

UDK 615.2(497.11)"2016"  
COBISS.SR-ID 278644492

ISSN 0350-2899. - Vol. 44, br. 2 (2019), str. 56-62.

## CONSUMPTION AND PHARMACEUTICAL-TECHNOLOGICAL FORMULATIONS OF HERBAL MEDICINES IN SERBIA

### POTROŠNJA I FARMACEUTSKO-TEHNOLOŠKE FORMULACIJE BILJNIH LEKOVA U SRBIJI

*Katarina D. Jeremić, Nemanja B. Todorović, Svetlana S. Goločorbin-Kon, Nebojša M. Pavlović, Nataša P. Milošević, Neda S. Gavarić, Mladena N. Lalić-Popović*

UNIVERSITY OF NOVI SAD, FACULTY OF MEDICINE NOVI SAD, DEPARTMENT OF PHARMACY, NOVI SAD, REPUBLIC OF SERBIA

**Summary:** Medicinal plants have an immense therapeutic potential that is not fully utilised. The poor results of clinical studies are often a consequence of bad biopharmaceutical characteristics (solubility and permeability) of herbal medicine. By developing new systems of administering medicine, it is possible to improve all three standards important for every medicine: efficiency, safety and quality. Data of consumption and characteristics of herbal medicine used in Serbia were taken from the official site of the Agency for Medicine and Remedies of Serbia. The absolute consumption of herbal medicine (given in euros) in 2016 in relation to 2006 has been increased by 1466.63%, while the relative consumption (in relation to absolute consumption of all medicine) has been increased by 811.11% in the same period. This substantial increase of the usage of herbal medicine was not followed by an increase in the presence of modern pharmaceutical dosage forms, since the observed period contained no registered herbal (or traditional) medicine formulated by the new medicine delivery system. Developing a new system for the delivery of herbal medicine, whose active ingredients has shown in vitro efficiency, could provide this efficiency when applied to humans. Registering these medications on the Serbian market would enable better quality use of such medicine in the healthcare system.

**Keywords:** medicinal herbs, herbal extracts, herbal medicine formulations, phytotherapy, consumption of herbal medicine

**Sažetak:** Lekovite biljke imaju veliki terapijski potencijal koji nije u potpunosti iskorišćen. Loši rezultati kliničkih studija često su posledica loših biofarmaceutskih karakteristika (rastvorljivosti i propusnosti) biljnih lekova. Razvijanjem novih sistema za davanje lekova moguće je poboljšati sva tri standarda važna za svaki lek: efikasnost, bezbednost i kvalitet. Podaci o potrošnji i karakteristikama biljnih lekova koji se koriste u Srbiji preuzeti su sa zvaničnog sajta Agencije za lekove i medicinska sredstva Srbije. Apsolutna potrošnja biljnih lekova (izražena u eurima) u 2016. godini u odnosu na 2006. godinu povećana je za 1466,63%, dok je relativna potrošnja (u odnosu na ukupnu potrošnju svih lekova) u istom periodu povećana za 811,11%. Ovo značajno povećanje upotrebe biljnih lekova nije praćeno povećanjem prisustva savremenih farmaceutskih doznih oblika, jer u posmatranom periodu nije bilo registrovanih biljnih (ili tradicionalnih) lekova formulisanih novim sistemom za dostavu lekova. Razvoj novog sistema za isporuku lekova za biljne lekove čiji aktivni sastojci imaju dokazanu in vitro efikasnost može obezbediti ovu efikasnost kada se primenjuje na ljude. Registracija ovih lekova na srpskom tržištu omogućila bi kvalitetnije korišćenje ovih lekova u zdravstvenom sistemu.

**Glavne reči:** lekovito bilje, biljni ekstrakti, formulacija fitopreparata, fitoterapija, konzumacija biljnih lekova

#### INTRODUCTION

Medicinal plants can be used in a raw state, but there are a lot of products made by their processing and they are named phytopreparations. All of them can be divided

in a few categories: cosmetics, dietary supplements (food), medical devices and medicines. According to the Serbian Drugs Law, the herbal medicine means a product which as an active ingredient contains one or more plants (in total or in parts) in a dry or

Adresa autora: Katarina D. Jeremić, Department of Pharmacy, Faculty of Medicine Novi Sad, 21000 Novi Sad  
E-mail: katarina.jeremic@mf.uns.ac.rs

Rad primljen: 12.02.2019. Elektronska verzija objavljena: 21.08.2019.

www.tmg.org.rs

fresh form or their untreated exudates; or which contains herbal preparations (got by pharmaceutical-technological treatment of herbal material) or a combination of these two categories. Except herbal medicines, in the group of medicines that contain the herbal material as active ingredient we can find traditional herbal medicines and homeopathic medicines. Magistral and galenic medicines are specific groups of medicines which can contain the herbal material as active ingredient too [1]. It is important to note that medicines which contain isolated phytomolecules do not belong to the group of herbal medicines.

Due to their complex content, the formulation of herbal medicines is very demanding from pharmaceutical-technological and posological standpoint. They often have several constituents responsible for the pharmacological effect, which, sometimes, are not fully recognized [2,3]. However, only herbal remedies prepared in accordance with the principles of rational phytotherapy have acceptable quality, which then guarantees their safety and efficiency [4]. This implies the formulation of the dosage form with precisely defined active principles and their standardization [5]. Phytopreparations that are registered as herbal medicines should meet these requirements to the fullest extent.

Common problem with preparations that as active principle contain plants or their products is a lack of evidences of efficiency. The possible reason for this is opportunity registration as non-medicines, and this only requires a safety certificate in most countries. However, there are studies that unambiguously confirm the efficacy for precisely defined indications of these group medicines. This creates the opportunity for bigger use of these drugs, and prescribing effective therapy with a reasonable level of side effects, of which patients would have the most of benefit [6,7].

In general, clinical efficacy of these medicines is less than evidenced efficacy in in-vitro conditions often due to the undesirable biopharmaceutical profile of active constituents. Poor lipid solubility and improper molecular size influence the final bioavailability, and consequently lead to reduced pharmacological efficacy. Great therapeutic potential of plants can be utilized by applying a novel drug delivery system during formulation of herbal medicines. The novel formulations have a significant advantage compared to the conventional formulations. Beside to efficacy, these systems

improve other two standards important for each medicine: safety and quality. They are good enhancers of biopharmaceuticals properties (solubility and permeability) and efficacy. They also facilitate delivering active constituents to the pharmacological target. Additionally, the novel drug delivery systems decrease toxicity, thus increasing the safety of herbal medicines. They protect from physical and chemical degradation and enhance stability [8]. Some of existing novel drug delivery systems which can be used for formulation of herbal medicines are:

#### Liposomes

Liposomes are created from one, several or multiple concentric bilayer membranes and hydrophilic core. They belong to the group of colloid, bearing in mind that sizes of their particles are between 0.05 and 5  $\mu\text{m}$  in diameter. The main advantage of liposomes is the ability to deliver almost all groups of molecules: hydrophilic, lipophilic, macromolecules and small molecules. This can be especially important for herbal extracts containing a complex mixture of compounds [8-10].

#### Phytosomes

Phytosomes involve the formation of a chemical bond between the bilayer membrane component and the plant extract component. This leads to a significant increase in absorption. The difference in relation to liposomes is that the active principle here is an integral part of the membrane [11,12].

#### *Ethosomes/Transfersomes*

Ethosomes are built from phospholipids and high concentrations of ethanol (20-45 %). Beside to ethanol, transfersomes are composed of surfactants that facilitate delivery of medicines. These systems are excellent carriers in transdermal drug delivery systems (TDDS) because successfully broke barrier function of skin [8-10].

#### Microemulsions

Emulsions are biphasic systems in which one phase is dispersed in other phase. One phase must be water (or aqueous phase), while other one must be oily liquid (non-aqueous). Generally, we can divide emulsions by size of dispersed phase at: ordinary emulsions (0.1-100  $\mu\text{m}$ ), micro-emulsions or nano-emulsions (10-100 nm), and sub-micro-emulsion or lipid emulsions (100-600 nm). Micro-emulsions are thermodynamically stable and they are suitable carriers for lipophilic medicines [8-9].

#### Nanocapsules and Nanospheres

These novel drug delivery systems belong to a group of polymeric nanoparticles (PNPs) and they are made by biocompatible and biodegradable polymers. The nanospheres have a matrix form in which the active principle is located, and the nanocapsules are made of two separate parts: membranes and core in which the active principle is. This type of novel system is excellent in overcoming the lack of conventional dosage forms. They significantly increase the efficacy and reduce a required dose [12-14].

The aim of the study was to determine the specificity of herbal medicines present on the market of Serbia in the period from 2006 to 2016.

#### METHOD

Data which were used in the study were taken from the official website of Agency for Medicines and Medical Devices of Serbia. Annual reports on the Turnover and Consumption of Medicines Intended for Human Use (Chapter 7b: Natural and financial overview of the achieved turnover of herbal medicines in the Republic of Serbia, according to the Anatomical and Chemical Classification of Herbal Medicines (HATC) and the

International Unprotected Drug Name (INN)) were observed for the period from 2006 to 2016 (these reports have been available online so far) [15-25]. Data about consumption were delivered to the agency by drug manufacturers or their representatives. Marketing Authorization Holder gives data about prices of medicines whose regime for issuing is without physician's prescription.

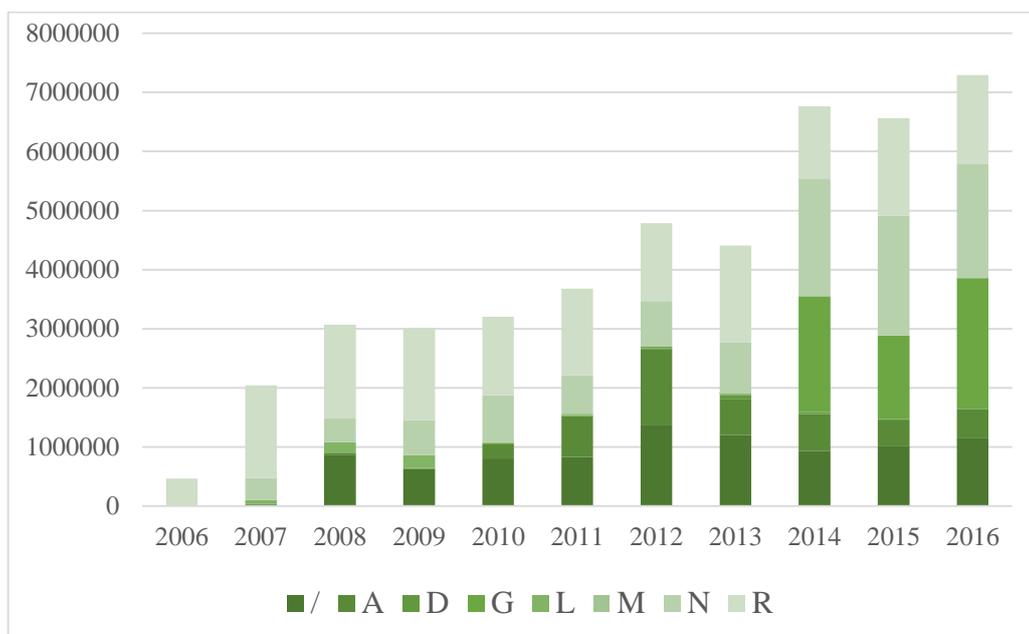
The conversion of consumption (expressed in Serbian dinars) in euros was made in accordance with the middle yearly exchange rate available on the website of the National Bank of Serbia [26].

Data analysis and graph drawing were done using the Microsoft Excel programme.

#### RESULTS AND DISCUSSION

Turnover of herbal and traditional medicines in 2016 compared to 2006 was increased by 15.67 times or by 1466.33 %. Medicines from HATC groups R, N, G (registered from 2014) and A were had the highest turnover. Graph 1 shows turnover of herbal and traditional medicines in the observed period.

Graph 1. Turnover expressed in euros, divided by HATC groups  
Grafikon 1. Promet izražen u eurima, podeljen po HATC grupama



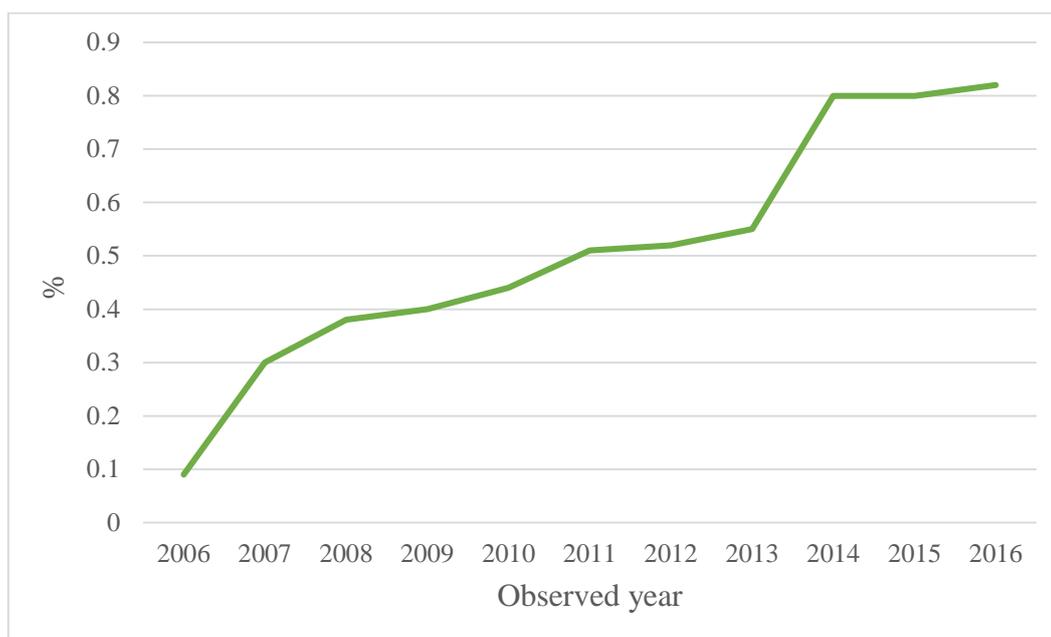
A significant percentage of medicines are not classified according to the HATC system, which points to the need for additional efficacy

studies that would facilitate the classification of this group of drugs.

Another key point is that herbal and traditional herbal medicines turnover were increased consumption share in total medicines turnover (Graph 2). The share of herbal and traditional drugs in the

consumption of all medicines increased from 0.09% (2006) to 0.82% (2016), i.e. the increase of share is by 9.11 times or by 811.11%

Graph 2. Share of herbal and traditional medicines in total consumption of medicines  
Grafik 2. Udeo biljnih i tradicionalnih lekova u ukupnoj potrošnji lekova



An increased rate of use of plants for the treatment of various diseases exists in the world too. Global botanical and plant-derived drugs' market have increasing trend and it was: \$23.2 billion in 2013, \$24.4 billion in 2014 and \$25.6 billion in 2015. It is expected that it will be \$35.4 billion in 2020 and will have a compound annual growth rate of 6.6% from 2015 to 2020 [27]. It is known that about 80% of people in developing countries use plants for treatment, but there is a significant rate of use of these drugs in developed countries. Research says that more than 50% of the population of developed countries (Europe, North America) use herbal medicine at least once in their lifetime [28]. In Germany and Canada, this percentage is between 70% and 90% [29]. Such a trend does not surprise because, apart from the low rate of side effects (in short-term use), good efficacy, low cost and good compliance, herbal medicines could potentially be used for the formulation of preparations for the treatment of very serious diseases such as asthma [30], HIV infection [31] or cancer [32].

It is suggested that the reasons for the increasing trend in the use of herbal remedies may be: consumer preferences for natural and alternative therapies, dissatisfaction with conventional therapy, affinity for self-medication, low cost, belief that these drugs are more effective and less dangerous, but also the modernization of pharmaceutical forms [33]. In addition, because these drugs belong to the group of OTC products for which advertising is permitted, an increasing number and quality of advertisements lead to increased use [34].

At the same time, the increase in the use of herbal medicines in Serbia is characterized by a poor knowledge about this group of medicinal products [35]. Analyzed data of used pharmaceutical forms in the observed period are shown in graph 3. As can be seen, there is downward trend in turnover of liquid pharmaceutical dosage forms, and upward trend turnover of solid forms. Generally, liquid forms are less stable than solid and additionally solid forms are more acceptable for use in most people. Soft

capsules had the highest consumption (especially in the last observed year), and topical preparations had very low turnover. When we talk about oromucosal preparations, compressed lozenges had higher turnover, but with downward trend, the opposite of pastilles.

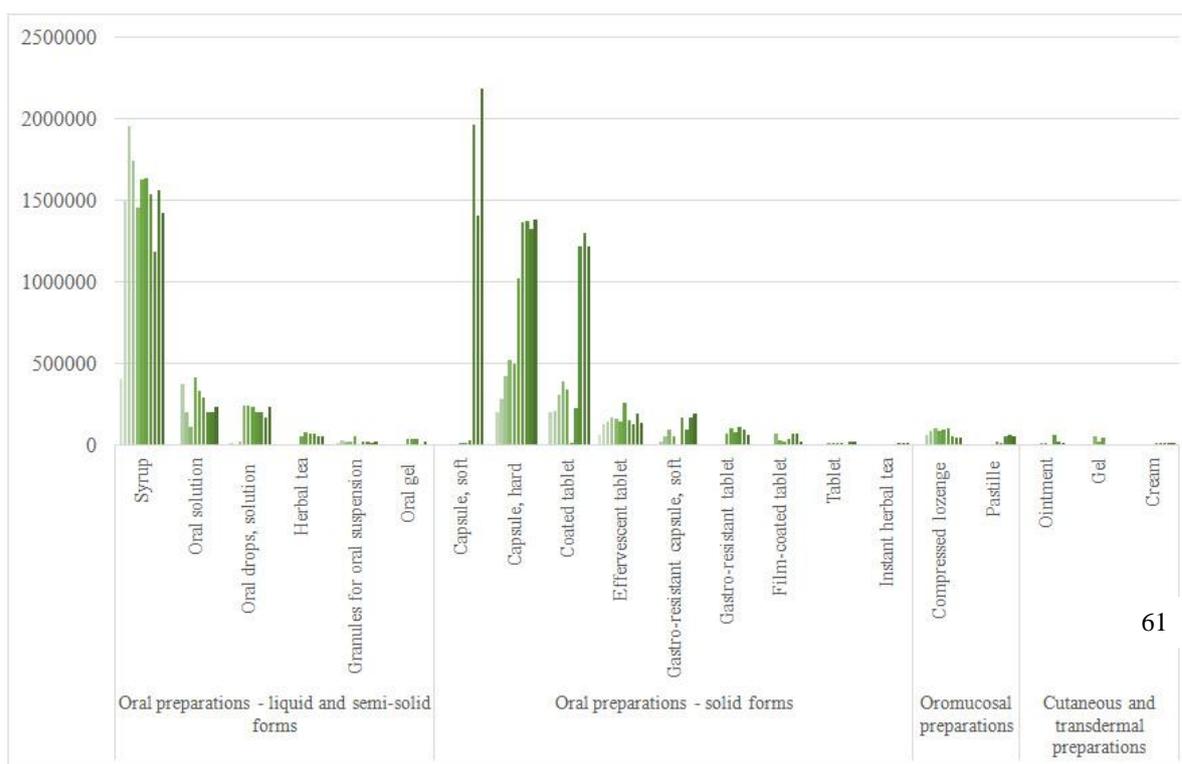
This significant increase in the use of herbal medicines was not followed by an increase in the presence of contemporary pharmaceutical dosage forms, since in the

observed period there were no registered herbal (or traditional) medicines formulated by novel drug delivery system. Definitely, we can say that modern forms of herbal medicines are not the cause of increasing their use. In other countries herbal products formulated with the help of novel drug delivery systems are not just part of the scientific researches, but they also exist in the market. Some of them are shown in Table 1.

Table 1. Existing modern forms of herbal preparations in other countries  
Tabela 1. Postojeći moderni oblici biljnih preparata u drugim zemljama

NOVEL DRUG DELIVERY SYSTEM (NDDS)	ACTIVE INGREDIENT/ ACTIVE CONSTITUENT (S)	ADVANTAGE OF NDDS	REFERENCE
<b>Nanoparticles</b>	Ginkgo biloba extract	Improving the cerebral blood flow and metabolism	36
	Ziziphus mauritiana extract	Enhanced immunomodulatory activity of extract	37
<b>Microspheres</b>	Cynara scolymusextract	Controlled release	38
<b>Liposomes</b>	Camellia sinensis extract (As White and Green tea)	Increase the bioavailability	39
	Hibiscus sabdariffa extract		
	Aloe barbadensis extract		
	Paullinia cupana extract		
<b>Phytosomes</b>	Sylibum marianum extract	Improving absorption	40
	Vitis vinifera extract		
	Hawthorn extract (Crataegus spp.)		

Graph 3. Turnover of different dosage forms of herbal (and traditional) medicines  
Grafik 3. Promet različitih oblika doziranja biljnih (i tradicionalnih) lekova



## CONCLUSION

Improving the quality of health care implies the application of guidelines for rational pharmacotherapy and phytotherapy. This implies giving the right medication, in the right dose for the right patient, right time and right route. Following the trends of developed countries (primarily Germany), the use of herbal drugs could be even greater. If herbal medicines on the Serbian market should be formulated according to the latest scientific

research, the effectiveness of these drugs would be even greater.

## Acknowledgement

This study was supported by the Grants of the Ministry of Education, Science and Technological Development of the Republic of Serbia, projects No 172058 and No 41012.

## Conflict of interest

There is no conflict of interest.

## REFERENCES:

- Zakon o lekovima i medicinskim sredstvima. Službeni glasnik RS, 2010, br. 30 [in Serbian]. Available at: [www.lat.rfzo.rs/download/zakon\\_lekovi-lat.pdf](http://www.lat.rfzo.rs/download/zakon_lekovi-lat.pdf).
- Schulz V, Hansel R, Tyler VE. Rational phytotherapy. A physician's guide to herbal medicine. 4th edn. Springer-Verlag, Berlin. 2001.
- Kunle, Folashade O, Egharevba, Omoregie H, Ahamadu, Ochogu P. Standardization of herbal medicines-A Review. *Int J BiodiverConser*. 2012;4(3):101-12.
- Colalto C. What phytotherapy needs: Evidence-based guidelines for better clinical practice. *Phytother Res*. 2018 Mar;32(3):413-25.
- Djordjevic SM. From Medicinal Plant Raw Material to Herbal Remedies. In: *Aromatic and Medicinal Plants-Back to Nature 2017*. InTech.
- Ernst E. The efficacy of herbal medicine—an overview. *Fundam Clin Pharmacol*. 2005 Aug;19(4):405-9.
- Maiti B, Nagori BP, Singh R. Recent trends in herbal drugs: a review. *Int J of Drug Res and Technol*. 2017 Apr 25;1(1).
- Saraf S. Applications of novel drug delivery system for herbal formulations. *Fitoterapia*. 2010;81(7):680-9.
- Chaturvedi M, Kumar M, Sinhal A, Saifi A. Recent development in novel drug delivery systems of herbal drugs. *Intl J Green Pharm*. 2011;5(2).
- Ambwani S, Tandon R, Ambwani TK, Malik YS. Current knowledge on nanodelivery systems and their beneficial applications in enhancing the efficacy of herbal drugs. *J Exp Biol Agric Sci*. 2018 Feb 1;6(1):87-107.
- Singh B, Awasthi R, Ahmad A, Saifi A. Phytosome: most significant tool for drug delivery to enhance the therapeutic benefits of phytoconstituents. *J Drug Deliv Therap*. 2018 Jan 15;8(1):98-102.
- Patil RY, Patil SA, Chivate ND, Patil YN. Herbal Drug Nanoparticles: Advancements in Herbal Treatment. *Res J Pharm Technol*. 2018;11(1):421-6.
- Khalil NM. Phytosomes: A Novel Approach for Delivery of Herbal Constituents. 2018.
- Ramos MA, Da Silva PB, Spósito L, De Toledo LG, Bonifácio BV, Rodero CF, Dos Santos KC, Chorilli M, Bauab TM. Nanotechnology-based drug delivery systems for control of microbial biofilms: a review. *Int J Nanomedicine*. 2018;13:1179.

15. \*Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2006. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2007.
16. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2007. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2008.
17. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2008. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2009.
18. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2009. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2010.
19. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2010. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2011.
20. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2011. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2012.
21. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2012. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2013.
22. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2013. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2014.
23. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2014. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2015.
24. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2015. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2016.
25. Radonjić V. Promet i potrošnja gotovih lekova za humanu upotrebu u 2016. godini. Beograd: Agencija za lekove i medicinska sredstva Srbije. 2017.
26. National Bank of Serbia [Internet]. Exchange Rate Lists For a Specific Period. [cited 2018 Nov 11]. Available at: [http://www.nbs.rs/export/sites/default/internet/english/scripts/kl\\_period.html](http://www.nbs.rs/export/sites/default/internet/english/scripts/kl_period.html).
27. BCC Research report. Botanical and Plant-derived Drugs: Global Markets. Report Buyer. (Accessed Aug 2015). 2015. Available at: <https://www.reportbuyer.com>.
28. \*\*Gunjan M, Naing TW, Saini RS, Ahmad A, Naidu JR, Kumar I. Marketing trends & future prospects of herbal medicine in the treatment of various disease. *World Journal of Pharmaceutical Research*. 2015;4(9):132-55.
29. Khan MS, Ahmad I. Herbal Medicine: Current Trends and Future Prospects. In *New Look to Phytomedicine 2019 Jan 1* (pp. 3-13). Academic Press.
30. Huntley A, Ernst E. Herbal medicines for asthma: a systematic review. *Thorax*. 2000 Nov 1;55(11):925-9.
31. Bekut M, Brkić S, Kladar N, Dragović G, Gavarić N, Božin B. Potential of selected Lamiaceae plants in anti (retro) viral therapy. *Pharmacological research*. 2017 c 16.
- 62 y A, Attre T, Bharadvaja N. Anticancer agent from medicinal plants: a review. 2017.
33. Bandaranayake WM. Quality control, screening, toxicity, and regulation of herbal drugs. *Modern phytomedicine: turning medicinal plants into drugs*. 2006. pp. 25-57.
34. Parle M, Bansal N. Herbal medicines: are they safe? 2006.
35. Samojlik I, Mijatović V, Gavarić N, Krstin S, Božin B. Consumers' attitude towards the use and safety of herbal medicines and herbal dietary supplements in Serbia. *International journal of clinical pharmacy*. 2013 Oct 1;35(5):835-40.
36. Shimada S. Composition comprising nanoparticle Ginkgo biloba extract with the effect of brain function activation IPC8 Class-AA61K914FI, USPC Class-424489; 2008.
37. Bhatia A, Sharda P, and Chopra D, Mishra T: Chitosan nanoparticles as carrier of immunorestoratory plant extract: synthesis, characterization and immunorestoratory efficacy. *International journal of drug delivery* 2011; 3:381-5.
38. Gavini E, Alamanni MC, Cossu M, Giunchedi P. *J Microencapsul* 2005;22(5):487-99.
39. Liposome Herbasec® [Internet]. Liposomal encapsulated, standardized botanicals in powder form. [Cited 2018 Nov 16] Available at: [https://www.in-cosmetics.com/\\_novadocuments/2319](https://www.in-cosmetics.com/_novadocuments/2319)
40. Integrative Therapeutics [Internet]. Super milk thistle @ X. [cited 2018 Nov 16]. Available at: <https://www.integrativepro.com/Products/Gastrointestinal/Super-Milk-Thistle>