminoethyl) lysine	Inhibition of iNOS and COX-2 expression via the down-regulation of NF- κ B binding activity and reduction in nuclear p65 protein levels	Park et al., 2005
Antimutagenic	<i>in vitro</i> . Ames test	Sclerotium	Subfractions from MeOH extract	Agar plates	50 μ g /plate	Negative control	Inhibition of mutagenesis induced in <i>Salmonella typhimurium</i> strain TA100 by the directly acting mutagen MNNG (0.4 μ g /plate) by 77.3-80.0%. Inhibition of 0.15 μ g /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	<i>in vitro</i> . DPPH assay	Sclerotium	Subfractions from MeOH extract	<i>in vitro</i> .	5–500 µg/mL	Negative control. Positive control: ascorbic acid, tocopherol, BHA	IC ₅₀ =69 µg/mL for subfraction 1	Ham et al., 2009
	<i>in vitro</i> . DPPH, hydroxyl radicals, superoxide anion radicals, H ₂ O ₂ assays	Sclerotium	Polysaccharide fractions IOP40, IOP60, IOP80 with yield 2.2%, 11.6%, 0.84%	<i>in vitro</i> .	62.5–1000 µg/mL	Negative control. Positive control: ascorbic acid	Order of reducing power in DPPH, H ₂ O ₂ , and hydroxyl-scavenging activity was IOP60 > IOP40 > IOP80	Du et al., 2013
	<i>in vitro</i> . ABTS, DPPH, superoxide anion radicals assays	Fruiting bodies	Isolated inonoblins A, B, and C, phelligrindins D, E, and G.	<i>in vitro</i> .	No data	Negative control. Positive control: trolox, caffeic acid	Inonoblin C was most active in ABTS assay (0.65 TEAC), phelligrindin D in superoxide anion radicals assay (IC ₅₀ =85.5 µM), Phelligrindin E in DPPH assay (1.57 TEAC)	Lee et al., 2007
Immunomodulatory	<i>in vivo</i> . 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 <i>in vitro</i> 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	<i>in vivo</i> . Ovalbumin (OVA)-sensitized BALB/c mice. <i>ex vivo</i> . 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 <i>ex vivo</i> .	Ko et al., 2011
Radioprotective	<i>in vivo</i> . 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	<i>in vivo</i> . 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 apathistical-aboluc 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 LD₅₀ 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). Intra-gastric 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 LD₅₀ 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*

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 *Rhodiola 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, VO₂, VCO₂, peak O₂ output, and peak CO₂ 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	<i>in vivo</i> . 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	<i>in vitro</i> . Human kidney cancer cell lines GRC-1 and 786-O	Roots	Isolated araloside A	in vitro	1, 3, 10, 30, 100 μ M	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	<i>ex vivo</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . 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 μ M	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 μ M. Inhibition of NF- κ B activity in 20.4, and 33.7% at 48 μ M, and 96 μ M respectively.	Lee et al., 2009
Antiulcer	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>In vitro</i> . Injury induced by H ₂ O ₂ in H9c2 cells	Root bark	Water-soluble polysaccharide AEP-w1 (Mr 4.5 × 10 ⁴ Da). Monosaccharide components: arabinogalactan, consisting of arabinose, galactose and trace glucose with molar ratios of 6.3:3.5:0.2. EtOH (50%) extracts	96-well plates	100, 200, 400 µg/ml	Negative control	Zhang et al., 2013
Gastroprotective	<i>in vivo</i> . Rats, cold-restraint stress (CRS), pylorus ligation	Roots		Intraperitoneal	50 mg/kg, 30 min pretreatment	Negative control.	Hernandez et al., 1988
Hypoglycemic	<i>in vivo</i> . Rats, glucose tolerance test (GTT)	Root bark	Isolated oleanolic acid and 9 oligoglycosides	Per oral	100 mg/kg, single administration	Negative control.	Yoshikawa et al., 1996
Hypoglycemic	<i>in vivo</i> . Rats, rabbits with high cholesterol diet.	Root	Saparyl (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.	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 an antihypertensive, dates from the early 1940s and needs further confirmation.

5.18.2. HERBA THERMOPSISIDIS 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 extractant) 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 cytosine (the main quinolizidine alkaloid in *T. lanceolata*) was studied in rats and mice. The LD₅₀ was estimated at 5–50 mg/kg body weight in rats after per oral administration. In repeated dose toxicity studies, cytosine 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	<i>in vivo</i> . 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	<i>in vivo</i> . 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	<i>in vitro</i> . Human lymphoblastoid Raji cells	Roots	Crude EtOH (40%) extract	<i>in vitro</i>	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	<i>in vivo</i> . 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	<i>in vitro</i> . Plaque reduction assay <i>in vivo</i> . 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 <i>in vitro</i> and <i>in vivo</i> . Salidroside modulate the mRNA expression of interferon-γ, interleukin-10 (IL-10), TNF-α, and interleukin-2 (IL-2).	Wang et al., 2009
Antiviral	<i>in vitro</i> . 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	<i>in vitro</i> .	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	<i>in vitro</i> . HIV-1 protease inhibition	Roots	MeOH extract	<i>in vitro</i> .	100 µg/mL	Negative control. Positive control: acetyl pepstatin	70.4% inhibition of HIV-1 protease	Min et al., 1999
Hypotensive	<i>in vivo</i> . 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	<i>in vivo</i> . 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 polygomi persicariae*

Activity tested	Model used	Plant part used	Extract type	Admin	Dosage/ duration	Control	Results	Reference
Anticancer	<i>in vitro</i> . 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	<i>in vitro</i> . Microbroth dilution assay. <i>C. albicans</i> , <i>S. cerevisiae</i> , <i>Cryptococcus neoformans</i> , <i>Aspergillus flavus</i> , <i>As. fumigatus</i> , <i>As. niger</i> , <i>Trichophyton rubrum</i> , <i>Tr. mentagrophytes</i> , <i>Microsporium gypseum</i> .	Aerial part	Dichlormethane extract. Isolated polygodial, isopolygodial, and cardamomin.	<i>in vitro</i> .	Initial concentration 100 µL	Negative control. Positive control: reticonazole, amphotericin, terbinafine	MIC (µg/mL) for dichloro-methane extract was 31.2 against <i>Tr. Mentagrophytes</i> ; polygodial 3.9 against <i>C. albicans</i> ; 7.8 against <i>C. neoformans</i> , <i>Tr. rubrum</i> , <i>Tr. Mentagrophytes</i> , and 15.6 against <i>S. cerevisiae</i> ; cardamomin 15.6 against <i>Tr. rubrum</i> , and <i>Tr. mentagrophytes</i>	Derita, Zacchino, 2011
Anti-inflammatory	<i>in vivo</i> . Carrageenan-induced edema in rats	Aerial part	EtOH extract	Intraperitoneal	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, cytosine 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 NaHCO₃) 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* (11th 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.

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