Review article

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HERBAL DRUGS AND TRADITIONAL HERBAL DRUGS IN THE REPUBLIC OF SERBIA

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According to the Law on Medicines and Medical Devices of the Republic of Serbia, which is harmonized with the European directives on medicines, a substance that is an active component of a medicine can be of plant origin. Herbal medicine - HM and traditional herbal medicine - THM are used for the prevention and treatment of certain diseases and conditions, their initial, mild, but also chronic and recurrent forms.

The guidelines on the pharmaceutical quality of HM and THM insist on a rigorous and detailed definition of plant raw materials, production process, and finished pharmaceutical products. Registration of these types of drugs is done by the Agency for Drugs and Medical Devices of Serbia (ALIMS). During the HM registration process, the Herbal Anatomical Therapeutic Chemical (HATC) system (an integral part of the WHO Drug Global Classification of products and substances) is applied. For now, the number of registered HMs and THMs in Serbia is modest in comparison to their number in most EU member states. ALIMS controls the content of the patient information leaflet for the medicine: all data on indications, dosage, contraindications, precautions, adverse effects, and interactions. Therefore, the application of registered HMs and THMs constitutes a modern phytotherapeutic approach and the safest way to use herbal medicinal substances and preparations.

In addition to medicinal, there are other categories of herbal products on the market (herbal supplements, herbal teas…) that are not intended for therapy and treatment. Dietary products are regulated by other laws and regulations, and after entry in the Register of Dietary Products of the Ministry of Health, they can be put in the Serbian market.

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Key words: *herbal medicines, traditional herbal medicines, Serbian market*

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Introduction

The use of plants for therapeutic purposes has a very long tradition. Today, both in developed and developing countries, there is a great interest in herbal medicinal products due to the numerous biological and pharmacological activities that can be manifested (1-3).

Phytotherapy is a treatment system based on the application of herbal medicinal products. It belongs not only to pharmacotherapy and conventional medicine, but also to traditional (folk) medicine, and complementary and alternative medicine (2, 4).

Rational phytotherapy encompasses the treatment, alleviation, and prevention of diseases and health problems with herbal medicines (herbal medicinal products of scientifically and clinically proven therapeutic efficacy – *evidence-based herbal medicines*). It is evidence-based phytotherapy (1, 5-7). However, with the increasing use of different categories of plant products in recent decades, the issue of safety of their application has become increasingly important. Although they usually have a favourable risk-benefit ratio, not all of them can be considered completely safe. Like conventional drugs, they can have adverse effects and/or interact with other substances. The pharmacovigilance of herbal medicinal products is a great challenge not only because of their unique characteristics, but also because of the way in which they are legally regulated, used and accepted (1-3).

The aim

To clarify the place and position of herbal medicinal products, this paper will present data on herbal medicines and traditional herbal medicines

from the markets of European countries and the Republic of Serbia, with special reference to data on their HATC (Herbal Anatomical Therapeutic Chemical Classification) and indication area. Further will be discussed pharmaceutical forms and pharmacovigilance of herbal medicines, but also their differences from other categories of herbal products on the market.

Results and discussion

Legislation currently in force

According to the Law on Medicines and Medical Devices of the Republic of Serbia, which is harmonized with the European directives on medicines (65/65 EEC and 2001/83/EC), a substance that is an active component of a (human) medicine can also be of plant origin (5, 8-10). Further, the Law of Republic of Serbia recognizes two types of drugs with an active component of herbal origin: herbal medicines and traditional herbal medicines (8).

It is good to be known, that terms "herbal substance" and "herbal preparation", which are used in the legal acts of the Republic of Serbia and European regulatory documents (documents published by EMA – the European Medicines Agency), correspond to the terms "herbal drug" and "herbal drug preparation", which are used in pharmacopoeias (for example European Pharmacopoeia – Ph. Eur.) and documents of the World Health Organization (WHO)) (5, 8-13).

A herbal medicine (HM) is "any medicine whose active ingredients are exclusively one or more (substances of plant origin) herbal substances or one or more herbal preparations or one or more herbal substances in combination with one or more herbal preparations" (8).

Traditional medicines are the result of tradition or other traditional therapeutic approaches and can be based on scientific principles. A traditional herbal medicine (THM) is "a medicine that has indications characteristic exclusively for THMs, which by their composition and purpose are intended for use without medical supervision, exclusively in accordance with the prescribed strength and dosage for oral or external use or inhalation, and for which there is sufficient data on the traditional use of the drug, or it has been shown that it is not harmful under the prescribed conditions of use as well as that its pharmacological effects or efficacy can be expected based on its long-term use and experience". If it contains vitamins or minerals of well-documented therapeutic safety, it can be considered a THM if the effect of these vitamins or minerals is only ancillary to the action of the active herbal ingredients in terms of the established indication or indications (7, 8, 10, 14).

The category of herbal medicines/traditional herbal medicines does not encompass dosed pharmaceutical forms in which the active ingredient is an isolated compound or mixture of pure substances isolated from herbal raw materials (e.g., digitoxin, lanatoside C, atropine, nicotine, morphine, codeine, vinca alkaloids, taxanes, podophyllotoxins) – these are conventional drugs (1, 6, 8).

Pharmacopoeias prescribe quality requirements and, within them, the health safety of herbal drugs and their preparations, i.e., substances of plant origin (15). Before being marketed, HMs and THMs must meet all the criteria concerning safety, quality, and efficacy, just like all other medicines. The HM and THM registers are maintained by the Agency for Medicines and Medical Devices of Serbia (Ser. Agencija za lekove i medicinska sredstva Srbije, ALIMS).

In order to market medicines with an active component of plant origin, both Serbia and the European Union offer three procedures for product registration – two for HMs and one for THMs (1, 14, 16) (Figure 1). The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) publishes EU monographs on herbal medicinal substances, which comprise preclinical and clinical data on HMPs with well-established use (WEU) as well as data on traditional use (TU) (7). Herbal monograph with WEU/TU is a solid base for registration of an HM/THM.

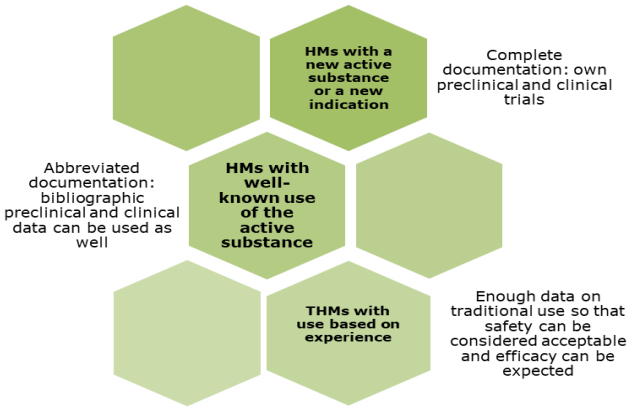

Figure 1. Registration procedures and requirements to be met by HMs and THMs in addition to certified pharmaceutical quality

Herbal Anatomical Therapeutic Chemical Classification (HATC)

The HM and THM quality guidelines insist on a rigorous and detailed definition of the starting plant materials – specific botanical identification includes the binomial nomenclature (species, genus, variety, and author), chemotype (when significant), name of the part of the plant used, knowledge of the location where the plant grows, and conditions for obtaining plant raw materials. Insisting on binomial nomenclature and the HATC (Herbal Anatomical Therapeutic Chemical) classification for HM is extremely important since many plant species have several folk names and one folk name often refers to several different plant species (which are not related and whose effects differ) (1, 17).

The HATC (Herbal ATC) system is an integral part of WHODrug Global for the classification of products and substances. It provides a classification of HMs according to the internationally approved classification of the Latin binomial name and common therapeutic use. It enables the collection, grouping, and aggregation of HM data at different levels of specificity. As with the ATC system, HMs in HATC are divided into groups according to therapeutic use. The first level consists of 14 anatomical groups marked with the letters A–V (the same in ATC and HATC). The following levels are similar in the two classifications, but in some cases, additional categories are introduced in the HATC for specific groups of plants. For example, a complete HATC classification of the Aloe ferox Mill. preparation, used as a laxative, is A06AB5001: A – alimentary tract and metabolism (level 1, main anatomical group); A06 – drugs for constipation (second level group, main therapeutic group); A06A – drugs for constipation (third-level group, therapeutic/pharmacological subgroup); A06AB – contact laxatives (fourth-level group, therapeutic/pharmacological/ chemical subgroup); A06AB5001 – *Aloe ferox* Mill., dry leaf juice (fifth-level group, individual raw herbal substance) (17).

Registers of herbal medicines and traditional herbal medicines in the Republic of Serbia

The total numbers of registred HMs and THMs in the RS (Table 1 and Table 2) are modest in comparison to their numbers in the EU. German market counts total of 1008 herbal medicinal products with completed marketing authorisation or registration procedure, from which 841 are single component and 167 fixed herbal combinations. Traditional herbal medicinal products with completed registration procedure in Germany counted in total 293 THMs in March 2022 (173 single component and 120 fixed combinations) (18). Germany is a leader in phytotherapy application among the EU members' countries. According to the latest survey (status December 31 2016) of Inspections, Human Medicines, Pharmacovigilance and Committees Division of EMA Germany definitely had the greatest total number (447) of "well-established use" medicinal product applications in EU Member States, while the order of numbers for "traditional use" medicinal product applications was 513, 450 and 315 in Germany, UK and Poland, respectively (19). In Serbia 38 HMs and 24 THMs were registered at the beginning of 2017 while in 2016, there was 1 THM less (20, 21). Since then, the total number of HM and THM has fallen from 62 to 50 (22).

Table 1. Herbal medicines in the Republic of Serbia (in June 2022) (22)

HATC	Herbal medicine	Active substance	HATC	Pharmaceutical form
HA ALIMENTARY TRACT AND METABOLISM				
HA03A medicine for functional bowel disorders	IBEROGAST	Bitter candytuft (*Iberis amara* L.), liquid extract of fresh whole plant, Angelica (*Angelica arhangelica* L.), liquid root extract, Lemon balm (*Mellissa officinalis* L.), liquid leaf extract, Caraway (*Carum carvi* L.), liquid fruit extract, Celandine (*Chelidonium majus* L.), liquid herb extract, Liquorice (*Glycyrrhiza glabra* L.), liquid root extract, Chamomile (*Matricaria recutita* L.), liquid flower extract, Peppermint (*Mentha piperita* L.), liquid leaf extract, Milk thistle (*Silybum marianum* L.), liquid fruit extract	HA03A	Oral drops 20 ml; 50 ml
BILE AND LIVER THERAPY				
A05BA PREPARATIONS IN THE TREATMENT OF LIVER DISEASE	ESSENTIALE® FORTE N	essential phospholipids 300 mg	A05BA	Hard capsules 3x10 pcs
	ESSENTIALE® MAX	600 mg		Hard capsules 5x6 pcs
LAXATIVES				
HA06AB CONTACT LAXATIVES	BEKUNIS	Senna alexandrina pods (*Sennae fructus angustifoliae*), dry aqueous extract	HA06AB06	Gastro-resistant tablets, 1x10 pcs and 1x45 pcs Instant herbal teas, 1x17.6 g
	BEKUNIS	Senna (*Cassia senna/Cassia angustifolia*), leaf	HA06AB06	Herbal teas,1x80 g

A06AC LAXATIVES THAT INCREASE THE VOLUME OF INTESTINAL CONTENTS	MUCOFALK® POMORANDŽA	Ispaghula Husk (*Plantago ovata*)	A06AC01	Granules for oral suspensions 20x5 g
	TRANSILANE			Powder for oral suspensions 20x7 g
RESPIRATORY SYSTEM				
COUGH AND COLD MEDICINES R05	BRONCHIPRET	Thyme (*Thymus vulgaris* L. and/or *Thymus zygis* L.), liquid herb extract, Ivy (*Hedera helix* L.), liquid leaf extract	HR05WA	Oral liquid 50 ml and 100 ml
	HERBION®LOZENGE OD BRŠLJANA	Ivy (Hedera helix L.), dry leaf extract	R05CA12	Compressed lozenges 2x8 pcs, 3x8 pcs and 4x8 pcs
R05CA EXPECTORANTS	BRONHOKLIR SYRUPS® BRŠLJAN	Ivy (*Hedera helix* L.), dry leaf extract	R05CA12	Syrup 125 mL**
	HEDELIX			Oral drops, Syrup 100 mL
	MUCOPLANT SIRUP ZA KAŠALJ SA EKSTRAKTOM BRŠLJANA			Oral liquid 100mL and 250 ml
	PROSPAN			Effervescent tablets 5x2 pcs, Pastilles 2x10 pcs, Syrup 100 mL and 200 mL
	PROSPAN® KAPI			Oral drops 20mL
	PROSPAN LIQUID			Oral liquid 15x5 mL, 21x5 mL, 100 mL and 200 mL
	TUSPAN®			Syrup 120 mL**
HR05WA DIAPHORETIC HERBS AND OTHER COUGH AND COLD MEDICINES	HERBION® SIRUP OD BRŠLJANA	Ivy (*Hedera helix* L.), dry leaf extract	HR05WA	Syrup 150 mL
HR07A OTHER COUGH AND COLD MEDICINES	GELOMYRTOL® FORTE	Distillate obtained from the mixture of rectified essential oils of eucalyptus, sweet orange, myrtle, and lemon, standardized at 1,8-cineole, d-limonene i (+)-alpha-pinene 300mg	HR07A	Gastro-resistant tablets 2x10 pcs
R05X OTHER COMBINED COUGH AND COLD MEDICINES	SINUPRET® FORTE	Dry extract derived from, flowers, herb, flower, and herb: Verbena (*Verbena officinalis* L.), powdered herb, gentian (*Gentiana lutea* L.), powdered root, sorrel (*Rumex acetosa* L.), powdered herb, elder (*Sambucus nigra* L.), powdered flower, primula (*Primula veris* (L.) and/or *Primula elatior* (L.) Hill), powdered flower and bud	R05X	Coated tablets 1x20 pcs
	SINUPRET®AKUT			Coated tablets 2x10 pcs
	SINUPRET®SIRUP			Syrup 100mL
PSYCHOLEPTICS				
N05CM OTHER HYPNOTICS AND SEDATIVES	PERSEN® NIGHT	Valerian (*Valeriana officinalis* L.), dry root extract	N05CM09	Coated tablets 2x15 pcs
NERVOUS SYSTEM				
N06DX OTHER MEDICINES FOR THE TREATMENT OF DEMENTIA	BILOBIL	Ginkgo (*Ginkgo biloba*), dry leaf extract	N06DX02	Capsules 40 mg 2x10 pcs and 6x10 pcs
	BILOBIL FORTE			Capsules 80 mg 2x10 pcs and 6x10 pcs
	BILOBIL INTENSE			Capsules 120 mg 2x10 pcs
	TANAKAN		HN06DX	Coated tablets 2x15 pcs** 6x15 pcs**
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE				
D06BB ANTIVIRAL DRUG	VEREGEN	Green tea (*Camellia sinensis* (L.) O. Kuntze), dry leaf extract	D06BB12	Ointment 1x15 g

* The same HM in the different package was considered as one medicine;
** one HM produced by 2 different manufacturers were considered as one medicine.

Table 2. Traditional herbal medicines in the Republic of Serbia (in June 2022) (22)

THM	Active substance	Pharmaceutical form	Traditional use
ARNIKAMED DOLO	Arnica (*Arnica montana* L.) flower tincture	Gel 50 g and 100 g	relief of bruises, sprains and localised muscular pain
BRONCHICUM® SIRUP S	Thyme (*Thymus vulgaris* L. and/or *Thymus zygis* L.), liquid herb extract	Syrup 100 mL	expectorant in cough associated with cold
BRONCHOSTOP® PASTILE	Thyme (*Thymus vulgaris* L./*Thymus zygis* L.), dry herb extract	Pastilles 2x10 pcs	expectorant in cough associated with cold

BRONCHOSTOP® SINE SIRUP	Thyme (*Thymus vulgaris* L./*Thymus zygis* L.), dry herb extract, marshmallow (*Althaea officinalis* L.), liquid root extract	Syrup 120 mL	demulcent for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough
CANEPHRON®	Common centaury (Centaurium erythraea Rafn s.l.), powdered herb, Lovage (Levisticum officinale Koch.), powdered root, Rosemary (Rosmarinus officinalis L.), powdered leaf	Coated tablets 2x15 pcs	prevention of recurrent formation of kidney stones and relief of symptoms of recurrent mild lower urinary tract infections in women
CARSIL	Milkthistle (*Silybum marianum* L. Gaertner), dry fruit extract	Capsules 5x6 pcs, Coated tablets 8x10 pcs	alleviation of liver dysfunction, cirrhosis of the liver, and toxic liver damage
CYNARIX	Artichoke (*Cynara scolymus* L.), dry leaf extract	Coated tablets 2x12 pcs	symptomatic relief of digestive disorders
FAVORA® SILYMARIN	Milkthistle (*Silybum marianum* L. Gaertner), dry fruit extract	Capsules 3x10 pcs	adjuvant therapy of chronic inflammatory liver disease, cirrhosis of the liver, and toxic liver damage
HERBION® SIRUP OD BOKVICE	Ribwort Plantain (*Plantago lanceolata*), liquid leaf extract, Mallow (*Malva sylvestris*), liquid flower extract, ascorbic acid	Syrup 150 mL	symptomatic treatment of dry, irritating cough
HERBION® SIRUP OD ISLANDSKOG LIŠAJA	Iceland moss (*Cetraria islandica*), soft thallus extract	Syrup 150 mL	for oral or pharyngeal irritation and associated dry cough
HERBION® SIRUP OD JAGORČEVINE	Primula (*Primula veris* L./*Primula elatior* Hill.), liquid root extract, Thyme (*Thymus vulgaris* L./*Thymus zygis* L.), liquid herb extract	Syrup 150 mL	expectorant in cough associated with cold
MUCOPLANT	Ribwort Plantain (*Plantago lanceolata*), liquid leaf extract	Syrup 100 mL and 250 mL	symptomatic treatment of oral or pharyngeal irritation and associated dry cough
PERSEN	Valerian (*Valeriana officinalis* L.), dry root extract, Lemon balm (*Melissa officinalis* L.), dry leaf extract, Peppermint (*Mentha piperita* L.), dry leaf extract	Coated tablets 4x10 pcs*	relief of mild symptoms of mental stress and help with insomnia
PERSEN® FORTE		Hard capsules 2x10 pcs	
PERSEN® FORTE N	Valerian (*Valeriana officinalis* L.), dry root extract, Passionflower (*Pasiflora incarnata* L.), dry herb extract	Capsules 2x10 pcs	relief of mild transient nervous tension and anxiety due to mental stress, and temporary difficulty sleeping
PROSTAMOL® UNO #	Saw Palmetto (*Serenoa repens* (Bartram) Small), soft fruit extract	Soft capsules 2x15 pcs and 4x15 pcs	relief of symptoms related to benign prostatic hyperplasia
ROWIREN	Rosemary Oil (*Rosmarinus officinalis* L.), essential oil	Cream 50 g and 90 g	relief of minor muscular and articular pain and in minor peripheral circulatory disorders (with symptoms such as cold feet)
TRIBESTAN	Tribulus (*Tribulus terrestris* L.), dry herb extract	Film tablets 6x10	in treatment of decreased libido and impotence in men
TUSSAVIT	Thyme (*Thymus vulgaris* L. and/or *Thymus zygis* L.), liquid herb extract, Ribwort Plantain (*Plantago lanceolata* L.), liquid leaf extract	Syrup 250 g	expectorant in cough associated with cold

* The same THM in the different package was considered as one medicine;
** one THM produced by 2 different manufacturers were considered as one medicine;
# Although the Agency for Drugs and Medical Devices of Serbia shows it as an HM on their site, PROSTAMOL® UNO is THM. Saw Palmetto soft fruit ethanolic (ethanol 96%, V/V) extract is an herbal medicinal substance with traditional use and in the patient information leaflet, PROSTAMOL® UNO is declared as THM.

Yet, *Hederae helicis folium,* followed by *Ginkgo folium,* was the most present herbal substance in the HMs in both the RS and the EU (22, 19). The largest number of HMs and THMs registered in the Republic of Serbia are intended for use in various respiratory disorders followed by alimentary tract complaints (Figure 2).

HMs and THMs registred in RS are widely used in different mild diseases and health problems (Table 1 and Table 2). However, they are mostly not recommended for use during pregnancy and lactation, and in the population of infants and young children due to insufficient data (7).

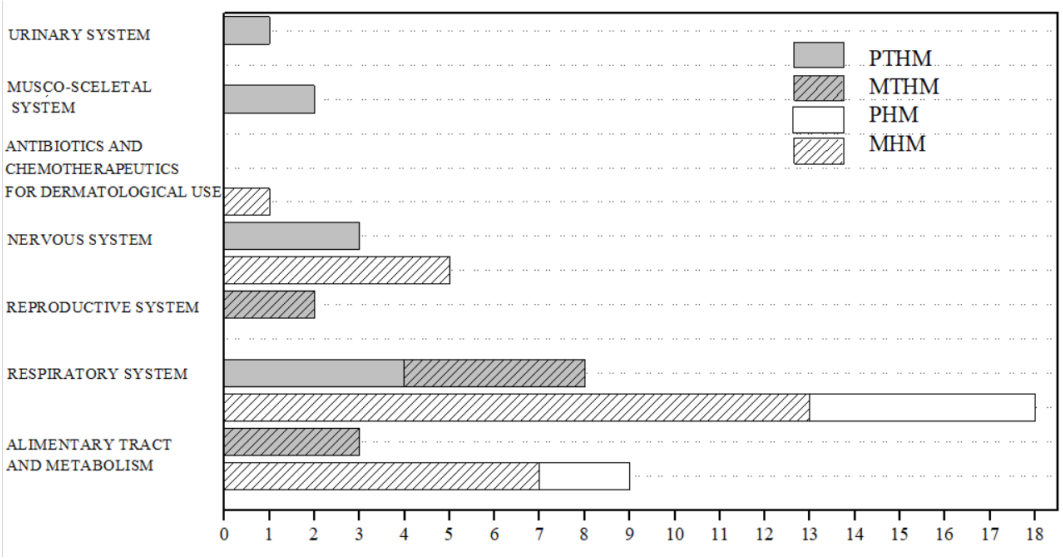

Figure 2. Number of polycomponent/monocomponent traditional herbal medicines (PTHM/MTHM) and polycomponent/monocomponent herbal medicines (PHM/MHM) by indication for use in the Republic of Serbia (in March 2022)

Pharmaceutical forms of herbal medicines

Herbal medicines and traditional herbal medicines are produced in a number of pharmaceutical forms. The first associations for herbal medicines are herbal teas. Solid dosage forms (e.g. herbal tea bags, powders, dry extract powders, granules, pills, capsules, tablets, lozenges) are most often found in the herbal medicine (23). Nevertheless, among HMs and THMs, there is only one herbal tea on the Serbian market currently (Table 1). Oral drops and liquids or syrups are made from simple tinctures as herbal drug preparations. Hard capsules may contain a powdered herbal drug or a dry most often enriched extracts, while tablets are generally produced from dry extracts. Further, liquid extracts can be included in liquid pharmaceutical forms for oral and skin application and semi-solid preparations (creams, gels) for local, rectal, vaginal, or oral mucosal application (24). The pharmaceutical forms of HMs and THMs also encompass herbal teas, instant herbal teas, ointments, film, coated, gastro-resistant and effervescent tablets, pastilles, compressed lozenges, granules, and powder for oral suspensions (Table 1, Table 2).

Medicinal herbs and consequently their products are very sensitive to external influences (temperature changes, moisture, and direct light). Since reactions of oxidation, degradation, hydrolysis, and evaporation can affect the quality of the final product, its stability, shelf life, and storage conditions must be defined (25). The quality control of these groups of medicines, in addition to the specifics of the control conditioned by the active component, also includes tests related to the pharmaceutical form in which they are produced as finished medicines or manufactured as galenic medicines (26). Also, to maintain quality of the final product, different quality parameters must be monitored for different pharmaceutical forms of HMs and THMs. Identification, appearance, and microbiological purity/safety, and/or complete health safety control are common parameters of quality control for all herbal medicinal products. Verification of components and their declared mass ratio, and verification of package weight must be done for mono-component teas and tea mixtures (25, 27). Additional parameters for liquid herbal preparations are loss on drying, the content of ethanol, relative density, and refractive index. pH value is important for semi-solid forms while solid-dosage forms also must be defined by the declared mass of single-dose preparations and disintegration (25).

Pharmacovigilance of herbal medicines

Herbal medicines are safe when properly applied and used in the recommended therapeutic doses, and the adverse effects consist primarily of mild and rare gastrointestinal problems or dermatological reactions. However, unlike most conventional medicines, which most frequently consist of a single chemically defined active substance, HMs and THMs are chemically rich, complex mixtures with hundreds of ingredients. Some HMs and THMs contain more herbal raw materials (herbal substances and preparations), which makes their composition more complex and complicates pharmacokinetic, pharmacodynamic, and toxicological studies. For many HMs and THMs, neither the exact chemical composition nor their complete safety profile is known. The chemical profile of the plant raw material varies depending on the plant organ used (not the same for the whole plant), inter - and intraspecific variations of the active compounds present, environmental factors (climate and plant growth conditions), and the harvesting/gathering time and processing procedure (storage, drying, processing, etc.).

The safety and efficacy of HMs and THMs should also be considered in the light of variations from different manufacturers and different preparations of the same herbal substance used (1, 3). The control of raw materials, intermediate products, and finished HMs and THMs is a prerequisite for quality and safe medicines on the market.

The end of the 20th century saw the establishment of the department for the adverse effects of herbal medicines at the WHO Collaborating Center in Uppsala (Global Pharmacovigilance Center). For HMs and THMs, as well as for other over-the-counter medications, doctors rarely report adverse effects, so there is not only an important role for pharmacists and the organization of a spontaneous reporting system through the pharmacy network, but also for spontaneous reporting of adverse effects by patients. Despite initiatives to encourage reporting of suspected adverse reactions associated with HMs and THMs, the number of these reports remains low compared to the number of reports for conventional medicines – only 0.5-1% of the total number of reports relate to herbal medicines (3, 28).

The history of safe traditional use provides some degree of certainty in the absence of acute toxicity, but mostly does not provide relevant information on many other safety aspects such as the effects of prolonged use, delayed and "hidden" adverse effects, impact on relatively new diseases (e.g., HIV infection), and concomitant use with conventional drugs (3).

Herbal medicinal products are widely used for maintaining health, preventing disease, and treating and self-treating chronic and recurrent conditions and diseases. They are dispensed in a pharmacy without a doctor's prescription or procured in other ways and are mostly used for self-treatment (4, 6). Such status is justified by the large therapeutic range, low toxicity, safety in overdose, minimal interactions, as well as indications that are well known to the patient/user. However, insufficient, or incorrect information on the product can lead to the occurrence of adverse effects or a delay in starting adequate therapy. When it comes to HMs and THMs, the possibility of error is very small since ALIMS controls the contents of the patient information leaflet for the medicine (which, among other things, lists all the information on contraindications, precautions, known and confirmed adverse effects and interactions) (29).

The other herbal products

Herbal products can also be found as cosmetic products for the protection and care of skin and mucous membranes, or as part of dietary products, as well as herbal teas. Although these product categories are not intended for therapy, they can be very useful if they are applied correctly. Special laws and bylaws regulate each product category. Usually, only the part related to the safety of their application is of concern to the ministry that deals with health affairs.

In the following of the study, more information will be given for certain products from the category of dietary products and one part of them: food supplements and herbal (food) supplements (30, 31).

Dietary products belong to the area of food and they are used to preserve and improve health as well as to reduce the risk of disease in later life; these products are not intended for therapy and treatment. In addition to nutritional statements, dietary products may also contain certain health statements. A health statement is any statement that states, indicates or suggests that there is a link between a category of food, a particular food or one of its ingredients and health. Also, a disease risk reduction statement is any health statement that states, indicates or suggests that consuming a certain category of food, a certain food or one of its ingredients significantly reduces the risk factor for developing the disease in humans. Only health statements approved by the Ministry of Health can be found in the dietary product declaration (32).

Until recently, there was a single rulebook that applied to all types of dietary products, but in 2022. a special rulebook regulating the area of food supplements was prepared (31).

Food supplements are foods that supplement the usual diet, and which are concentrated sources of nutrients or other ingredients with nutritional or physiological effect, individually or in combination, and are marketed in dosage forms such as capsules, lozenges, tablets and the like, powder bags, ampoules of liquid, dropper bottles, and other similar forms of liquid and powder intended for taking in small, metered quantities. "Food supplements as an active ingredient may contain herbs, herbal raw materials, herbal preparations, or ingredients isolated from herbal raw materials, individually or as a mixture" (Article 11); "When the food supplement contains plants, plant raw materials, preparations of plant raw materials or ingredients isolated from plant material, their amount in the daily dose of the product should not be less than 15% and more than 65% in relation to the known lowest therapeutic daily dose of that plant raw material or preparations, as defined in the monographs of the European Medicines Agency (EMA), the European Scientific Association for Phytotherapy (ESCOP), the World Health Organization (WHO), the German Commission E and the Physicians' Desk Reference for Herbal Medicines" (Article 12); "Food supplements must not contain plants, parts of plants or plant preparations that contain ingredients of strong pharmacological activity, regardless of their share in the product, as well as plants, parts of plants or plant preparations for which relevant data have harmful effects on human health" (Article 13) (31).

The placing on the market of such dietary products is based on other laws and regulations relating to food. In this case, there is a division of responsibilities between the Ministry of Agriculture and the Ministry of Health. The Ministry of Agriculture is responsible for the production itself, the Ministry of Health is responsible for the safety of application and health safety. Placing plant supplements on the market can be realized after entry in the Register of dietary products, for which the Ministry of Health is responsible (31).

Herbal teas can be monocomponent and multicomponent and are classified into different product categories. Thus, herbal teas can be uncategorized products, herbal food supplements, THMs, and HMs. The list of galenic medicines used in human medicine currently includes about twenty galenic medicines with herbal raw materials, and the majority of them are herbal teas, but lot of tea mixtures can be found on the markets based on special rulebook for herbal teas (33, 27).

Conclusion

Although the total number of registered herbal medicines and traditional herbal medicines in the Republic of Serbia is modest in comparison to most of the EU country members, the legal procedures for registration of these products are the same. The application of registered HMs and THMs constitutes a modern phytotherapeutic approach and a part of pharmacotherapy that has yet to find its place in evidence-based medicine.

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BILJNI I TRADICIONALNI BILJNI LEKOVI U REPUBLICI SRBIJI

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Prema Zakonu o lekovima i medicinskim sredstvima Republike Srbije, koji je usklađen sa evropskim direktivama o lekovima, supstanca koja predstavlja aktivnu komponentu leka može biti i biljnog porekla. Biljni lekoviti proizvodi (biljni lekovi – BL i tradicionalni biljni lekovi – TBL) primenjuju se za prevenciju i lečenje određenih oboljenja i stanja, njihovih početnih, blažih, ali i hroničnih i rekurentnih oblika.

U smernicama o farmaceutskom kvalitetu BL i TBL insistira se na rigoroznom i detaljnom definisanju polaznih biljnih sirovina, proizvodnog procesa i gotovih farmaceutskih proizvoda. Registracija ovih vrsta lekova obavlja se u Agenciji za lekove i medicinska sredstva Srbije. Tokom procesa registracije BL primenjuje se „Herbal Anatomical Therapeutic Chemical" sistem koji je je sastavni deo WHODrug Global sistema za klasifikaciju proizvoda i supstanci (HATC). Za sada je broj registrovanih BL i TBL u Srbiji skroman, u poređenju sa njihovim brojem u većini zemalja članica Evropske Unije. Agencija za lekove i medicinska sredstva Srbije kontroliše uputstva za lekove u kojima moraju biti naznačeni, između ostalog, i svi podaci o indikacijama, doziranju, kontraindikacijama, merama opreza, neželjenim reakcijama i interakcijama. Dakle, primena registrovanih BL i TBL predstavlja savremeni fitoterapijski pristup i najbezbedniji način korišćenja biljnih lekovitih supstanci i preparata.

Pored lekovitih, na tržištu postoje i druge kategorije biljnih proizvoda (biljni dodaci ishrani, biljni čajevi itd.), koji nisu namenjeni terapiji i lečenju. Stavljanje u promet dijetetskih proizvoda zasniva se na drugim zakonima i pravilnicima, a može se realizovati posle upisa u Registar dijetetskih proizvoda, za šta je nadležno ministarstvo za poslove zdravstva.

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Ključne reči: *biljni lekovi, tradicionalni biljni lekovi, tržište Republike Srbije*