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Plant Products for Musculoskeletal, Respiratory, Circulatory, and Genitourinary Disorders in Eastern and South-Eastern Serbia – Folk Uses Comparison with Official Recommendations

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Abstract: Eastern and south-eastern Serbia is a cultural crossroads between East and West, and due to its economic underdevelopment, the traditional use of medicinal plants remains crucial in healthcare even today. This study aimed to collect and preserve ethnopharmacological knowledge about musculoskeletal, respiratory, circulatory, and genitourinary disorders, which are common in the local population. Information was collected using semi-structured anonymous ethnobotanical interviews with location informants. According to respondents, monographs of official international authorities (European Pharmacopoeia, ESCOP, WHO, EMA, and PDR) have been reviewed to confirm the traditional use of medicinal plants. Out of a total of 161 respondents, 58 (36%) declared that they use plants to treat musculoskeletal diseases, 147 (91.3%) to treat respiratory diseases, 113 (70.19%) to treat circulatory diseases, and 25 (15.53%) to treat genitourinary diseases. Among the plants that are traditionally used for the treatment of diseases of these organ systems, the following are highlighted for future research: *Verbascum phlomoides*, *Inula helenium*, and *Rosmarinus officinalis* for musculoskeletal; *Ocimum basilicum*, *Robinia pseudoacacia* and *Primula vulgaris* for respiratory; *Urtica dioica*, *Allium ursinum*, and *Rosa canina* for circulatory and *Apium graveolens*, *Zea mays* and *Calendula officinalis* for treatment of genitourinary system.

Keywords: Ethnopharmacological study; Balkan region; musculoskeletal; respiratory; circulatory; genitourinary disorders.

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Plant products for musculoskeletal, respiratory, circulatory, and genitourinary disorders

1. Introduction

As defined by the World Health Organization, traditional medicine is the body of knowledge, skills, and practices based on the theories, beliefs, and experiences of diverse cultures. Whether or not justifiable, it is used to maintain health and to prevent, diagnose, alleviate, or treat physical and mental illness [1]. The practice of traditional medicine depends on many factors, such as history, culture, philosophy, and personal attitudes, and therefore varies greatly from region to region [2]. Although long historical experience passed down from generation to generation largely proves efficacy and safety, scientific pharmacological validation is needed to justify the rational use. The results of the scientific evaluation of herbal medicinal products, taking into account all available information, including preclinical and clinical trials, as well as data on traditional use, are summarized in monographs published by official international authorities such as the European Science Cooperative Phytotherapy (ESCOP), Physician's Desk Reference (PDR), World Health Organization (WHO), European Medicines Agency (EMA), and European Pharmacopeia (Ph. Eur.). The recording and validation of indigenous traditional knowledge are the first and most important steps toward implementing safe and effective traditional medicine that contributes to health care. Besides, inquiry guided by traditional knowledge is a well-trodden pathway in identifying new bioactive compounds and developing new medicines. Aspirin, atropine, artemisinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, paclitaxel, tubocurarine, vincristine, vinblastine are just a few examples of medicines used in modern pharmacotherapy that have been developed in this way [3].

The Balkan Peninsula is one of Europe's most important centers of floristic biodiversity, with about 6340 vascular plant taxa, compared to the 10500 taxa recorded in the Flora Europaea [4]. One of the best-known experts on folk medicine in this part of Europe, university professor Dr. Jovan Tucakov, points out that the health culture of the Balkan peoples is interesting and complex as the medical approaches of the West, East, and the Mediterranean strongly influence its development. All of this is integrated into the "folk medicine of illiterate warriors and shepherds" that developed due to the hardships of poverty and the numerous wars fought in these areas, which forced the population to rely on their own resources to treat diseases with natural medicines from their environment [5]. Research efforts to preserve this traditional knowledge have recently led to the publication of several ethnobotanical studies from the countries of the Balkan Peninsula, including Serbia [2,5-17]. The rural areas of eastern and south-eastern Serbia, with their agricultural production, underdeveloped infrastructure, and limited provision of public services, including health care, are among the poorest regions in this part of Europe. Economic devastation has caused the depopulation of this region in recent decades. As a result, the region is mainly inhabited by an elderly population for whom traditional medicine is the prevailing form of health care in prevention and treatment. Considering the depopulation, it is a critical time to conduct an ethnopharmacological study of the medicinal plants used. A recent study by our research group focused on the traditional use of autochthonous plants for nutritional, medicinal, and ritual purposes, with particular emphasis on the role of cultural differences between ethnic communities in east and south-east Serbia [18].

As previously reported by the Institute of Public Health, the leading diseases in the population of this region are respiratory, circulatory, musculoskeletal, and urogenital [19]. According to the WHO, cardiovascular, respiratory, and kidney diseases are among the leading causes of death worldwide [20], while musculoskeletal disorders are the second most common cause of disability [21]. Although the treatment for these diseases is based on modern medicine, ethnopharmacological approaches are being sought for the long-term relief of symptoms. Due to their low cost, ease of use, and lack of adverse effects compared to modern medications, medicinal plants are still widely used. Additionally, traditional uses of medicinal plants illuminate new fields of study, leading to a growing appreciation of their significance [22]. Against this background, the main objective of the present ethnopharmacological study was to find the plants used in folk medicine to treat these four organ systems in eastern and south-eastern Serbia and to compare them with official recommendations from a pharmacological point of view. Our other objectives were to (1) collect and keep data on plants used for diseases related to these organs, (2) compare the collected data on folk medicine use with data from official sources (monographs of official international authorities in this field: Ph. Eur., ESCOP,

WHO, EMA, and PDR), (3) conduct a literature review for plants without official monographs on particular herbal medicinal substance (WOM) reported to be widely used in order to provide insight into phytochemicals and biological activities associated with ethnopharmacological use, and (4) propose the most frequently reported plants WOM for further research.

2. Materials and Methods

This study builds upon previous research conducted in eastern and south-eastern Serbia, focusing on exploring cultural differences in the use of plants among different ethnic groups in this area [18]. The current study specifically investigates the traditional use of medicinal plants. It thoroughly examines the utilization of medicinal plants in the treatment of musculoskeletal, respiratory, circulatory, and genitourinary disorders, which have been identified as the most common among the local population according to data from the local Institute of Public Health [19] and are also of global public health interest [20-21].

2.1. Study Area

The research area encompassed the Timok region (ten municipality villages in the Timok River valley) as well as the Svrljig region (ten municipality villages in the Svrljig Mountains) located in eastern and south-eastern Serbia, respectively, along the border with Bulgaria. The studied areas comprise mountainous valleys characterized by significant climatic conditions, landscape type, and altitude variations. The region's diverse geomorphological, geological, and pedological features and the impact of distinct climates have contributed to the lush vegetation and highly diverse ecosystems in these regions. Additionally, these regions exhibit severe poverty, with prevailing negative demographic trends, an aging population, and significant depopulation. Socioeconomic development is low, and there is a high degree of illiteracy, particularly in rural households. Furthermore, the region is marked by inadequate or substandard road infrastructure and traditional small-scale agricultural practices.

2.2. Ethnopharmacological Survey

The research was conducted over three years, from 2015 to 2017. The survey involved 161 informants who permanently reside in the study area (66% females and 34% males; 94 from the Timok region and 67 from the Svrljig region), with ages ranging from 20 to 90 (median age of 67 years). Semi-structured anonymous ethnopharmacological interviews were used to collect data on the traditional use of medicinal plants. Prior to the interviews, all participants gave their consent according to ethical guidelines prescribed by the International Society of Ethnobiology Code of Ethics [23] (with 2008 additions) (http://ethnobiology.net/code-of-ethics/). During the fieldwork, we recorded the local Serbian name, the specific parts or organs of each botanical taxon used, the indication for use, as well as the corresponding method of preparation and administration. Samples of all reported plants were collected with the help of the informants and further authenticated according to Flora of Serbia and Flora Europaea. All voucher specimens are deposited in the herbarium collection of the Herbarium Moesiacum Niš at the Department of Biology and Ecology, Faculty of Science and Mathematics (University of Niš).

2.3. Data Analysis

The data collected during the field studies were processed using MS Office Excel. All reported plants are categorized into two groups based on the presence or absence of monographs in recognized international sources specific to each organ system. The first group comprises plants with an official monograph on a particular herbal medicinal substance (WM), characterized by having documented pharmacological properties in the aforementioned official sources. The second group consists of plants

WOM. The monographs used to compare the data collected on the plants included authoritative sources such as the European Scientific Cooperative Phytotherapy (ESCOP), the European Medicines Agency (EMA), the Physician's Desk Reference for Herbal Medicines (PDR), the World Health Organization (WHO), and the European Pharmacopoeia (Ph. Eur.). Graphics in the form of heat maps for plants WM and WOM were generated using R Studio (version 4.0.3) and are presented in Figure 1. Plants WOM were considered only when two or more independent informants mentioned their use. Furthermore, three plants with the most frequently cited usage WOM were selected for each organ system. These selected plants underwent a critical assessment through a literature review of confirmed biological activities and phytochemical studies to evaluate the justification of their traditional use and propose further research.

3. Results and Discussion

3.1. Musculoskeletal Disorders

Medicinal plants reported to be used for musculoskeletal disorders, classified into plants WM and WOM, are presented in Table 1. Out of 161 respondents, 58 respondents (36%) stated that they used plants to treat musculoskeletal disorders (9.9%, 75 use reports). These medicinal plants belong to 16 families represented mainly by Scrophulariaceae (17.3%, 13 cit.), Asteraceae (14.7%, 11 cit.), Rosaceae (10.7%, 8 cit.), and Lamiaceae (9.3%, 7 cit.). The most used parts were roots (44%, 33 cit.), flowers (41.3%, 31 cit.), leaves (32%, 24 cit.), aerial parts (24%, 18 cit.), fruits (14.7%, 11 cit.), and seeds (4%, 3 cit.). The most commonly used preparations were tea (76%, 57 cit.), tincture (54.7%, 41 cit.), poultice (53.3%, 40 cit.), ointment (25.3%, 19 cit.), syrup (10.7%, 8 cit.), oil extract (8%, 6 cit.), macerate (4%, 3 cit.), and bath (2.7%, 2 cit.). As reported in the EMA, ESCOP, PDR, and WHO monographs, four out of 18 plants used (22.2%) and 11 out of 75 applications reported (14.7%) have already been indicated for musculoskeletal disorders. It should be noted that three medicinal plants (*Filipendula ulmaria*, *Hedera helix*, and *Symphytum officinale*) have EMA monographs, and two (*Hedera helix* and *Urtica dioica*) have PDR monographs, but no single plant has a confirmed indication for musculoskeletal disorders by ESCOP and WHO. In the 10th European Pharmacopoeia, *Filipendulae ulmariae* herba is mentioned as an official medicinal product, but there is no information on the use of its leaves and flowers. In addition, respondents mentioned using nettle roots, aerial parts, leaves, and seeds, of which only the leaf and root (*Urticae folium* and *Urticae radix*) are listed as official medicinal products in the 10th European Pharmacopoeia.

The most frequently treated diseases can be divided into three categories: arthritis (71.9%, 46 use reports), gout (23.4%, use reports), and rickets (4.7%, use reports). Our results show that *Verbascum phlomoides* is the most commonly used herb to treat arthritis (13 of a total of 64 use reports, 25%). Further, the most frequently reported uses were *Inula helenium* (8 use reports, 12.5%, 5 for arthritis and 3 for gout), *Rosmarinus officinalis* (7 use reports for arthritis, 10.9%), *Sambucus ebulus*, and *Rosa canina* (6 use reports, 9.4%, 2 for arthritis and 4 for gout). Notably, although *Symphytum officinale* is listed in the EMA monographs, it is not used to treat arthritis.

According to our results, the most frequently treated disease is arthritis. Arthritis is an acute or chronic inflammation of the joints [24]. Pathological changes that lead to cartilage deterioration and articular degeneration include neovascularization, inflammatory cell infiltration, and synovial membrane hyperplasia [25]. Nonsteroidal anti-inflammatory medications such as indomethacin, ibuprofen, aspirin, and naproxen are primarily used to treat arthritis. Because these drugs suppress cyclooxygenases (COX-1 and COX-2) and pro-inflammatory cytokines (IL-1 interleukin-1, IL-6 interleukin-6, TNF-α tumor necrosis factor α, etc.), they have anti-inflammatory and anti-arthritic properties that treat arthritis [26]. These drugs can have gastrointestinal side effects, such as bleeding, stomach ulcers, belching, and irritation of the gastric mucosa, while long-term use can damage liver and kidney function, putting the patient at risk for cardiovascular disease [27]. Additionally, musculoskeletal conditions can contribute to the development of chronic diseases; estimates from 10 independent studies found that people with musculoskeletal disorders have a 17% higher risk of developing chronic diseases than those without them [28]. Medicinal plants can be excellent sources of antioxidants and anti-arthritic and anti-inflammatory agents; they usually have milder side effects

and are readily available and inexpensive. Therefore, medicinal plants could be an important complementary and alternative therapy for musculoskeletal disorders.

3.1.1. Verbascum phlomoides L., Scrophulariaceae (Orange mullein, Local Name "divizma")

Mullen is a highly valued medicinal plant whose leaves, flowers, and roots are used in folk medicine as a diuretic, antirheumatic, and externally for treating wounds [29,30]. *In vivo* anti-inflammatory effects have been confirmed for some *Verbascum* species: *V. salviifolium* Boiss. [31], *V. pycnostachyium* Boiss. & Heldr. [32], *V. latisepalum* Hub.-Mor., *V. mucronatum* Lam., *V. pterocalycinum* var. *mutense* Hub.-Mor. [33,34], *V. lasianthum* Boiss. ex Benth [35]. The anti-inflammatory potential of *V. phlomoides* flowers was investigated *in vitro* by determining ICAM-1 (intercellular adhesion molecule 1) expression in TNF-*α*-stimulated endothelial cells and by the rat paw edema assay. Depending on the concentration, the extract significantly inhibited TNF-*α*-induced ICAM-1 expression on human umbilical vein endothelial cells but did not reduce protein-induced rat paw edema [36]. A possible reason for the lack of anti-inflammatory effect is the absence of the phenylethanoid glycoside verbascoside in the flower extract of *V. phlomoides*. According to Bradley [37], verbascoside is only present in trace amounts in the flower of *V. phlomoides*. Verbascoside reduces the production of superoxide radicals and exerts exquisite corticosteroid-like inhibition of proinflammatory chemokines, which explains its beneficial effect in treating inflammatory diseases. In addition, *V. phlomoides* contains various polyphenolic compounds, which play an important role in antioxidant activity, but their influence on anti-inflammatory activity is weak [38,39]. Dimitrova et al. [40] found that the crude extract of *V. phlomoides* strongly inhibited the expression of COX-1 by macrophages *in vivo*.

3.1.2. Inula helenium L., Asteraceae (Elecampane, Local name "beli oman")

Elecampane is a medicinal plant widely used as a herbal remedy throughout Europe and Asia [41]. It is used to treat respiratory organs, skin diseases, and wounds, regulates menstruation, and treats rheumatism [5]. *I. helenium* is a rich source of eudesmane-type sesquiterpene lactones, mainly alantolactone and isoalantolactone, which have various pharmacological functions [42-44]. Several studies have demonstrated the *in vitro* [42-45] and *in vivo* [42-43] anti-inflammatory activity of *I. helenium*. A hexane fraction of methanol root extract *in vivo* inhibited iNOS (inducible nitric oxide synthase) and COX-2 protein and reduced carrageenan-induced paw edema in a model of acute inflammation [42]. After oral administration of root extract in the adjuvant-induced arthritis and collagen-induced arthritis models, arthritic severity was reduced. The root extract of *I. helenium*, containing alantolactone and isoalantolactone, showed *in vitro* an inhibitory effect on the expression of MMP-3 (matrix metalloproteinase-3), IL-1, and MCP-1 (monocyte chemoattractant protein-1) in TNF-*α*-activated synovial fibroblasts as well as the expression of IL-1, IL-6 and iNOS in LPS (lipopolysaccharides)-activated macrophage cells [43]. A similar effect was noted in an *in vitro* study by He et al. [45]. In addition to treating arthritis, the respondents in our study reported using *I. helenium* for gout. Medicinal plants with anti-inflammatory effects are usually used to treat acute gout or to reduce the risk of gout recurrence during the initiation of urate-lowering therapy [46].

Table 1. Medicinal plants used for musculoskeletal diseases in eastern and south-eastern Serbia, WM and WOM

Medicinal plants WM used for musculoskeletal diseases

Popular use (Number of use-reports for treated diseases)	Botanical taxa, Serbian name (S), Voucher number	Part used	Active compound (HPLC analysis)	Preparation and administration	Monograph
Arthritis (2)	*Filipendula ulmaria* (L.) Maxim., Rosaceae, medunika (S), 13 373	Leaf*, flower*	Leaf – catechin, rutin, isoquercitrin, cynaroside, astragalin, gallic acid, protocatechuic acid, caftaric acid, chlorogenic acid, *p*-coumaric acid, ellagic acid [60] Flower – rutin, isoquercitrin, spiraeoside, cynaroside, gallic acid, protocatechuic acid, caftaric acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ellagic acid, salicylic acid [60]	Tea, poultice, tincture	EMA Ph. Eur. (herba)
Arthritis (2)	*Hedera helix* L., Araliaceae, bršljan (S), 13 383	Leaf	Leaf – chlorogenic acid, rutin, nicotiflorin, hederacoside C, hederasaponin B, α-hederin [61]	Tea, poultice, tincture	EMA, PDR Ph. Eur. (folium)
Arthritis (6)	*Symphytum officinale* L., Boraginaceae, gavez (S), 13 462	Root, flower*	Root – *m*-methoxybenzoic acid, 5 caffeoylquinic acid, caffeic acid, 3-caffeoylquinic acid, rosmarinic acid, 1-caffeoylquinic acid, coumarin, lithospermic acid, salicylic acid, *m*-hydroxybenzoic acid [62] Flower – fructan [63] caffeic acid, *p*-coumaric acid, *m*-hydroxybenzoic acid [64]	Tincture, poultice, ointment, syrup	EMA
Arthritis (1)	*Urtica dioica* L., Urticaceae, kopriva (S), 13 472	Root, aerial part, leaf, seed*	Root – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Aerial part – caffeic acid derivative [66] esculetin, skopoletin, secoisolaicirisenol, quinic acid, neochlorogenic acid, kaempferol, amentoflavon, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-glucoside, quercetin-3-*O*-rutinoside [67] Leaf – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Seed – chlorogenic acid, caffeic acid, gallic acid, transferulic acid, coumaric acid, rutin, myricetin, kaempferol 3-*O*-rutinoside-7-*O*-rhamnoside [68]	Tea, tincture, boiled	PDR Ph. Eur. (leaf, radix)

Plants WOM used for musculoskeletal diseases (mentioned by two or more informants)

Affliction	Botanical taxa, Serbian name (S), Voucher number	Part used	Active compound (HPLC analysis)	Preparation form	Number of use-reports for treated diseases
Arthritis (46)	*Adonis vernalis* L., Ranunculaceae, gorocvet (S), 13 321	Aerial part	Aerial part – cymarin, adonitoxin, 16-hydroxy-strophanthidin, acetyladonitoxi, vernadigin, 3-acetylstrophadogenin, strophanthidine, fucosidedigitoxigenin, adonilide, adonivernith, homoadonivernith, orientin, homoorientin, isoorientin, luteolin, vitexin [69]	Poultice	2
	Arctium lappa L., Asteraceae, čičak (S), 13 331	Root, leaf	Root – oleanolic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, cinnamic acid, gallic acid [70] Leaf-arctiin, arctigenin [71]	Tea, poultice, ointment	3
	Armoracia rusticana Gaertn., Brassicaceae, ren (S), 13 334	Root, leaf	Root – syringic acid, caffeic acid, ferulic acid, epicatechin, kaempferol-3-*O*-rutinoside, kaempferol-*O*-glucoside, apigenin, kaempferol [72] Leaf – sinigrin, gluconapin, glucobrassicanapin, progoitrin, napoliferin, glucoiberin, glucoiberverin, glucoraphanin, glucoraphenin gluconasturtiin, glucobrassicin, 4-hydroxyglucobrassicin, 4-methoxyglucobrassicin [73]	Tea, poultice, tincture, Fresh	4
	Galium odoratum (L.) Scop., Rubiaceae, lazarkinja (S), 13 376	Aerial part	Aerial part – coumarin, chlorogenic acid, asperuloside, monotropein, geniposidic acid [74]	Tea, tincture, bath	2
	Inula helenium L., Asteraceae, beli oman (S), 13 392	Root	Root – 3,5-dihydroxybenzoic acid, catechin gallate, chlorogenic acid, alantolactone, caffeic acid, galloyl-caffeoylhexose, kaempferol-7-*O*-dipentoside, dicaffeoylquinic acid, quercetin-3-*O*-*β*-glucopyranosid, 5-*O*-feruloylquinic acid, 9-*O*-*β*-D-glucopyranosyl-9-hydroxythymol, dihydrocaffeic acid derivative, 14-6”-*O*-malonyl genistein, 2-epicatechin, 3- *p*-hydroxybenzoic acid, 9,10-dihydroxy-8-methoxythymol, ferulic acid-4-*O*-glucoside, dehydro-9,10-isobutyryloxythymol, caffeic acid hexose, quercetin-7-*O*-galactoside, quercetin-rhamnosyl-glucoside, dihydroquercetin pentosyl rutinoside, 3-feruloyl-4-caffeoylquinic acid, 3,4,5-tricaffeoylquinic acid [75]	Tea, poultice, ointment	5

Ononis spinosa L., Fabaceae, grmotrn (S), 13 451	Aerial part, root	Aerial part – caffeic acid hexoside, ferulic acid hexoside, caffeic acid, *cis*-chicoric acid, *trans* chicoric acid, quercetin-*O*-hexoside-pentoside, kaempferol-*O*-dihexoside, spinonin-*O*-hexoside, quercetin-3-*O*-glucoside, kaempferol-*O*-hexoside-pentoside, acetylquercetin-*O*-hexoside, kaempferol-*O*-hexoside, kaempferol-3-*O*-glucoside, pseudobaptigenin-*O*-hexoside, formononetin derivative, formononetin-*O*-malonyl-hexoside [76] Root – formononetin, calycosin, pseudobaptigenin, maackiain, medicarpin [77]	Tea, tincture	2
Physalis alkekengi L., Solanaceae, ljoskavac (S), 13 626	Aerial part, fruit	Aerial part – 5,6-*O*-*epoxy*-physalin C isomer, 4-hydroxy-neophysalin A isomer, physalin A, B, C, O, L, N, M, Z, luteolin, isophysalin B [78] Fruit – physalin A, O, L, B, 4,7-didehydroneophysalin B, luteoloside, luteolin, citric acid malic acid, tartaric acid, ascorbic acid [79]	Poultice, tea	2
Rosa canina L., Rosaceae, šipak (S), 13 439	Flower, fruit	Flower – cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3,5-diglucoside, pelargonidin-3-glucoside, peonidin-3,5-diglucoside, peonidin-3-glucoside, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-glucuronide, quercetin-3-arabinofuranoside, quercetin-3-xyloside, quercetin-3-rhamnoside, quercetin-hexoside-rhamnoside, quercetin-galloylhexoside, quercetin-dihexoside, quercetin-acetyl-hexoside-rhamnoside, quercetin-hexosyl-pentoside, kaempferol-di-hexoside, kaempferol-3-rhamnoside, kaempferol-3-galactoside, kaempferol-3-glucoside, kaempferol-3-glucuronide, kaempferol-acetylglucoside, kaempferol-galloylhexoside, kaempferol-pentoside, kaempferol-pentoside-hexoside, kaempferol-rhamnoside-hexoside, kaempferol-acetyl-hexoside-	Tea, tincture, oil extract	2

			rhamnoside [80] Frut – apigenin, caffeic acid, catechin, chlorogenic acid, ferulic acid, epicatechin, gallic acid, kaempferol, *p*-coumaric acid, phloroglucinol, protocatechuic acid, quercetin, quercetin-3-glucoside, resveratrol [81]		
	Rosmarinus officinalis L., Lamiaceae, ruzmarin (S), 13 440	Aerial part, leaf	Aerial part – carnosic acid, carnosol, rosmarinic acid [82] Leaf – carnosol, carnosic acid, rosmadial, rosmanol, genkwanin, homoplantagini, scutellarein, cirsimaritin, rosmarinic acid [83]	Tea, tincture	7
	Sambucus ebulus L., Caprifoliaceae, burjan (S), 13 449	Root	Root – gallic acid, protocatechuic acid, catechin, chlorogenic acid, caffeic acid, naringin [84]	Poultice	2
	Verbascum phlomoides L., Scrophulariaceae, divizma (S), 13 477	Flower	Flower – verbascoside, diosmin, apigenin, luteolin, tamarixetin 7-rutinoside, tamarixetin 7-glucoside [85]	Tea	13
	Viola odorata L., Violaceae, ljubičica (S), 13 479	Aerial part, leaf, flower	Aerial part – vitexin, isovitexin, rutin, kaempferol-6-glucoside [86] Leaf – hydroquinone, gallic acid, resorcinol, pyrocatechol, catechin, chlorogenic acid, caffeic acid, salicylic acid [87] Flower – quercetin-3-*O*-*α*-rhamnopyranosyl- (1→2)-[*α*-rhamnopyranosyl (1→6)]-*β*-glucopyranoside-7-*O*-*α*-rhamnopyranoside, kaempferol 3-*O*-*α*-rhamnopyranosyl-(1→2)-[*α*-rhamnopyranosyl(1→6)]-*β*-glucopyranoside-7-*O*-*α*-rhamnopyranoside, quercetin-3-*O*-α-rhamnopyranosyl(1→2)-[*α*-rhamnopyranosyl- (1→6)]-*β*-glucopyranosid, kaempferol-3-*O*-*α*-rhamnopyranosyl (1→2)[*α*-rhamnopyranosyl-(1→6)]-*β*-glucopyranosid, rutin; 6 quercetin-3-*O*-glucopyranosid, nikotiflorin, kaempferol-3-*O*-glucopyranoside, kaempferol-7-*O*-glucopyranoside, apigenin-7-*O*-glucopyranoside [88]	Tea, tincture	2
Gout (15)	*Colchicum autumnale* L., Colchicaceae, mrazovac (S), 13 353	Root, seed	Root – colchicoside, 2-demethyl colchicine, 3-demethyl colchicine, demecolcine, colchifoline, N-deacetyl-N-formyl colchicine, colchicine, cornigerine [89] Seed – colchicine, colchicoside	Tincture	2

		[90]		
Inula helenium L., Asteraceae, beli oman (S), 13 392	Root	Root – 3,5-dihydroxybenzoic acid, catechin gallate, chlorogenic acid, alantolactone, caffeic acid, galloyl-caffeoylhexose, kaempferol-7-*O*-dipentoside, dicaffeoylquinic acid, quercetin-3-*O*-*β*-glucopyranosid, 5-*O*-feruloylquinic acid, 9-*O*-*β*-D-glucopyranosyl-9-hydroxythymol, dihydrocaffeic acid derivative, 14-6”-*O*-malonyl genistein, 2-epicatechin, 3-*p*-hydroxybenzoic acid, 9,10-dihydroxy-8-methoxythymol, ferulic acid-4-*O*-glucoside, dehydro-9,10-isobutyryloxythymol, caffeic acid hexose, quercetin-7-*O*-galactoside, quercetin-rhamnosyl-glucoside, dihydroquercetin pentosyl rutinoside, 3-feruloyl-4-caffeoylquinic acid, 3,4,5-tricaffeoylquinic acid [75]	Tea, poultice, ointment	3
Rosa canina L., Rosaceae, šipak (S), 13 439	Flower, fruit	Flower – cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3,5-diglucoside, pelargonidin-3-glucoside, peonidin-3,5-diglucoside, peonidin-3-glucoside, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-glucuronide, quercetin-3-arabinofuranoside, quercetin-3-xyloside, quercetin-3-rhamnoside, quercetin-hexoside-rhamnoside, quercetin-galloylhexoside, quercetin-dihexoside, quercetin-acetyl-hexoside-rhamnoside, quercetin-hexosyl-pentoside, kaempferol-di-hexoside, kaempferol-3-rhamnoside, kaempferol-3-galactoside, kaempferol-3-glucoside, kaempferol-3-glucuronide, kaempferol-acetylglucoside, kaempferol-galloylhexoside, kaempferol-pentoside, kaempferol-pentoside-hexoside, kaempferol-rhamnoside-hexoside, kaempferol-acetyl-hexoside-rhamnoside [80] Frut – apigenin, caffeic acid,	Tea, tincture, oil extract	4

			catechin, chlorogenic acid, ferulic acid, epicatechin, gallic acid, kaempferol, *p*-coumaric acid, phloroglucinol, protocatechuic acid, quercetin, quercetin-3-glucoside, resveratrol [81]		
	Sambucus ebulus L., Caprifoliaceae, burjan (S), 13 449	Root	Root – gallic acid, protocatechuic acid, catechin, chlorogenic acid, caffeic acid, naringin [84]	Poultice	4
	Symphytum officinale L., Boraginaceae, gavez (S), 13 462	Root, flower	Root – *m*-methoxybenzoic acid, 5-caffeoylquinic acid, caffeic acid, 3-caffeoylquinic acid, rosmarinic acid, 1-caffeoylquinic acid, coumarin, lithospermic acid, salicylic acid, m-hydroxybenzoic acid [62] Flower – fructan [63] caffeic, *p*-coumaric, *m*-hydroxybenzoic acid [64]	Tincture, poultice, ointment, syrup	2
Rickets (3)	*Juglans regia* L., Juglandaceae, orah (S), 13 394	Leaf, fruit	Leaf – neochlorogenic acid, myricetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, quercetin-3-*O*-rhamnoside, kaempferol-*O*-pentoside, esculetin, epicatechin, 3-*p*-coumaroylquinic acid [91] Fruit – gallic acid, chlorogenic acid, ellagic acid, sinapic acid, protocatechuic acid, (+)-catechin, juglone [92]	Tea, poultice, macerate, fresh, tincture	3

Ph: Pharmacopeia; a Different parts used * Use not reported in monographs

3.1.3. Rosmarinus officinalis L., Lamiaceae (Rosemary, Local Name "ruzmarin")

Rosemary is a common houseplant originating in the Mediterranean region but is found worldwide [47]. The leaves of *R. officinalis* are used in folk medicine as an ingredient in teas for skin irritation and hair growth, as a carminative, as an astringent, etc. [5,48]. Traditionally, the leaves are recommended for external use for rheumatism, myalgia, and neuralgia [30]. Considering the inflammatory nature of arthritis and the oxidative stress caused by the disease, *R. officinalis* can lessen the oxidative and inflammatory damage caused by the disease. The antioxidant activity of the main compounds identified from rosemary, including carnosol, carnosic acid, rosmanol, rosmarinic acid, oleanolic acid, and ursolic acid, has been the subject of numerous *in vitro* studies [49-51]. An aqueous extract of *R. officinalis* leaves can attenuate oxidative stress *in vivo* in the liver, brain, and plasma in arthritic rats by reducing oxidative damage, increasing antioxidant capacity, and nearly normalizing the activity of several antioxidant enzymes [52]. The most common *in vivo* methods to evaluate the anti-inflammatory effect of *R. officinalis* essential oil are the paw edema and ear edema models (in rats or mice) [52-54]. The presence of *1,8*-cineole in the essential oil may have a synergistic effect with myrcene, and the suppression of prostaglandin synthesis or the release of other endogenous mediators was responsible for the *in vivo* anti-inflammatory effects of the essential oils [55]. According to a review article on recent preclinical and cinical trials conducted by Juergens, *1,8*-cineol inhibits 5-LOX (5-lipoxygenase) and COXs, thereby inhibiting the production of inflammatory arachidonic acid metabolites [56]. Also, camphor, which is present in essential oil, showed the highest number of interactions with therapeutic targets of inflammation, such as COX-2 *in vivo* [57]. The presence of

terpenes and their propensity to suppress NF-*κβ* (nuclear factor kappa *β*) transcription may contribute to the anti-inflammatory potential of essential oils [58]. The antioxidant potential was also investigated in addition to the anti-inflammatory effect. The *β*-pinene, limonene, *γ*-terpinene, linalool, terpinen-4-ol, *α*-terpineol, and *β*-caryophyllene are components of essential oil that could alleviate oxidative stress [59].

3.2. Respiratory Disease

Medicinal plants reported to be used for respiratory disorders and classified into plants WM and WOM are presented in Table 2. According to our study, out of 161 respondents, 147 (91.3%) stated that they used plants to treat respiratory diseases; 294 use-reports out of a total of 755 pharmaceutical uses (38.9%). These reports include 45 medicinal plants belonging to 23 families, mainly represented by Lamiaceae (37.1%, 109 cit.), Sambucaceae (15.3%, 45 cit.), Rosaceae (7.5%, 22 cit.), Asteraceae and Primulaceae (5.8%, 17 cit., each), and Brassicaceae and Polygonaceae (5.1%, 15 cit., each). The most frequently used plant parts were the aerial part (53.4%, 157 cit.), flower (46%, 137 cit.), leaf (45.6%, 134 cit.), bark (15.9%, 47 cit.), root (9.5%, 28 cit.), rhizome (4.1%, 12 cit.), and fruit (3.4%, 10 cit.). Furthermore, the most important forms of preparation were tea (97.6%, 287 cit.), tincture (27.9%, 82 cit.), ointment (17.7%, 52 cit.), and syrup (13.9%, 41 cit.).

Twenty-eight plants (62.2%) with 207 (70.4%) reports of respiratory use have already been indicated in EMA, ESCOP, PDR, and WHO monographs. The largest proportion of monographs came from PDR (75%), followed by the EMA (67.9%), WHO (25%), and ESCOP (14.3%). In addition, eighteen of the plants are listed in the 10th European Pharmacopoeia, where *Althaea officinalis* leaf and root (*Althaeae folium*, *Althaeae radix*) are noted as an official drug, but there is no information on flower usage. Moreover, it indicated the use of the *Armoracia rusticana* leaves, but there are no monographs about them. In our study, respondents indicated that the leaves and flower of *Tilia cordata* are used to treat productive cough and bronchitis, while the 10th European Pharmacopoeia names only the flower (*Tiliae flos*) as an official drug. In addition, leaf buds of *Pinus sylvestris* and the rhizome, aerial part, and flower of *Primula veris* were used to treat productive cough. Respondents reported the use of flowers of *Fragaria vesca*, *Tussilago farfara*, and *Symphytum officinale*, as well as leaves of *Polypodium vulgare* and *Trifolium pratense*, which were not previously listed in the PDR, EMA or WHO monographs. Furthermore, although the use of leaf, flower, and aerial part of *Tropaeolum majus* was noted, the leaves were not mentioned as an official medicinal product in monographs.

The remaining 37.8% (17 plants) and 29.6% (87 use reports) for respiratory disease can be divided into the following categories: productive cough (65.5%, 57 use reports), bronchitis (19.5%, 17 use reports), pharyngitis and sinusitis (4.6%, 4 use reports each), asthma (3.4%, 3 use reports), and tuberculosis (2.4%, 2 use reports). According to our results, the most commonly used herb is *Satureja montana* (16 out of 87 total use reports, 18.4%). Also, the most reported uses were those of *Ocimum basilicum* (15 out of 87 use reports, 17.9%), *Robinia pseudoacacia* (11 out of 87 use reports, 13.1%), *Primula vulgaris* (8 out of 87 use reports, 9.2%), and *Daucus carota* (5 out of 87 use reports, 5.7%). Traditionally, these plant species are used in our folk medicine, as in neighboring countries.

The medications that are now used to treat respiratory disorders, however, do not have full therapeutic efficacy and exhibit serious adverse effects [93]. Therefore, creating new medications for treating respiratory illnesses that are more effective and have fewer adverse reactions is necessary.

3.2.1. Satureja montana L.,Lamiaceae (Winter savory or Mountain savory, Local Name"rtanjski čaj")

Winter savory or mountain savory is a perennial semi-shrub that grows in rocky, dry environments [94]. *S. montana* is a well-known medicinal plant with a wide range of activities and uses. Extracts and essential oils obtained from *S. montana* have many pharmacological activities, including antibacterial, antiviral, antioxidant, anti-catarrhal, anticancer, stimulant, and expectorant properties [94-98]. The essential oil has a strong antiseptic effect due to the presence of phenolic compounds and is therefore used to treat the respiratory tract, digestive system, and urinary tract, as well as externally to treat various inflammations of the skin and mucous membranes [5]. Carvacrol,

one of the components of essential oils, has a relaxing effect on the tracheal chains *in vitro* [99]. Savory honey is a very common ingredient in folk remedies for the treatment of bronchitis [98]. Ethanolic extracts of *S. montana* showed antiviral activity against avian infectious bronchitis before, during, and after infection *in vitro* [100]. The use of this species in the treatment of respiratory infections and cough has also been reported in other ethnobotanical studies [8, 11].

3.2.2. Ocimum basilicum L., Asteraceae (Sweet basil, Local Name "bosiljak")

Sweet basil is an aromatic species highly valued as a spice and medicinal plant. It is traditionally used in several regions to treat respiratory diseases [2,8,17]. The macerate and Soxhlet extracts of *O. basilicum* showed relaxing (bronchodilatory) properties on the tracheal cords of guinea pigs *in vitro*. The bronchodilator effects of *O. basilicum* have been attributed to several mechanisms, including stimulation of *β*-adrenergic receptors, blocking of histamine H_1 receptors, anticholinergic activity, methylxanthine-like activity, and inhibition of phosphodiesterase [101-102]. Adenoviruses, one of the viruses that cause bronchitis, can be successfully combatted with crude aqueous and ethanolic extracts of *O. basilicum* leaves [101,103]. Ursolic acid and linalool are the most potent anti-adenoviral components in *O. basilicum* aqueous extracts, with strong antiviral properties against all types of tested adenoviruses (ADV-3, ADV-8, and ADV-11) *in vitro* [103]. In addition, *O. basilicum* has *in vitro* and *in vivo* anti-inflammatory properties that may contribute to its use in cough and bronchitis therapy [104-107].

3.2.3. Robinia pseudoacacia L., Fabaceae (Black locust, Local name "bagrem")

Black locust is the most extensively planted tree species worldwide due to its rapid growth, ability to fix nitrogen, and very hard and durable wood, which can thrive in a variety of environments [107]. These taxa contain toxalbumins, robin, and phasin in their leaves, bark, and seeds, which have a toxic inhibitory effect on protein synthesis. Despite the potential risks associated with the toxicity of black locust, there are only a few reports of toxicity to humans following consumption [108]. The flowers have been shown to contain various bioactive and volatile chemicals. The primary phenolic phytochemicals are rutin, kaempferol, epigallocatechin, quercetin and its derivatives, ferulic acid, and myricetin [109], which possess antiviral, anti-inflammatory, and antioxidant activities [110-111]. Tea made from *R. pseudoacacia* flowers is used to treat colds and relieves expectoration [5,30]. Furthermore, linalool, phenyl ethyl alcohol, methyl anthranilate, 1-hexanol, and 3-methyl pyridine have been extracted from the flower essential oil [112]. According to the literature data and the obtained results, additional research on *R. pseudoacacia* use in the treatment of cough, bronchitis, and asthma is needed.

Table 2. Medicinal plants used for respiratory diseases in eastern and south-eastern Serbia, WM and WOM

Medicinal plants WM used for respiratory diseases

Popular use (Number of use-reports for treated diseases)	Botanical taxa, Serbian name (S), Voucher number	Part used	Active compound (HPLC analysis)	Preparation and administration	Monograph
Productive cough (1)	*Agrimonia eupatoria L.*, Rosaceae, petrovac (S), 13 322	Aerial part	Aerial part – catechin, procyanidin B1, B2, B3, B6, B7, C1, C2, epicatechin, catechin, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-(6″-*O*-*p*-coumaroyl)-glucoside, apigenin-6-C-glucoside [113]	Tea	EMA Ph. Eur. (herba)
Productive cough (1)	*Allium cepa* L., Amaryllidaceae, crni luk (S), 13 324	Bulb, dry scales*	Bulb – quercetin-3,7,4′-triglucoside, quercetin-7,4′-diglucoside, quercetina-3,4′-diglucoside, isorhamnetin-3,4′-diglucoside, quercetin-3-*O*-glucoside, quercetin-4-*O*-glucoside, isorhamnetin-4′-glucoside, quercetin, cyanidin 3-glucoside, cyanidin 3-laminaribioside, cyanidin 3-(3″-malonylglucoside), cyanidin 3-(6″-malonylglucoside), cyanidin 3-malonyl-laminaribioside (cyanidin 3-malonylglucosylglucoside) [114] Dry scales – protocatechuic acid, 2-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxy-3(2H)-benzofuranone, quercetin 4′-*O*-*β*-D-glucopyranoside, quercetin, 4′-*O*-*β*-D-glucopyranoside of quercetin dimer, quercetin dimer [115]	Tea, poultice, boiled	EMA, PDR, WHO
Dry cough (7), productive cough (2), bronchitis (1)	*Althaea officinalis* L., Malvaceae, beli slez (S), 13 328	Root, leaf*, flower*	Root – N-phenylpropenoyl-L-amino acid amides, glucose, fructose, raffinose, xylose, galactose, rhamnose, asparagine, arginine, proline, glycine betaine, hypolaetin diglycoside [116] Leaf – chlorogenic acid, quercetin, benzoic acid, apegenin, cinnamic acid, ferulic acid, kaempferol [117] Flower – syringic acid, gallic acid, caffeic acid, *p*-coumaric acid, *trans*-ferulic acid, catechin, apigenin, chrysin, quercetin, kaempferol, genistein, rutin trihydrate and galangin [118]	Macerate	ESCOP, EMA, PDR, WHO Ph. Eur. (folium, radix)

Sinusitis (9), bronchitis (4), productive cough (2)	*Armoracia rusticana Gaertn.*, Brassicaceae, ren (S), 13 334	Root, leaf*	Root – syringic acid, caffeic acid, ferulic acid, epicatechin, kaempferol-3-*O*-rutinoside, kaempferol-*O*-glucoside, apigenin, kaempferol [72] Leaf – sinigrin, gluconapin, glucobrassicanapin, progoitrin, napoliferin, glucoiberin, glucoiberverin, glucoraphanin, glucoraphenin gluconasturtiin, glucobrassicin, 4-hydroxyglucobrassicin, 4-methoxyglucobrassicin [73]	Tea, poultice, tincture, fresh	PDR
Asthma (2)	*Artemisia absinthium L.*, Asteraceae, beli pelin (S), 13 335	Aerial part, leaf*	Aerial part – tannic acid, gallic acid, chlorogenic acid, hemihydrate, caffeic acid, vanillic acid, syringic acid, ferulic acid, *p*-coumaric acid, rosmarinic acid, *trans*-cinnamic acid, catechin, epicatechin, naringenin, myristin, quercetin dehydrate, campherol, apigenin, coumarin [119] Leaf - caffeic acid, naringenin, *p*-hydroxybenzoic acid, quercetin, *p*-coumaric acid [120]	Tea, fresh, tincture	EMA Ph. Eur. (herba)
Productive cough (2)	*Fragaria vesca L.*, Rosaceae, divlja jagoda (S), 13 374	Leaf, flower*	Leaf – caffeic acid, phenolic acid, ellagitannin, kaempferol glucuronyl-rhamnoside, kaempferol glucuronide, quercetin glucuronyl-rhamnoside, quercetin glucuronide, ellagic acid [121] Flower – ellagic acid, cyanidin, pelargonidin, quercetin, kaempferol, gallic acid derivatives, and catechin derivatives [122]	Tea	EMA
Productive cough (2)	*Juniperus communis L.*, Cupressaceae, kleka (S), 13 395	Fruit	Fruit – isoscutellarein, 8-hydroxyluteolin, hypolaetin glycosides, amentoflavone, hynokiflavone, cupressoflavone [123]	Tea, tincture, oil extract	EMA Ph. Eur. (cone berry)
Productive cough (2)	*Malva sylvestris* L., Malvaceae, crni slez (S), 13 406	Stem*, leaf, flower	Stem – α-tocopherol, β-tocopherol, γ-tocopherol, α-linoleic acid [124] Leaf – gallic acid, 4-hydroxybenzoic acid, chlorogenic acid, caffeic acid, vanillic acid, epicatechin, syringic acid, *p*-coumaric acid, salicylic acid, quercetin-3-glucoside, myricetin, rosmarinic acid, quercetin, 5,7-dimethoxycoumarin, genistein, kaempferol, 1,1-dimethylallyl caffeate chrysin, caffeic acid phenethyl ester [125] Flower – gallic acid, 3-hydroxytyrosol, 4-hydroxybenzoic acid, chlorogenic acid, caffeic acid, vanillic acid, epicatechin, syringic acid, *p*-coumaric acid, salicylic acid, quercetin-3-glucoside, myricetin, rosmarinic	Tea	EMA, PDR Ph. Eur. (flos, folium)

			acid, quercetin, 5,7-dimethoxycoumarin, genistein, kaempferol, 1,1-dimethylallyl caffeate chrysin, caffeic acid phenethyl ester [125]		
Bronchitis (4), productive cough (11)	*Marrubium vulgare* L., Lamiaceae, bela očajnica (S), 13 407	Aerial part	Aerial part – apigenin, luteolin, kaempferol, quercetin, caffeic acid, syringic acid, sinapic acid, ferulic acid, 2-hydroxy cinnamic acid, rosmarinic acid, *trans*-cinnamic acid, *p*-coumaric acid [126]	Tea	ESCOP, EMA, PDR Ph. Eur. (herba)
Pharyngitis (1)	*Matricaria chamomilla* L., Asteraceae, kamilica (S), 13 408	Flower	Flower – cosmosiin, skimmin, daphnetin, daphnin, umbelliferone, herniarin [127]	Tea, poultice	EMA, PDR, WHO Ph. Eur. (flos, aetheroleum)
Productive cough (20), bronchitis (2)	*Melissa officinalis* L., Lamiaceae, matočina (S), 13 409	Aerial part*	Aerial part – caffeic acid, rosmarinic acid, myricetin, quercetin, luteolin, kaempferol, apigenin, quercetin-3-*β*-D-glucoside, luteolin-7-glucoside, apigenin-7-glucoside, isorhamnetine, vitexin [128]	Tea, syrup	WHO Ph. Eur. (folium)
Bronchitis (1)	*Mentha* x *piperita* L., Lamiaceae, đoz, nana (S) 13 411	Aerial part	Aerial part – epicatechin, quercetin, gallic acid, syringic acid, kaempferol, caffeic acid, coumaric acid [129]	Tea	EMA, PDR Ph. Eur. (folium)
Productive cough (2)	*Origanum vulgare* L., Lamiaceae, vranilovka (S), 13 417	Aerial part	Aerial part – rosmarinic acid, gallic acid, ferulic acid, chlorogenic acid, luteolin, naringenin, carvacrol, thymol [130]	Tea, poultice	PDR Ph. Eur. (herba)
Productive cough (2)	*Papaver rhoeas* L., Papaveraceae, bulka (S), 13624	Flower	Flower – delphinidin-3-*O*-glucoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, peonidin-3-*O*-glucoside, petunidin-3-*O*-glucoside, petunidin-3-acetylglucoside, delphinidin-3-*p*-coumaroylglucoside [131]	Syrup, tea	PDR Ph. Eur. (flos)
Productive cough (3)	*Pinus sylvestris* L., Pinaceae, beli bor (S), 13 425	Leaf buds	Leaf buds – pinosylvin, kaempferol, quercetin, taxifolin [132]	Tea	PDR Ph. Eur. (aetheroleum)
Bronchitis (3), productive cough (12)	*Polygonum aviculare* L., Polygonaceae, troskot (S), 13 427	Aerial part	Aerial part – delphinidin, cyanidin, pelargonidin, delphinidin-3-arabinoside, pelargonidin-3-galactoside, leonurine, avicularin [133]	Tea	EMA, PDR
Asthma (1)	*Polypodium vulgare* L., Polypodiaceae, slatka paprat (S), 13 428	Rhizome, leaf*	Rhizome – osladin, 20-hydroxyecdysone, polypodine B, catechin, naringenin, resveratrol, quercetin [134]	Tea	EMA
Productive cough (9)	*Primula veris* L., Primulaceae, jaglika (S), 13 430	Rhizome, aerial part*, flower	Rhizome – primulaverin, primeverin, priverosaponin B-22-acetate, primulasaponin I and II [135] Flower – primulasaponin I and II [135] Aerial part – apigenin, quercetine, kaempferol, cinarozid, rutin,	Tea, syrup	EMA, PDR Ph. Eur. (radix)

			hyperozid [136]		
Pharyngitis (6)	*Salvia officinalis* L., Lamiaceae, žalfija (S), 13 447	Aerial part*, leaf	Aerial part – quinic acid, 3,4-dihydroxyphenyllactic acid, protocatechuic acid, chicoric acid, protocatechuic aldehyde, caffeic acid, luteolin-7-*O*-*β*-D-rutinoside, luteolin-7-*O*-*β*-D-glucoside, luteolin 7-*O*-*β*-D-glucuronide, rosmarinic acid, apigenin-7-glucoside, luteolin, apigenin, carnosol, carnosic acid, methyl carnosate [137] Leaf – carnosic acid, carnosol [138]	Tea, tincture	ESCOP, EMA, PDR Ph. Eur. (folium)
Bronchitis (28), productive cough (17)	*Sambucus nigra* L., Sambucaceae (Adoxaceae), bz (S), 13 450	Bark, leaf, flower	Bark – caffeic acid, ferulic acid, 3,4,5-trimethoxybenzoic acid, chlorogenic acid [139] Leaf – astragalin, caffeic acid, chlorogenic acid, 3,5-dicaffeoylquinic acid, isoquercetin, kaempferol, myricetin, neochlorogenic acid, *p*-coumaric acid, quercetin, rutin [140] Flower – quinic acid, coumaroyl-caffeoylquinic acid, dicaffeoylquinic acid, coumaroylquinic acid, feruloylquinic acid, quercetin-3-rutinoside, quercetin-acetyl glucoside, kaempferol rutinoside, isorhamnetin-rutinoside, isorhamnetin acetylhexoside [141]	Tea, tincture, ointment	EMA, PDR, WHO Ph. Eur. (flos)
Pharyngitis (1), bronchitis (2)	*Symphytum officinale* L., Boraginaceae, gavez (S), 13 462	Root, flower*	Root – *m*-methoxybenzoic acid, 5-caffeoylquinic acid, caffeic acid, 3-caffeoylquinic acid, rosmarinic acid, 1-caffeoylquinic acid, coumarin, lithospermic acid, salicylic acid, *m*-hydroxybenzoic acid [62] Flower – fructan [63] caffeic, *p*-coumaric, *m*-hydroxybenzoic acids [64]	Tincture, poultice, ointment, syrup	EMA, PDR
Productive cough (16), bronchitis (12)	*Thymus spp.*, Lamiaceae, majčina dušiica (S), 13 468	Aerial part	Aerial part – 6,8-di-C-glucosylapigenin, chlorogenic acid, 6-hydroxyluteolin 7-*O*-glucoside, caffeic acid, luteolin 7-*O*-glucuronide, apigenin glucuronide, salvianolic acid K isomer, rosmarinic acid, salvianolic acid [142]	Tea, extract	ESCOP, EMA, PDR, WHO Ph. Eur. (aetheroleum, herba)
Productive cough (4), bronchitis (1)	*Tilia cordata* Mill., Tiliaceae, lipa (S), 13 469	Leaf*, flower	Leaf – quercetin-3,7-di-*O*-rhamnoside, kaempferol-3,7-di-*O*-rhamnoside, tiliroside [143] Flower – catechin, quercetin-3-*O*-glucoside, kaempferol-3-*O*-glucoside, tiliroside [144]	Tea	EMA, PDR Ph. Eur. (flos)

Pharyngitis (3)	*Trifolium pratense* L., Fabaceae, crvena detelina (S), 13 634	Leaf*	Leaf – biochanin A, formononetin, quercetin, kaempferol, phaselic acid, prunetin [145]	Tea	PDR, WHO
Productive cough (2), bronchitis (1)	*Tropaeolum majus* L., Tropaeolaceae, dragoljub (S), 13 635	Leaf*, flower, aerial part	Leaf – gallic acid, *p*-coumaric, chlorogenic acid, rutin [146] Flower – delphinidin, cyanidin, pelargonidin [147] Aerial part – *p*-coumaroylquinic acid, chlorogenic acid, quercetin, kaempferol, glucotropaeolin [148]	Tincture, juice, eat	PDR
Productive cough (5),	*Tussilago farfara* L., Asteraceae, podbel (S), 13 471	Leaf, flower*	Leaf – caffeic acid, ferulic acid, 3,4-hydroxybenzoic acid, dicaffeoylquinic acid, quercetin-pentoside [149] Flower – 3,5-dicaffeoylquinic acid, 3,4-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid [150]	Tea, poultice, syrup	PDR
Productive cough (3)	*Verbascum phlomoides* L., Scrophulariaceae, divizma (S), 13 477	Flower	Flower – verbascoside, diosmin, apigenin, luteolin, tamarixetin-7-rutinoside, tamarixetin-7-glucoside [85]	Tea	ESCOP, EMA
Productive cough (1)	*Viola tricolor* L., Violaceae, dan i noć (S), 13 480	Leaf, flower	Leaf – violanthin [151] Flower – rutin [152]	Tea	EMA, PDR Ph. Eur. (herba cum flore)

Plants WOM used for respiratory diseases (mentioned by two or more independent informants)

Affliction	Botanical taxa, Serbian name (S), Voucher number	Part used	Active compound (HPLC analysis)	Preparation form	Number of use-reports for treated diseases
Asthma (3)	*Robinia pseudoacacia* L., Fabaceae, bagrem (S), 13 438	Leaf, flower	Leaf – gallic acid, (+) -catechin, syringic acid, vanillin, (–)-epicatechin, *p*-coumaric acid, rutin, resveratrol, quercetin [153] Flower - vanillic acid rutin, gallic acid, catechin hydrate, syringic acid, epicatechin, caffeic acid, *p*-coumaric acid [154]	Tea	3
Bronchitis (17)	*Achillea millefolium* L., Asteraceae, hajdučka trava (S), 13 320	Flower, aerial part	Flower – chlorogenic acid, vicenin-2, luteolin-3',7-di-*O*-glucoside, luteolin-7-*O*-glucoside, rutin, apigenin-7-*O*-glucoside, luteolin, apigenin [155] Aerial part – vicenin-2, luteolin-3,7-di-*O*-glycoside, luteolin-7-*O*-glycoside, rutin, apigenin-7-*O*-glycoside, luteolin, apigenin [156]	Tea, tincture	2
	Ocimum basilicum L., Lamiaceae, bosiljak (S), 13 414	Aerial part	Aerial part – gallic acid, caffeic acid, ferulic acid, sinapic acid, syringic acid, quercetin, luteolin, rutin, apigenin, kaempferol [157]	Tea, inhalation	3
	Plantago major L., Plantaginaceae, žilovlak (S), 13 426	Leaf	Leaf – lupeol, benzimidazo[2,1-a] isoquinoline, *β*-amyrin, lup-20(29)-en-3-ol acetate, (3*β*)-acid, *β*-sitosterol, *α*-amyrin, carveol [158]	Tea, poultice	2

	Robinia pseudoacacia L., Fabaceae, bagrem (S), 13 438	Leaf, flower	Leaf – gallic acid, (+)-catechin, syringic acid, vanillin, (–)-epicatechin, *p*-coumaric acid, rutin, resveratrol, quercetin [153] Flower – vanillic acid, rutin, gallic acid, catechin hydrate, syringic acid, epicatechin, caffeic acid, *p*-coumaric acid [154]	Tea	2
	Satureja montana L., Lamiaceae, rtanjski čaj (S), 13 454	Aerial part	Aerial part – hydroxybenzoic acid, hydroxycinnamic acid, chlorogenic acid, dicaffeoylquinic acid isomer 3, kaempferol 3-*O*-glucoside, dicaffeoylquinic acid isomer 2, patuletin-7-glucoside, quercetin 3-*β*-D-glucoside, dicaffeoylquinic acid isomer 4, quercetagetin-7-*β*-D-glucoside [159]	Tea	6
	Teucrium chamaedrys L., Lamiaceae, podubica (S), 13 466	Aerial part	Aerial part – teucrin A, dihydroteugin teucrin E, teucrin F, teucrin G, teuflidin, teuchamaedryn B, teuchamaedryn A, teuchamaedryn C, teugin teucroxide chamaedroxide 6-epiteucrin A, 6*α*-hydroxyteuscordin isoteuflidin teucvin teucvidin [160]	Tea	2
Pharyngitis (4)	*Achillea millefolium* L., Asteraceae, hajdučka trava (S), 13 320	Flower, aerial part	Flower – chlorogenic acid, vicenin-2, luteolin-3',7-di-*O*-glucoside, luteolin-7-*O*-glucoside, rutin, apigenin-7-*O*-glucoside, luteolin, apigenin [155] Aerial part – vicenin-2, luteolin-3,7-di-*O*-glycoside, luteolin-7-*O*-glycoside, rutin, apigenin-7-*O*-glycoside, luteolin, apigenin [156]	Tea, tincture	2
	Rubus vestitus Weihe, Rosaceae, divlja kupina (S), 13 441	Leaf, flower	Leaf – quercetin, kaempferol, ellagic acid [161]	Tea	2
Productive cough (57)	*Anacamptis morio* (L.) Orchidaceae, kaćun (S), 13 416	Flower	Flower – orchicyanin I, orchicyanin II, ophrysanin, chrysanthemin, cyanin, seranin [162]	Tea	2
	Daucus carota L., Asteraceae, sram (S) 13 364	Flower	/	Tea	5
	Elymus repens Poaceae, pirevina (S), 13 323	Aerial part, rhizome	Rhizome – tryptophan, caffeoylquinic acid, feruloylquinic acid, caffeic acid, feruloylquinic acid, coumaric acid, ferulic acid [163]	Tea, ointment	2
	Galium odoratum (L.) Scop., Rubiaceae, lazarkinja (S), 13 376	Aerial part	Aerial part – coumarin, chlorogenic acid, asperuloside, monotropein, geniposidic acid [74]	Tea, tincture, bath	3

	Ocimum basilicum L., Lamiaceae, bosiljak (S), 13 414	Aerial part	Aerial part – gallic acid, caffeic acid, ferulic acid, sinapic acid, syringic acid, quercetin, luteolin, rutin, apigenin, kaempferol [157]	Tea, inhalation	10
	Phaseolus vulgaris L., Fabaceae, pasulj (S), 13 422	Fruit	Fruit – hydroxycinnamic acid, cyaniding-3-*O*-glucoside, pelargonidin-3-*O*-glucoside, malvidin-3-*O*-glucosides [164]	Tea	2
	Picea abies (L.), Pinaceae, smreka (S), 13 423	Twigs, bark, fruit	Bark – ferulic acid, syringic acid, vanillic acid, *p*-coumaric acid, sinapinic acid [165] Fruit – resin acid [166]	Tea, tincture, ointment	2
	Primula vulgaris Huds., Primulaceae, jagorčevina (S), 13 627	Aerial part, flower	Aerial part – gallic acid, protocatechuic acid, *ρ*-hydroxbenzoic acid, vanillic acid, caffeic acid, *ρ*-coumaric acid, syringic acid, ferulic acid, *trans*-cinnamic acid, catechin, epicatechin, rutin, luteolin [167] Flower – (+)-catechin, orientin, rutoside, hyperoside, isorhamnetin-3-*O*-rutinoside, isorhamnetin-3-*O*-glucoside, astragalin, chlorogenic acid [168]	Tea	8
	Robinia pseudoacacia L., Fabaceae, bagrem (S), 13 438	Leaf, flower	Leaf – gallic acid, (+)-catechin, syringic acid, vanillin, (–)-epicatechin, *p*-coumaric acid, rutin, resveratrol, quercetin [153] Flower – vanillic acid, rutin, gallic acid, catechin hydrate, syringic acid, epicatechin, caffeic acid, *p*-coumaric acid [154]	Tea	6
	Rubus idaeus L., Rosaceae, divlja malina (S), 13 442	Leaf, fruit	Leaf – quercetin-3-*O*-rutinoside, myrycetin, quercetin-3-*O*-glucoside, quercetin, luteolin [169] Fruit – cyanidin-3-*O*-sophoroside, cyaniding-3-*O*-glucoside, cyanidin-3-*O*-glucosyl-rutinoside, cyanidin-3-*O*-rutinoside, catechin, epicatechin, procyanidin B [170]	Tea, juice	4
	Rubus vestitus Weihe, Rosaceae, kupina (S), 13 441	Leaf, flower	Leaf – quercetin, kaempferol, ellagic acid [161]	Tea	3
	Satureja montana L., Lamiaceae, rtanjski čaj (S), 13 454	Aerial part	Aerial part – hydroxybenzoic acid, hydroxycinnamic acid, chlorogenic acid, dicaffeoylquinic acid isomer 3, kaempferol 3-*O*-glucoside, dicaffeoylquinic acid isomer 2, patuletin-7-glucoside, quercetin-3-*β*-D-glucoside, dicaffeoylquinic acid isomer 4, quercetagetin 7-*β*-D-glucoside [159]	Tea	10
Sinusitis (4)	*Mentha aquatica* L., Lamiaceae, barska nana (S), 13 412	Aerial part	Aerial part – rosmarinic acid, luteolin-7-*O*-rutinoside, eriodictyol-7-*O*-rutinoside, naringenin-7-*O*-rutinoside, hesperitin-7-*O*-rutinoside [171]	Tea	2

	Ocimum basilicum L., Lamiaceae, bosiljak (S), 13 414	Aerial part	Aerial part – gallic acid, caffeic acid, ferulic acid, sinapic acid, syringic acid, quercetin, luteolin, rutin, apigenin, kaempferol [157]	Tea, inhalation	2
Tuberculosis (2)	*Pulmonaria officinalis* L., Boraginaceae, plućnjak (S), 13 435	Leaf	Leaf – naringin, hesperidin, apigenin-7-glucoside, rutin, chlorogenic acid, myricetin, hyperoside, acacetin, gallic acid [172]	Tea	2

Ph: Pharmacopeia; a Different parts used * Use not reported in monographs
Q2

3.3. Circulatory Disease

Medicinal plants reported to be used for circulatory disorders, classified into plants WM and WOM, are presented in Table 3. In recent decades, a significant increase in the global incidence of cardiovascular diseases has been observed [173]. It is noted that plants rich in polyphenolic compounds possess considerable antioxidative potential, which might be responsible for their cardioprotective activity [174]. For the treatment of circulatory diseases, 113 respondents (70.19%) reported 192 pharmaceutical uses (25.4%) of plants. These reports included 26 medicinal plants belonging to 13 families, among which Rosaceae (44.3%, 85 cit.), Urticaceae (20.3%, 39 cit.), Amaryllidaceae (7.8%, 15 cit.), Amaranthaceae (5.7%, 11 cit.), and Fagaceae (5.2%, 10 cit.) were the most common. The most frequently used plant parts were leaves (60.9%, 117 cit.), fruits (47.9%, 92 cit.), flowers (42.7%, 82 cit.), aerial parts (32.8%, 63 cit.), roots (29.7%, 57 cit.), and seeds (21.9%, 42 cit.). Medicinal plants are reportedly prepared in various pharmaceutical forms, such as tea (73.9%, 142 cit.), tincture (43.75%, 84 cit.), juice (13%, 25 cit.), and poultice (8.3%, 16 cit.). *Aesculus hippocastanum*, *Allium sativum*, and *Crataegus monogyna* has a confirmed indication for circulatory disease by ESCOP, PDR, WHO, and EMA, while the use of *Capsicum annum*, *Cichorium intybus*, and *Rubus idaeus* in circulatory diseases has only been confirmed by PDR. The seeds of *Aesculus hippocastanum* and the flowers of *Calendula officinalis* are mentioned as official medicinal products in the 10th European Pharmacopoeia and monographs of the EMA and WHO. In addition, the PDR claims that the root of *Cichorium intybus* is used to treat hemorrhoids. The remaining 19 plants (73.1%) should be evaluated with recognized scientific methods to determine their effects, as they are used for circulatory disorders. Considering only the uses mentioned by two or more informants (87 use reports), the most frequently treated diseases can be divided into six categories: cardiac insufficiency (36.8%, 56 use reports), anemia (27.6%, 42 use reports), blood vessels (15.8%, 24 use reports), hemorrhoids (8.6%, 13 use reports), antihypertensives (5.9%, 9 use reports), and reduction of blood fat (5.3%, 8 use reports). According to the results, the most reported use is that of *Urtica dioica* (39 out of a total 152 uses; 25.7%, 34 for anemia and 5 for cardiac insufficiency), *Allium ursinum* (14 out of 152 use reports, 9.2%), *Rosa canina* (13 out of 152 use reports, 8.6%), *Beta vulgaris* and *Cornus mas* (11 out of 152 use reports, 7.2% each).

Adverse drug reactions are commonly observed in patients with cardiovascular disease because they usually take several medications; therefore, monitoring them and adjusting treatment as needed is essential [175]. Since ancient times, people have used herbs to treat cardiovascular conditions such as congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, and arrhythmia [176]. Herbs have long been used as a source of medicinal compounds, such as digitoxin from *Digitalis purpurea* and reserpine from *Rauwolfia serpentine* [177]. The need to incorporate herbal remedies in modern medical systems is greater than ever. This is due to a number of factors, the two most important of which are the popular perception of safety and their therapeutic promise of being less expensive than conventional modern medicines.

3.3.1. Urtica dioica L., Urticaceae (Common nettle, Local Name "kopriva")

Common nettle is a perennial plant widely distributed in Europe, Asia, America, and Africa [178]. The EMA has already monographed the roots, leaves, and herba of *U. dioica*, but they do not mention indications for circulatory diseases. Numerous ethnobotanical, phytochemical, and pharmacological studies suggest that this medicinal plant is effective in circulatory disorders. Due to its high iron content, which may help increase erythrocytes and, more specifically, the mean corpuscular hemoglobin concentration, nettle is used to treat anemia. The aqueous extract of leaves increases the red blood cell count, hemoglobin, and white blood cell count and promotes the differentiation of T lymphocytes *in vivo* [179]. Nettle is used in folk medicine for the prevention and treatment of anemia. Also, it increases lowered blood pressure, bringing it back to normal, so it is often given as an adjunct with digitalis in the treatment of heart patients [5]. *U. dioica* extract could improve cardiac performance by decreasing both systolic and diastolic blood pressure [180]. Its acute *in vivo* hypotensive potential was due to diuretic and natriuretic effects [181]. In clinical placebo-controlled, randomized research with hypertensive participants, the systolic and diastolic blood pressures significantly decreased after a 16-week treatment with plant extracts of *U. dioica* each day [182]. Thanks to the vasorelaxing effect, which is mediated by the release of endothelial nitric oxide and the opening of potassium channels, as well as the negative inotropic effect, hypotensive responses can occur [178]. Several clinical studies showed an antihyperlipidemic effect [183-185]. The antihyperlipidemic effects of *U. dioica* come on via inhibiting HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase and reducing lipid peroxidation through antioxidant activities [186]. Extract of *U. dioica* also appears to be an effective scavenger of free radicals, including superoxide anion radicals and hydrogen peroxide [187].

3.3.2. Allium ursinum L., Amaryllidaceae (Ramson, Local name "sremuš")

Ramson is a wild-growing plant widely distributed in Europe and Asia [188]. Traditionally, it is used as an antihypertensive [8, 48] and to lower cholesterol levels [8, 17, 30], which correlates with our results. *A. ursinum* is especially rich in *γ*-glutamyl peptides, which appear to play an important part in the plant's strong hypotensive effect [189]. Rietz et al. [190] and Sendl et al. [191] reported that *A. ursinum* has the potential for *in vitro* and *in vivo* ACE (angiotensin-converting enzyme) inhibition, which could contribute to the lowering of blood pressure and cardioprotective effects. The proposed active substance was *γ*-L-glutamyl-(+)-S-allyl-L-cysteine sulfoxide, which fits in a molecular model of the ACE active site. In addition, a possible mechanism of the antihypertensive effect is the decreased free radical formation [192], which acts as a direct vasodilator in randomized, placebo-controlled, double-blind cross-over study in apparently healthy subjects [193]. Also, one of the ways blood pressure is lowered is by the effect of flavonol compounds present in the plant on the nitric oxide system *in vitro* [194-195]. The chloroform and chloroform/acetone extracts of the bulb of *A. ursinum* reduced cholesterol production by 49.3 and 48.9%, respectively [188]. Sendl et al. [196] reported that ajoene, methyl ajoene, 2-vinyl-4H-1,3-dithiin, and allicin were the strongest cholesterol synthesis inhibitors *in vitro*. The leaf lyophilisate, containing alliin, reduced cholesterol levels in hypercholesterolemic rabbit *in vivo* [197]. In addition, the noted antioxidant activity of different *A. ursinum* extracts could contribute to its overall effects [198]. Wild garlic has not been the subject of clinical trials, and its potential circulatory benefits can be hypothesized based on its chemical composition; however, there is still little preclinical evidence for this. The results of the conducted studies show that *A. ursinum* has cardioprotective effects, indicating its possible use in the prevention and treatment of hypertension and the reduction of fat in the blood.

3.3.3. Rosa canina L., Rosaceae (Dog Rose, Local Name "šipak")

The dog rose is widespread in Europe, Asia, North America, and Northern Africa [199]. *R. canina* exhibits *in vitro* antioxidative [200-201] and *in vitro/in vivo* anti-inflammatory effects [202-203] and regulates the levels of lipids and glucose in the blood *in vivo* [204-205], which can contribute to cardioprotective action. These effects are attributed to polyphenolic compounds, including

flavonoids, anthocyanins, flavan-3-ols, procyanidins, catechin, quercetin, phenolic acids, such as gallic and ellagic acids, kaempferol, apigenin, and resveratrol, as well as vitamins (A, B3, C, D, E, and P), carotenoids, tocopherols, tannins, organic acids, amino acids, and pectin [206-207]. Nasrolahi et al. [208] found that the extract of *R. canina* fruits protects heart tissue *in vivo* by decreasing the overproduction of ROS (reactive oxygen species) induced by heat stress in the cardiomyocytes in male Wistar rats. Additionally, *R. canina* has been shown to protect against ischemia-reperfusion damage in the isolated rat heart. Since aqueous and ethanol preparations may cause diastolic cardiac arrest *in vitro* in isolated frog hearts, care must be taken when using this plant species [209]. After the rose solutions were removed, a 30% increase in contractility was seen, which was accompanied by favorable inotropic and unfavorable chronotropic effects [209]. Compared to the test product, the rosehip drink was not effective in lowering systolic blood pressure in a randomised and double-blind pharmacological study in humans [206].

Table 3. Medicinal plants used for circulatory diseases in eastern and south-eastern Serbia, WM and WOM

Plants WM used for circulatory diseases					
Popular use (Number of use-reports for treated diseases)	**Botanical taxa, Serbian name (S), Voucher Number**	**Part used**	**Active compound (HPLC analysis)**	**Preparation and administration**	**Monograph**
Varicose veins (2)	*Aesculus hippocastanum L.*, Sapindaceae, divlji kesten (S), 13 605	Leaf	Leaf – esculin, fraxin, neochlorogenic acid, gallic acid, 5-hydroxy methylfurfural [210]	Poultice	ESCOP, EMA[a], PDR, WHO[a] Ph. Eur. (semen)
Hypertension (1)	*Allium sativum* L., Amaryllidaceae, beli luk (S), 13 326	Bulb	Bulb – allicin, allyl-methyl-/methyl-allyl-thiosulfinate, methyl-thiosulfinate [211]	Poultice, fresh	ESCOP, EMA, PDR, WHO Ph. Eur. (bulbi pulvis)
Blood vessels (1), Hemorrhoids (1)	*Calendula officinalis L.*, Asteraceae, neven (S), 13 344	Aerial part, flower	Aerial part – rutin, quercetin-3-*O*-glucoside, scopoletin-7-*O*-glucoside, isorhamnetin-3-*O*-glucoside, gallic acid [212] Flower – gallic acid, syringic acid, cinnamic acid, resveratrol, ferulic acid, rutin [213]	Tea, tincture, ointment	EMA, PDR, WHO Ph. Eur. (flos)
Accelerates blood circulation (1), Cardiac insufficiency (2)	*Capsicum annuum L.*, Solanaceae, paprika (S), 13 347	Fruit	Fruit – capsaicin, dihydrocapsaicin [214]	Poultice, fresh	PDR Ph. Eur. (fructus)
Hemorrhoids (1)	*Cichorium intybus L.*, Asteraceae, gologuzija (S), 13 352	Root, aerial part*, flower*	Root – gallic acid, caffeic acid, rutin, apigenin, kaempferol, quercetin [215] Aerial part – cichoric acid, isoquercitrin, rutin, quercitrin, luteolin, apigenin [216] Flower – 3,5-di-*O*-(6-*O*-malonyl-*β*-d-glucoside), delphinidin 3-*O*-(6-*O*-malonyl-*β*-d-glucoside)-5-*O*-*β*-D-glucoside, delphinidin 3-*O*-*β*-D-glucoside-5-*O*-(6-*O*-malonyl-*β*-d-glucoside), delphinidin 3,5-di-*O*-*β*-D-glucoside [217]	Tea	PDR

Cardiac insufficiency (29)	*Crataegus monogyna* Jacq. Rosaceae, glog (S), 13 355	Leaf, flower, fruit	Leaf – procyanidin, epicatechin, catechin, chlorogenic acid, caffeic acid, vitexin-2-*O*-rhamnoside, vitexin, rutin hyperoside [218] Fruit – cyanidin-*O*-hexoside, cyanidin-3-*O*-glucoside; peonidin-*O*-hexoside [219]	Tea, fresh	ESCOP, EMA, PDR, WHO Ph. Eur. (fructus, folium cum flore)
Blood vessels (2)	*Rubus idaeus* L., Rosaceae, divlja malina (S), 13 442	Leaf, fruit	Leaf – quercetin-3-*O*-rutinoside, myricetin, quercetin-3-*O*-glucoside, quercetin, luteolin [169] Fruit – cyanidin-3-*O*-sophoroside, cyaniding-3-*O*-glucoside, cyanidin-3-*O*-glucosyl-rutinoside, cyanidin-3-*O*-rutinoside, catechin, epicatechin, procyanidin B [170]	Tea, juice	PDR

Plants WOM used for circulatory diseases (mentioned by two or more informants)

Affliction	**Botanical taxa, Serbian name (S), Voucher number**	**Part used**	**Active compound (HPLC analysis)**	**Preparation form**	**Number of use-reports for treated diseases**
Anemia (42)	*Beta vulgaris* var. *crassa* Alef., Amaranthaceae, crvena cvekla (S), 13 340	Root	Root – quercetin, sinapic acid, *p*-coumaric acid, syringic acid, gallic acid, coumarin, caffeic acid, chlorogenic acid, catechin [220]	Fresh	4
	Urtica dioica L., Urticaceae, kopriva (S), 13 472	Root, aerial part, leaf, seed	Root – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Aerial part – caffeic acid derivative [66] esculetin, scopoletin, secoisolariciresinol, quinic acid, neochlorogenic acid, kaempferol, amentoflavone, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-glucoside, quercetin-3-*O*-rutinoside [67] Leaf – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Seed – chlorogenic acid, caffeic acid, gallic acid, transferulic acid, coumaric acid, rutin, myricetin, kaempferol-3-*O*-rutinoside-7-*O*-rhamnoside [68]	Tea, tincture, boiled	34

	Vaccinium myrtillus L., Ericaceae, borovnica (S), 13 473	Leaf, fruit, seed	Leaf – hydroxycinnamic acid, chlorogenic acid, caffeic acid, protocatechuic acid, *p*-coumaric acid [221] Fruit – delphinidin-3-*O*-galactoside, delphinidin-3-*O*-glucoside, cyaniding-3-*O*-galactoside, delphinidin-3-*O*-arabinoside, cyaniding-3-*O*-glucoside, petunidin-3-*O*-galactoside, cyanidin-3-*O*-arabinoside, petunidin-3-*O*-glucoside, peonidin-3-*O*-galactoside, petunidin-3-*O* arabinoside, peonidin-3-*O*-glucoside, malvidin-3-*O*-galactoside, malvidin-3-*O*-glucoside, malvidin-3-*O*-arabinoside [222]	Tea, fresh juice, boiled	4
Antihypertensive (lower blood pressure) (9)	*Allium ursinum* L., Amaryllidaceae, sremuš (S), 13 327	Leaf, flower, aerial part	Leaf – gallic acid, kaempferol derivate, S-methyl methanethiosulfonate, allyl sulfide, diallyl disulfide [223] Flower – *p*-coumaric acid, ferulic acid [224]	Tincture, fresh	6
	Prunus spinosa L., Rosaceae, trnjina (S), 13 434	Leaf, flower, fruit	Leaf – delphinidin, cyanidin, malvidin, pelargonidin [225] Flower – chlorogenic acid, *p*-coumaroylquinic acid, feruloylquinic acid, (+)-catechin, (−)-epicatechin, quercetin, kaempferol [226] Fruit – neochlorogenic acid, caffeic acid, quercetin, myricetin, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, peonidin-3-*O*-glucoside [227]	Tea, fresh, juice	3
Blood vessels (24)	*Aronia spp.*, Rosaceae, aronija (S), 13 610	Fruit	Fruit – neochlorogenic acid, chlorogenic acid, rutin, taxifolin [228]	Eat, tincture	2
	Beta vulgaris var. crassa Alef., Amaranthaceae, crvena cvekla (S), 13 340	Root	Root – quercetin, sinapic acid, *p*-coumaric acid, syringic acid, gallic acid, coumarin, caffeic acid, chlorogenic acid, catechin [220]	Fresh	5
	Cornus mas L., Rosaceae, dren (S), 13 354	Twigs, fruit	Fruit – cyanidin-3-galactoside, pelargonidin-3-glucoside, delphinidin-3-galactoside [229]	Fresh juice, tea	3
	Herniaria glabra L.Caryophyllaceae, sitnica (S), 13 387	Aerial part	Aerial part – licoagroside B, apiorutin, rutin, narcissin [230]	Tea, poultice	3
	Malus sylvestris (L.) Mill., Rosaceae, kiseljka (S), 13 405	Fruit	Fruit – rutin, chlorogenic acid, gallic acid [231]	Vinegar	2

Rosa canina L., Rosaceae, šipak (S), 13 439	Flower, fruit	Flower – cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3,5-diglucoside, pelargonidin-3-glucoside, peonidin-3,5-diglucoside, peonidin-3-glucoside, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-glucuronide, quercetin-3-arabinofuranoside, quercetin-3-xyloside, quercetin-3-rhamnoside, quercetin-hexoside-rhamnoside, quercetin-galloylhexoside, quercetin-dihexoside, quercetin-acetyl-hexoside-rhamnoside, quercetin-hexosyl-pentoside, kaempferol-di-hexoside, kaempferol-3-rhamnoside, kaempferol-3-galactoside, kaempferol-3-glucoside, kaempferol-3-glucuronide, kaempferol-acetylglucoside, kaempferol-galloylhexoside, kaempferol-pentoside, kaempferol-pentoside-hexoside, kaempferol-rhamnoside-hexoside, kaempferol-acetyl-hexoside-rhamnoside [80] Fruit – apigenin, caffeic acid, catechin, chlorogenic acid, ferulic acid, epicatechin, gallic acid, kaempferol, *p*-coumaric acid, phloroglucinol, protocatechuic acid, quercetin, quercetin-3-glucoside, resveratrol [81]	Tea, tincture, oil extract	3
Rubus vestitus Weihe, Rosaceae, kupina (S), 13 441	Leaf, flower	Leaf – quercetin, kaempferol, ellagic acid [161]	Tea	4
Taraxacum campylodes G.E.Haglund, Asteraceae, maslačak (S), 13 465	Root, leaf, flower	Root – udesmanolides, tetrahydroridentin B, taraxacolide-*O*-*β*-glucopyranoside, taraxasterol [231] Leaf – taraxinic acid-*β*-D-glucopyranoside, 11,13-dihydrotaraxinic acid-*β*-D-glucopyranoside, *p*-hydroxyphenylacetic acid, *β*-sitosterol, luteolin-7-*O*-glucoside, luteolin-7-*O*-rutinoside, isorhamnetin-3-*O*-glucoside, quercetin-7-*O*-glucoside, apigenin-7-*O*-glucoside [231] Flower – chlorogenic acid, dicaffeoyltartaric acid, monocaffeoyltartaric acid [231]	Tea, tincture	2

Cardiac insufficiency (56)	*Aronia spp.*, Rosaceae, aronija (S), 13 610	Fruit	Fruit – neochlorogenic acid, chlorogenic acid, rutin, taxifolin [228]	Eat, tincture	2
	Beta vulgaris var. crassa Alef., Amaranthaceae, crvena cvekla (S), 13 340	Root	Root – quercetin, sinapic acid, *p*-coumaric acid, syringic acid, gallic acid, coumarin, caffeic acid, chlorogenic acid, catechin [220]	Fresh	2
	Cornus mas L., Rosaceae, dren (S), 13 354	Twigs, fruit	Fruit – cyanidin-3-galactoside, pelargonidin-3-glucoside, delphinidin-3-galactoside [229]	Fresh juice, tea	8
	Crataegus rhipidophylla Gand., Rosaceae, crveni glog (S), 13 357	Leaf, flower	Leaf – gallic acid, chlorogenic acid, rutin [233] Flower – procyanidin dimer (type B), 3-*O*-*p*-coumaroylquinic acid, quercetin-3-*O*-rutinoside, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside [234]	Tea	8
	Fragaria x ananassa (Duchesne ex Weston) Duchesne ex Rozier, Rosaceae, jagoda (S), 13 618	Fruit	Fruit – quercetin, kaempferol, quercetin-3-malonylglucoside, cyanidin-3-glucoside, pelargondin-3-glucoside, *p*-coumaric acid, ellagitannins [235]	Juice, eat	5
	Prunus avium (L.) L., Rosaceae, divlja trešnja (S), 13 432	Peduncle, fruit	Peduncle – dihydrowogonine-7-*O*-glucoside [236] Fruit – ferulic acid, gallic acid, quercetin, syringic acid, *p*-coumaric acid, *m*-coumaric acid [237]	Tea	2
	Quercus robur L., Fagaceae, hrast (S), 13 436	Fruit	Fruit – quinic acid, malic acid, quercetin, luteolin, naringenin, hesperetin [238]	Tea	10
	Rosa canina L., Rosaceae, šipak (S), 13 439	Flower, fruit	Flower – cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3,5-diglucoside, pelargonidin-3-glucoside, peonidin-3,5-diglucoside, peonidin-3-glucoside, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-glucuronide, quercetin-3-arabinofuranoside, quercetin-3-xyloside, quercetin-3-rhamnoside, quercetin-hexoside-rhamnoside, quercetin-galloylhexoside, quercetin-dihexoside, quercetin-acetyl-hexoside-rhamnoside, quercetin-hexosyl-pentoside, kaempferol-di-hexoside, kaempferol-3-rhamnoside, kaempferol-3-galactoside, kaempferol-3-glucoside, kaempferol-3-glucuronide, kaempferol-acetylglucoside, kaempferol-galloylhexoside, kaempferol-pentoside, kaempferol-pentoside-hexoside, kaempferol-rhamnoside-hexoside, kaempferol-acetyl-	Tea, tincture, oil extract	10

			hexoside-rhamnoside [80] Frut – apigenin, cafeic acid, catechin, chlorogenic acid, ferulic acid, epicatechin, gallic acid, kaempferol, *p*-coumaric acid, phloroglucinol, protocatechuic acid, quercetin, quercetin-3-glucoside, resveratrol [81]		
	Rosmarinus officinalis L., Lamiaceae, ruzmarin (S), 13 440	Aerial part, leaf	Aerial part – carnosic acid, carnosol, rosmarinic acid [82] Leaf – carnosol, carnosic acid, rosmadial, rosmanol, genkwanin, homoplantagini, scutellarein, cirsimaritin, rosmarinic acid [83]	Tea, Tincture	4
	Urtica dioica L., Urticaceae, kopriva (S), 13 472	Root, aerial part, leaf, seed	Root – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Aerial part – caffeic acid derivative [66] esculetin, scopoletin, quinic acid, neochlorogenic acid, kaempferol, amentoflavon, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-glucoside, quercetin-3-*O*-rutinoside [67] Leaf – cinnamic acid, chlorogenic acid, dihydroxy-benzoic acid, ellagic acid, syringic acid, vanillic acid, pyrocatechin, catechin, epicatechin, rutin, quercetin, quercitrin [65] Seed – chlorogenic acid, caffeic acid, gallic acid, transferulic acid, coumaric acid, rutin, myricetin, kaempferol-3-*O*-rutinoside-7-*O*-rhamnoside [68]	Tea, Tincture, Boiled	5
Hemorrhoids (13)	*Ficaria verna* Huds., Ranunculaceae, ledinjak (S), 13 437	Root, leaf, flower, fruit	Leaf – orientin, kaempferol, vitexin, quercetin, isovitexin, isoorientin [236] Flower – orientin, kaempferol, vitexin, quercetin, isovitexin, isoorientin [239]	Tea, tincture	4
	Iris x germanica L., Iridaceae, perunika (S), 13 393	Rhizome	Rhizome – irisolone, irigenin, iridin, germanaism [240]	Tea, poultice, ointment	7
	Rubus vestitus Weihe, Rosaceae, kupina (S), 13 441	Leaf, flower	Leaf – quercetin, kaempferol, ellagic acid [161]	Tea	2
Reduce fat in the blood (8)	*Allium ursinum* L., Amaryllidaceae, sremuš (S), 13 327	Leaf, flower, aerial part	Leaf – gallic acid, kaempferol derivate, S-methyl methanethiosulfonate, allyl sulfide, diallyl disulfide [223] Flower – *p*-coumaric acid, ferulic acid [224]	Tincture, fresh	8

Ph: Pharmacopeia; a Different parts used * Use not reported in monographs

3.4. Genitourinary Disorders

Medicinal plants reported to be used for genitourinary disorders, classified into plants WM and WOM, are presented in Table 4. Over the last few decades, kidney problems, particularly kidney stones, have become more common. Herbal medicines and remedies with significant nephroprotective activity are efficient in removing ascending bacteria, crystallization nuclei, and other inflammatory agents from patients with urinary tract infections [241].

Out of 161 respondents, 25 (15.53%) said they used 25 medical plants to treat genitourinary diseases (25.7%, 194 use reports). The plants belong to 19 families, mainly represented by Apiaceae (35.1%, 68 cit.), Poaceae (11.9%, 23 cit.), Polygonaceae (7.2%, 14 cit.), and Asteraceae and Betulaceae (6.2%, 12 cit. each). The most frequently used parts are the leaf (50%, 97 cit.), aerial part (42.8%, 83 cit.), root (34.5%, 67 cit.), flower (30.9%, 60 cit.), and fruit and seed (11.9%, 23 cit., each). They were prepared in various pharmaceutical forms, such as tea (64,5%, 189 cit.), poultice (10.9%, 32 cit.), tincture (8.5%, 25 cit.), eat (8.2%, 24 cit.), and ointment (4.4%, 13 cit.). Fourteen out of 25 plants (56%) and 106 out of 194 uses (54.6%) have already been confirmed in the monographs of the EMA, ESCOP, PDR and WHO for diseases of the genitourinary system. The most significant proportion of monographs came from the EMA (92.9%), followed by the PDR (71.4%), ESCOP (21.4%), and the WHO (14.3%). Eight of them are also included in the 10th European Pharmacopoeia, where they were listed as official drugs. In addition to the *Uvae ursi folium*, the respondents mentioned using their flowers and fruits. Respondents also claimed that the *Betula pendula* seed, leaf, and bark were used for kidney colic, but there are no monographs for the seed. The leaf and aerial parts of *Epilobium parviflorum* are used for kidney colic and prostate. Meadowsweet herba (*Filipendulae ulmariae herba*) is mentioned as an official drug, but there is no information on the use of leaves and flowers. The aerial part and leaf of *Levisticum officinale* are used for urinary infections and as a diuretic, as are the aerial part and root of *Ononis spinosa*, but only *Levisticum radix* and *Ononidis radix* are known as official drugs. There are no monographs on the use of *Petroselinum crispum* leaves or *Vitis vinifera* fruits. The remaining 44% (11 plants) and 45.4% (88 uses) were mostly used to treat conditions in four pathological categories: kidney colic (50%, 44 use reports), urinary infections (28.4%, 25 use reports), painful menstruation (14.8%, 13 use reports), and as a diuretic (6.8%, 6 use reports). The results showed that the most commonly used medicinal plant is *Apium graveolens* (38.6%, 34 uses, 24 for kidney colic and 10 for urinary infection), followed by *Zea mays* (21 out of 88 use reports, 23.9%), *Calendula officinalis* (11 out of 88 use reports, 12.5%), *Cucumis sativus* (9 out of 88 use reports, 10.2%), and *Galium verum* (6 out of 88 use reports, 6.8%).

3.4.1 Apium graveolens L., Apiaceae (Celery, Local Name "celer")

Celery is often used as a diuretic, urinary tract antiseptic and antirheumatic [5,30,48]. This study showed that the aerial part, leaf, and root of *A. graveolens* are used for treating urinary tract infections and kidney colic. Aqueous celery extracts significantly increased urine volume, reduced the rate of crystal formation, helped flush out crystals, and raised urine pH, which stopped the formation of stones by preventing salt precipitation. Additionally, the supplementation of aqueous extract to urolithiatic rats resulted in lower calcium, oxalate, and phosphate concentrations in the urine and kidneys as well as higher magnesium levels, which prevented the formation of stony deposits, improving function and the glomerular filtration rate significantly *in vivo* [242]. The *in vitro* antimicrobial activity of different extracts of *A. graveolens* has been related to compounds that can combine with the proteins and carbohydrates in bacterial cell walls, inhibit certain enzymes, or accumulate in membranes, leading to energy depletion [243]. The bacterium *Staphylococcus aureus*, which produces morphological and histological degenerative lesions of the kidney cortex and medulla tissue, was injected intraperitoneally into rabbits. Blood urea nitrogen, creatinine, and creatinine kinase values significantly improved in rabbits after intraperitoneal administration of an aqueous extract of *A. graveolens*. The limonene and carvone present in the extract have a strong antibacterial effect on *S. aureus* [244]. Hussain and Khalaf [245] confirmed the *in vitro* inhibitory activity of different concentrations of *A. graveolens* extract on Gram-negative bacteria, *Klebsiella*, and Gram-

positive bacteria, *S. aureus*. Pretreating mice with hydroalcoholic extract can significantly reduce the severity of infection and could be utilized to prevent future infections [246]. The hydroalcoholic and acetone extracts of the fruit showed concentration-dependent antiadhesive activity against *E. coli*. Phthalides were found to be the main active compounds in extracts, which exert strong antiadhesive activity against uropathogenic *E. coli* [247].

3.4.2. Zea mays L., Poaceae (Maize, Local Name "kukuruz")

Potassium salts and other compounds in corn silk allow its use as a diuretic, a remedy for bladder problems, urinary concrements, chronic cystitis, nephritis, and similar diseases [5,30]. The aqueous extract of *Z. mays* has diuretic effects, increasing urine flow and sodium and potassium excretion *in vivo* [248-249]. A similar effect was noted with an infusion of *Z. mays* on guinea pigs and male white mice [250]. In a placebo controlled, double-blind study with 38 individuals who used an aqueous extract, there was no significant difference in urine, sodium, or potassium excretion [251]. There is a possibility that the dosage was too low to be effective. Therefore, more clinical studies are needed. *Z. mays* may induce mesangial cells to contract, reducing their surface area and, as a result, changing the glomerular filtration rate and filtration coefficient. Other possibilities include vasomotor effects, such as an arterial smooth muscle contraction or an efferent dilation, which could lower the glomerular capillary hydrostatic pressure and, as a result, lower glomerular filtration [252]. In our research, respondents stated that they use the female flower of *Z. mays* in the treatment of kidney colic. The administration of *Z. mays* in urolithic rats increased the passage of urinary stones through the urinary tract and played an important role by increasing the vasodilation of the urinary tract, which led to an increase in urinary output. When the potassium content is high, calcium ions in the kidney stone are displaced, and potassium combines with carbonate, oxalate, phosphate, or uric acid to form water-soluble compounds [253]. The use of plant species as a diuretic has been recorded in research studies [2,8,12-13]. Ethnobotanical research [11,15,17] has shown that the species is used in treating kidney colic.

3.4.3. Calendula officinalis L., Asteraceae (Marigold, Local name "neven")

Marigold is a medicinal plant used in homeopathic and traditional medicine [254]. The EMA has approved the traditional use of its topical preparations for the symptomatic treatment of mild skin inflammation and mouth and throat inflammation. According to Tasić et al. [30] and Tucakov [5], it is used in the form of tea for irregular menstruation as well as to reduce menstrual bleeding [255]. *C. officinalis* can be used to treat cramps due to its spasmolytic and spasmogenic constituents, which mediate their effects by blocking calcium channels and cholinergic activity, respectively [256]. The flowers of *C. officinalis* are known for their anti-inflammatory effects [257]. Calendula oil obtained from flowers shortens nerve cell axons, preventing uterine nerve cell messages from reaching the brain and delaying the transfer of pain signals from the brain to the uterus [258-259]. In a double-blind, randomized, placebo-controlled trial, a reduction in the severity of dysmenorrhea was noted [260]. Although there is little information on its use for painful periods, there is a lot of ethnobotanical data for this species. The *C. officinalis* flower already has a monograph issued by the EMA, but there is no mention of its use for genitourinary disease. The EMA is currently debating monographs for the aerial part of *C. officinalis*.

According to our results, the above-mentioned plant species are the most frequently used in treating diseases that affect the residents of eastern and south-eastern Serbia. Musculoskeletal, respiratory, circulatory, and genitourinary diseases are also a growing medical problem worldwide, especially in developing countries [113,261-263]. A review of the literature on plants considered widely used and for which there are no monographs has shown that they have therapeutic value, as they have been tested experimentally and clinically. The EMA already has monographs for *V. phlomoides* and *R. officinalis*, but these do not mention their use in arthritis. Thus, additional studies on chemical compounds and isolates are needed to determine the clinical safety and efficacy of these plant species in arthritis.

U. dioica and *C. officinalis* have monographs but not for circulatory or genitourinary diseases. Our findings suggest that these medicinal plants may be used to develop affordable, efficient, and safe treatments.

Table 4. Medicinal plants used for genitourinary disorders in eastern and south-eastern Serbia, WM and WOM

Medicinal plants WM used for genitourinary disorders					
Popular use (Number of use-reports for treated diseases)	**Botanical taxa, Serbian name (S), Voucher number**	**Part used**	**Active compound (HPLC analysis)**	**Preparation and administration**	**Monograph**
Urinary infection (4)	*Arctostaphylos uva-ursi* (L.) Ericaceae, uva (S), 13 332	Leaf, flower*, fruit*	Leaf – arbutin, gallic acid, caffeic acid, chlorogenic acid, hyperoside, catechin [264]	Tea	ESCOP, EMA, PDR, WHO Ph. Eur. (leaf)
Kidney colic (12)	*Betula pendula* Roth., Betulaceae, breza (S), 13 341	Leaf, seed*, bark tree	Leaf – myricetin-3-*O*-galactoside, quercetin-3-*O*-galactoside, quercetin-3-*O*-arabinoside, quercetin-3-*O*-rhamnoside, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-glucuronide, quercetin-3-*O*-glucuronide [265] Bark tree – betulinic acid [266]	Tea	ESCOP, EMA, PDR, Ph. Eur. (leaf)
Kidney colic (4); painful menstruation (3)	*Capsella bursa-pastoris*, Brassicaceae, hoću-neću (S), 13 346	Aerial part	Aerial part – quercetin-6-C-glucoside, quercetin-3-*O*-glucoside, kaempferol-3-*O* rutinoside, quercetin, kaempferol [267]	Tea	EMA, PDR
Kidney colic (2), prostate (3)	*Epilobium parviflorum* Schreb., Onagraceae, sitnocvetna mlečika (S), 13 368	Aerial part, leaf*	Aerial part – oenothein B, caffeic acid–pentose ester, myricetin-3-*O*-hexose-gallate, myricetin-3-*O*-hexoside, ellagic acid–pentoside, myricetin-3-*O*-rhamnoside, ellagic acid–hexoside, quercetin-3-*O*-rhamnoside, kaempferol-3-*O*-rhamnoside [268]	Tea, poultice	EMA
Kidney colic (5), urinary infections (2), diuretic (3)	*Equisetum arvense L.*, Equisetaceae, rastavić (S), 13 368	Aerial part	Aerial part – caftaric acid, kaempferol-3,7-di-*O*-glucoside, kaempferol-3-*O*-rutinoside, isoquercetin [269]	Tea, poultice	EMA, PDR Ph. Eur. (herba)
Diuretic (2)	*Filipendula ulmaria* (L.) Maxim., Rosaceae, medunika (S), 13 373	Leaf, flower	Leaf – catechin, rutin, isoquercitrin, cynaroside, astragalin, gallic acid, protocatechuic acid, caftaric acid, chlorogenic acid, *p*-coumaric acid, ellagic acid [60] Flower – rutin, isoquercitrin, spiraeoside, cynaroside, gallic acid, protocatechuic acid, caftaric acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ellagic acid, salicylic acid [60]	Tea, poultice, tincture	EMA, PDR Ph. Eur. (herba)
Bladder diseases (2), kidney colic (1)	*Herniaria glabra L.*, Caryophyllaceae, sitnica (S), 13 387	Aerial part	Aerial part – licoagroside B, apiorutin, rutin, narcissin [230]	Tea, poultice	EMA, PDR

Diuretic (2)	*Juniperus communis L.*, Cupressaceae, kleka (S), 13 395	Fruit	Fruit – isoscutellarein, 8-hydroxyluteolin, hypolaetin glycosides, amentoflavone, hynokiflavone, cupressoflavone [123]	Tea, tincture, oil extract	EMA Ph. Eur. (cone berry)
Urinary infections (2), diuretic (2)	*Levisticum officinale* W.D.J.Koch., Apiaceae, selen (S), 13 399	Aerial part, leaf*	Aerial part – 5-*O*-caffeoylquinic acid, 3-*O*-caffeoylquinic acid, quercetin-3-*O*-rutinoside, maclurin-3-C-glucoside [270] Leaf – 4-caffeoylquinic acid, 5-caffeoylquinic acid, quercetin-3-*O*-deoxyhexoside-*O*-hexosid, apterin, rutin, kaempferol-3-*O*-deoxyhexoside-O- hexoside, caffeic acid and apterin ester, sinapic acid and apterin ester, *p*-coumaric acid and apterin ester, ferulic acid and apterin ester, ligustilide, ligustlide, caffeic acid [271]	Tea, fresh	EMA[a], PDR
Kidney colic (2)	*Ononis spinosa* L., Fabaceae, grmotrn (S), 13 451	Aerial part*, root	Aerial part – caffeic acid hexoside, ferulic acid hexoside, caffeic acid, *cis*-chicoric acid, *trans*-chicoric acid, quercetin-*O*-hexoside-pentoside, kaempferol-*O*-dihexoside, spinonin-*O*-hexoside, quercetin-3-*O*-glucoside, kaempferol-*O*-hexoside-pentoside, acetylquercetin-*O*-hexoside, kaempferol-*O*-hexoside, kaempherol-3-*O*-glucoside, pseudobaptigenin-*O*-hexoside, formononetin derivative, formononetin-*O*-malonyl-hexoside [76] Root – formononetin, calycosin, pseudobaptigenin, maackiain, medicarpin [77]	Tea, tincture	ESCOP, EMA, PDR Ph. Eur. (radix)
Kidney colic (25), urinary infections (11), inflammation of the bladder (2)	*Petroselinum crispum* (Mill.) Apiaceae, peršun (S), 13 420	Root, leaf*	Root – imperatorin, 5-methoxypsoralen, psoralen, isopimpinellin, 8-methoxypsoralen, oxypeucedanin [272] Leaf – apigenin, luteolin, quercetin, kaempferol [273]	Tea	PDR
Kidney colic (14)	*Polygonum aviculare* L., Polygonaceae, troskot (S), 13 427	Aerial part	Aerial part – delphinidin, cyanidin, pelargonidin, delphinidin-3-arabinoside, pelargonidin-3-galactoside, leonurine, avicularin [133]	Tea	EMA
Urinary infections (1)	*Taraxacum campylodes* G.E. Haglund, Asteraceae, maslačak (S), 13 465	Root, leaf, flower	Root – eudesmanolides tetrahydroridentin B, taraxacolide-*O*-*β*-glucopyranoside, taraxasterol [231] Leaf – taraxinic acid *β*-D-glucopyranoside, 11,13-dihydrotaraxinic-acid *β*-D-glucopyranoside, *β*-sitosterol, luteolin 7-*O*-glucoside, luteolin 7-*O*-rutinoside, isorhamnetin 3-*O*-glucoside, quercetin 7-*O*-glucoside, apigenin 7-*O*-glucoside	Tea, tincture	EMA, PDR, WHO Ph. Eur. (herb with root, root)

			[231] Flower – chlorogenic acid, dicaffeoyltartaric acid, monocaffeoyltartaric acid [231]		
Diuretic (2)	*Vitis vinifera* L., Vitaceae, grožđe (S), 13 481	Fruit*	Fruit – chlorogenic acid, catechin, gallic acid, caffeic acid, epicatechin gallate, epicatechin, cinnamic acid, benzoic acid, coumaric acid, esculetin, hesperidin, rutin, quercetin, quercitrin, kaempferol, rhamnetin [274]	Fresh juice, fresh	EMA

Plants WOM used for genitourinary disorders (mentioned by two or more informants)

Affliction	Botanical taxa, Serbian name (S), Voucher number	Part used	Active compound (HPLC analysis)	Preparation form	Number of use-reports for treated diseases
Diuretic (6)	*Petroselinum crispum* (Mill.) Apiaceae, peršun (S), 13 420	Root, leaf	Root – imperatorin, 5-methoxypsoralen, psoralen, isopimpinellin, 8-methoxypsoralen, oxypeucedanin [272] Leaf – apigenin, luteolin, quercetin, kaempferol [273]	Tea	2
	Rosa canina L., Rosaceae, šipak (S), 13 439	Flower, fruit	Flower – cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3,5-diglucoside, pelargonidin-3-glucoside, peonidin-3,5-diglucoside, peonidin-3-glucoside, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-glucuronide, quercetin-3-arabinofuranoside, quercetin-3-xyloside, quercetin-3-rhamnoside, quercetin-hexoside-rhamnoside, quercetin-galloylhexoside, quercetin-dihexoside, quercetin-acetyl-hexoside-rhamnoside, quercetin-hexosyl-pentoside, kaempferol-di-hexoside, kaempferol-3-rhamnoside, kaempferol-3-galactoside, kaempferol-3-glucoside, kaempferol-3-glucuronide, kaempferol-acetylglucoside, kaempferol-galloylhexoside, kaempferol-pentoside, kaempferol-pentoside-hexoside, kaempferol-rhamnoside-hexoside, kaempferol-acetyl-hexoside-rhamnoside [80] Frut - apigenin, caffeic acid, catechin, chlorogenic acid, ferulic acid, epicatechin, gallic acid, kaempferol, *p*-coumaric acid, phloroglucinol, protocatechuic acid, quercetin, quercetin-3-glucoside, resveratrol [81]	Tea, tincture, oil extract	2

	Zea mays L., Poaceae, kukuruz (S), 13 482	Female flower	Female flower – caffeic acid, *trans-p*-coumaric acid, ferulic acid [275]	Tea	2
Kidney colic (44)	*Allium ampeloprasum* L., Amaryllidaceae, praziluk (S), 13 325	Stem, seed	Seed – gallic acid , coumaric acid, caffeic acid, tannic acid, vanillic acid, chlorogenic acid, kaempferol, quercetin [276]	Tea	2
	Apium graveolens L. Apiaceae, celer (S), 13 609	Aerial part, leaf, root	Aerial part – junipediol A 4-*O*-glucoside, junipediol A 8-*O*-glucoside, graveobioside A, graveobioside B, senkyunolide J, senkyunolide N, 3-butylhexahydro-1(3*H*) isobenzofuranone (3-butylhexahydrophthalide), apiumetin-*O*-glucoside, 2-(1,2-dihydroxy-1-methylethyl)-2,3-dihydro-7*H*furo[3,2g][1]benzopyran7-one, celereoin, osthenol [277] Leaf - choline, pantothenic acid, riboflavin, phylloquinone, vitamin E succinate, apiin, apigenin, rutin, cyanidin, 3,7-dihydroxyflavone, peucedanin, elemicin, diosmetin, safflomin A, α-ionone, α-linolenic acid, oleic acid [278] Root – junipediol A 4-*O*-glucoside, junipediol A 8-*O*-glucoside, 3a,4-dihydro-3-(3-methylbutylidene)-1(3*H*) isobenzofuranone (isovalidene3a,4-dihydrophthalide), senkyunolide J, senkyunolide N, 3-butylhexahydro-1(3*H*) isobenzofuranone (3-butylhexahydrophthalide), apiumetin-*O*-glucoside, celereoin, osthenol [277]	Tea, eat	10
	Elymus repens Poaceae, pirevina (S), 13 323	Aerial part, rhizome	Rhizome – tryptophan, caffeoylquinic acid, feruloylquinic acid, caffeic acid, feruloylquinic acid, coumaric acid, ferulic acid [163]	Tea, ointment	2
	Galium verum L., Rubiaceae, golemo cveće (S), 13 377	Aerial part, flower	Aerial part – asperuloside, asperulosidic acid, neochlorogenic acid, chlorogenic acid, kaempferol-*O*-glucoside, isorhamnetin-3-*O*-rutinoside, quercetin [279] Flower – asperuloside, asperulosidic acid, rutin, quercetin-3-rutinoside-7-glucoside, isorhamnetin-3-*O*-rutinoside-7-*O*-glucoside, kaempferol-*O*-glucoside, isorhamnetin-3-*O*-rutinoside, quercetin [279]	Tea	6

	Geranium macrorrhizum L., Geraniaceae, zdravac (S), 13 619	Aerial part, flower, leaf	Aerial part – hyperoside, ellagic acid, isoquercitrine, quercetol, kaempherol, caftaric acid, rutoside, quercitrine [280] Leaf – quercetin, kaempherol, myricetin, gallic acid, ellagic acid, 4-galloylquinic acid, quercetin-3-*β*-glucopyranoside, quercetin-3-*β*-galactopyranoside, quercetin-4′-*β*-glucopyranoside [281]	Tea, poultice, tincture	3
	Juniperus communis L., Cupressaceae, kleka (S), 13 395	Fruit	Fruit – isoscutellarein, 8-hydroxyluteolin, hypolaetin glycosides, amentoflavone, hynokiflavone, cupressoflavone [123]	Tea, tincture, oil extract	2
	Zea mays L., Poaceae, kukuruz (S), 13 482	Female flower	Female flower – caffeic acid, *trans*-*p*-coumaric acid, ferulic acid [275]	Tea	19
Painful menstruation (13)	*Calendula officinalis* L., Asteraceae, neven (S), 13 344	Aerial part, flower	Aerial part – rutin, quercetin-3-*O*-glucoside, scopoletin-7-*O*-glucoside, isorhamnetin-3-*O*-glucoside, gallic acid [212] Flower – gallic acid, syringic acid, cinnamic acid, resveratrol, ferulic acid, rutin [213]	Tea, tincture, ointment	11
	Thymus spp., Lamiaceae, majčina dušica (S), 13 468	Aerial part	Aerial part – 6,8-di-C-glucosylapigenin, chlorogenic acid, 6-hydroxyluteolin-7-*O*-glucoside, caffeic acid, luteolin-7-*O*-glucuronide, apigenin glucuronide, salvianolic acid K isomer, rosmarinic acid, salvianolic acid [142]	Tea, extract	2
Urinary infections (25)	*Apium graveolens* L. Apiaceae, celer (S), 13 609	Aerial part, leaf, root	Aerial part – junipediol A 4-*O*-glucoside, junipediol A 8-*O*-glucoside, graveobioside A, graveobioside B, senkyunolide J, senkyunolide N, 3-butylhexahydro-1(3*H*) isobenzofuranone (3-butylhexahydrophthalide), apiumetin-*O*-glucoside, 2-(1,2-dihydroxy-1-methylethyl)-2,3-dihydro-7*H*furo[3,2g][1]benzopyran7-one, celereoin, osthenol [277] Leaf – choline, pantothenic acid, riboflavin, phylloquinone, vitamin E succinate, apiin, apigenin, rutin, cyanidin, 3,7-dihydroxyflavone, peucedanin, elemicin, diosmetin, safflomin A, *α*-ionone, *α*-linolenic acid, oleic acid [278] Root – junipediol A 4-*O*-glucoside, junipediol A 8-*O*-glucoside, 3a,4-dihydro-3-(3-methylbutylidene)-1(3*H*) isobenzofuranone (isovalidene3a,4-dihydrophthalide), senkyunolide J, senkyunolide N, 3-	Tea, eat	14

		butylhexahydro-1(3*H*) isobenzofuranone (3-butylhexahydrophthalide), apiumetin-*O*-glucoside, celereoin, osthenol [277]		
Cucumis sativus L., Cucurbitaceae, krastavac (S), 13 359	Seed, fruit	Seed – kaempferol, quercetin, luteolin [282] Fruit -ascorbic acid [283]	Tea, fresh, poultice	9
Vaccinium vitis-idaea L., Ericaceae, brusnica (S), 13 474	Leaf, fruit	Leaf – astragalin, avicularin, hyperoside quercitrin, arbutin, (+)-catechin (-)-epicatechin procyanidin C1, A2 chlorogenic acid, cryptochlorogenic acid [284] Fruit – cyanidin-3-*O*-galactoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-arabinoside, procyanidin A1, A2, A4, B1, B2, B3, C [285]	Tea	2

Ph: Pharmacopeia; a Different parts used * Use not reported in monographs

3.5. Comparative Ethnobotanical Analyses

Of the 14 plants our respondents reported using in the treatment of arthritis, gout, and/or rickets, compared to previous studies [2,5-17], all but *Adonis vernalis* and *Colchicum autumnale* were mentioned in some of the above studies. However, none of these plants was used in the aforementioned ethnobotanical studies for the treatment of musculoskeletal disorders.

According to previous studies, *Daucus carota* is used for sand and stones in the urinary tract, to strengthen the immune system, and as a diet component [8] to treat gastric ulcers and dysentery [14]. The respondents in our study used it to treat productive cough. According to the results of our research, the respondents used *Picea abies* and *Primula vulgaris* in the treatment of productive cough, while in Bosnia and Herzegovina, these plant species are used for other indications [15]. Mustafa et al. [11] reported that respondents used the aerial parts of *Phaseolus vulgaris* to prepare infusions, such as an antidiabetic; in a survey by Pieroni et al. [12], it was used as a staple food; Quave and Pieroni [13] indicated that it was used as a remedy for dog bite, and we found that *P. vulgaris* fruits were used against productive cough. Our respondents use the fruits and leaves of *Rubus idaeus* in the form of tea and juice to treat productive cough; however, this use was not mentioned in any of these studies [2,8,10-13,15,17]. The aerial part of *Ocimum basilicum* is used by our subjects to treat sinusitis, and this treatment was not documented in other studies [2,8,11-12,14-15,17]. *Pulmonaria officinalis* is used for pulmonary ailments, and our respondents said that they use its leaf to treat tuberculosis. The root of *Beta vulgaris* is mentioned in the treatment of anemia, blood vessels, and cardiac insufficiency, while respondents reported using it as a textile dye in the study by Mustafa et al. [11] and as a galactagogue for cows and humans in the study by Quave and Pieroni [13].

In Bosnia and Herzegovina, the aerial part of Herniaria glabra is used as a tea against kidney stones and urinary tract infections, while our respondents said that they use the aerial part of this plant to treat the blood vessels [15]. In our region, the flower and aerial parts of Rosa canina were found to be used for treating circulatory system diseases, while respondents from other regions did not report this use [2,6-14,16-17]. The stem and seeds of Allium ampeloprasum are used for the treatment of renal colic, whereas [8] reported its usage as an antidiabetic and [13] for eating. Apium graveolens roots are used in the Šar Mountains (southern Kosovo) as a diuretic [2]; in Bosnia and Herzegovina, the aerial part is used to treat sterility [11], while our results showed that the aerial part, leaf, and root were used for renal colic and urinary tract infections. According to the obtained data, the aerial part, flower, and leaf of Geranium macrorrhizum are used to treat renal colic. In another study, respondents mentioned that this plant is used for inflammation of the skin and mucous membranes [10]. In our region, the flower and aerial parts of Calendula officinalis are used to treat painful menstruation, while respondents from other regions did not report this use [2,8-9,11,15,17].

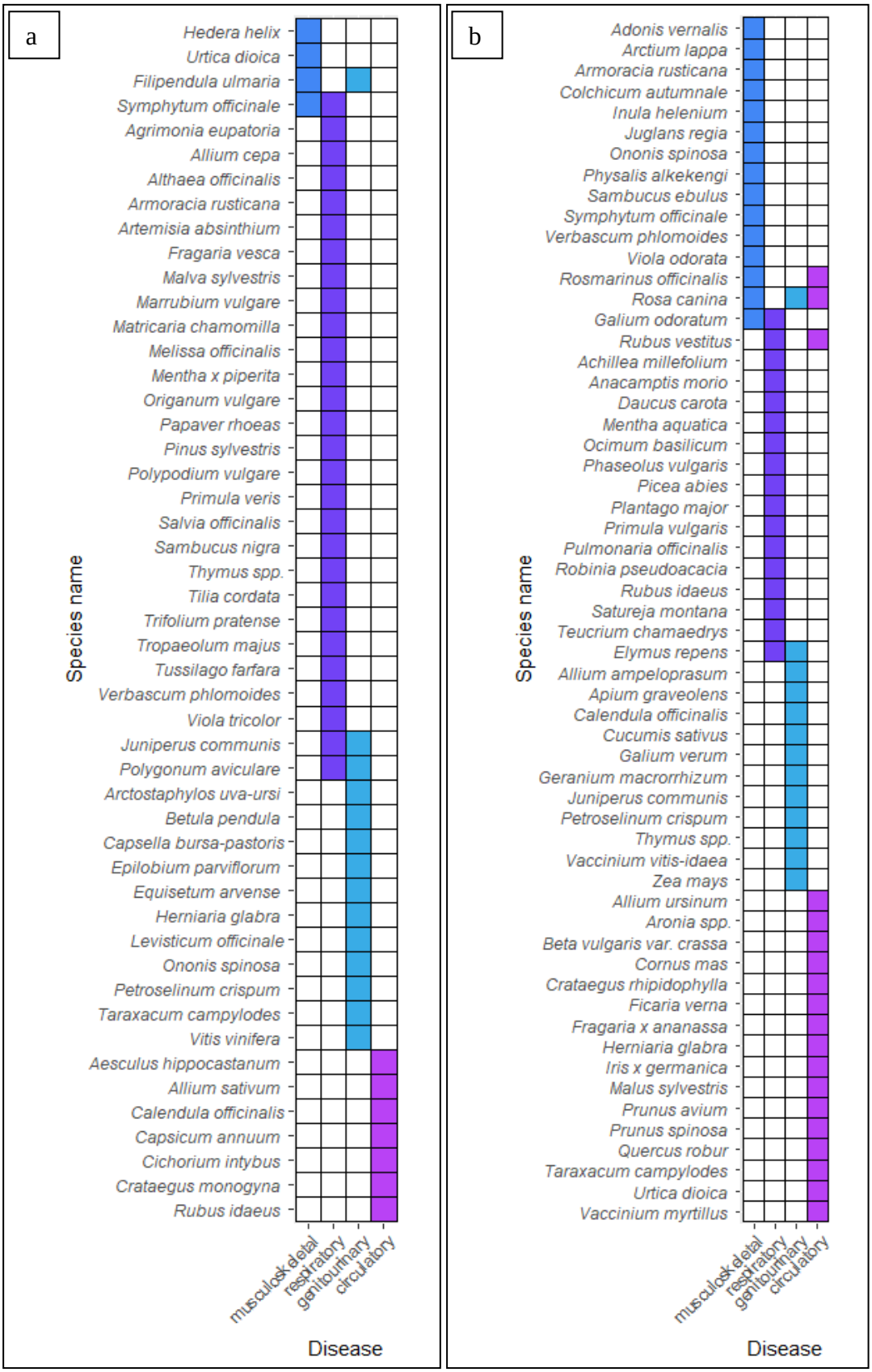

Figure 1. Heat maps of medicinal plants used in folk medicine of eastern and south-eastern Serbia: a) plants WM; b) plants WOM.

Our findings show that respondents use a single plant to treat many diseases (Figure 1). Several herbs (*Filipendula ulmaria*, *Symphytum officinale*, *Juniperus communis*, and *Polygonum aviculare*) exhibit a wide range of beneficial properties that have been shown to be useful in treating various ailments, according to official sources. However, many of the plants that the respondents said they use for treating diseases of various systems still do not have monographs. For example, *Rosa canina* was found to have medicinal properties that could treat three different systems: musculoskeletal, genitourinary, and cardiovascular. It is further recorded that *Rosmarinus officinalis* and *Galium odoratum* are used in the treatment of musculoskeletal diseases, but the former is also used for cardiovascular diseases and the latter for respiratory diseases. Additionally, respondents in eastern and south-eastern Serbia treat respiratory system diseases with *Rubus vestitus* and *Elymus repens*. According to our findings, *R. vestitus* is also used to treat diseases of the cardiovascular system, and *E. repens* to treat the genitourinary system. The health-promoting effects of these medicinal plants are believed to be initiated by phytochemicals found in them or by their interactions with other constituents. However, additional research is needed to confirm the beneficial effects of these medicinal herbs on human health.

4. Conclusions

Based on the local population's experience, medicinal plants are still an integral part of the health system in eastern and south-eastern Serbia for the prevention and treatment of various diseases. The most common diseases in this region are musculoskeletal, genitourinary, respiratory, and circulatory, which are also global medical problems, especially in emerging countries. Based on these findings, traditional knowledge about these four systems was evaluated to select plants that represent a potential resource for further research.

The performed ethnopharmacological survey showed that 95 different plant taxa were used for treating diseases of these four organ systems. Some medicinal plants are used to treat diseases of multiple systems simultaneously. Official international organizations have already confirmed the pharmacological effect of 22.2% of the medicinal plants mentioned, which are used for musculoskeletal disorders. Of the remaining 77.8% WOM, *Verbascum phlomoides*, *Inula helenium*, and *Rosmarinus officinalis* deserve special attention as the most commonly used among the local population. Additionally, *V. phlomoides* and *R. officinalis* have monographs issued by the European Medicines Agency, but there is no mention of their use for arthritis. Regarding traditional use for treating respiratory diseases, 62.2% of the cited plants have monographs by official international authorities. Of the remaining 37.8%, we propose *Ocimum basilicum*, *Robinia pseudoacacia*, and *Primula vulgaris* for future research. Among the medical plants used for circulatory problems, 26.9% have monographs by official international authorities. Of the remaining 73.1%, we highlight *Urtica dioica*, *Allium ursinum*, and *Rosa canina* as worthy of future research. The root, leaf, and aerial part of *U. dioica* have monographs issued by the EMA without mention of their use for circulatory problems. Fifty-six percent of medical plants have already been confirmed for genitourinary disease. Among the 44% of plants reported for genitourinary disease but WOM, we suggest three species for future research: *Apium graveolens*, *Zea mays*, and *Calendula officinalis*. The flowers of *C. officinalis* have an EMA monograph, but there is no mention of their use for genitourinary disease. The EMA is currently debating monographs for the aerial part of *C. officinalis*.

Numerous ethnobotanical, pharmacological, and phytochemical studies indicate that the proposed medicinal plants could be useful in the treatment of these systems. The presented findings provide a strong platform for further study into these plants, which may be useful for developing new, relatively affordable, effective, and safe medicines. Further preclinical and clinical studies are required to scientifically justify and confirm the effectiveness of the proposed, traditionally used medicinal plants.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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