



Original article

An epidemiological study on herbal product self-medication practice among psychotic outpatients from Serbia: A cross-sectional study

Gordana Nikolić^{a,b}, Nikola M. Stojanović^{a,*}, Pavle J. Randjelović^c, Snežana Manojlović^d, Niko S. Radulović^e^a Faculty of Medicine, University of Niš, Zorana Đinđića 81, 18000 Niš, Serbia^b Clinic for Mental Health, Clinical Center Niš, 18000 Niš, Serbia^c Department of Physiology, Faculty of Medicine, University of Niš, Zorana Đinđića 81, 18000 Niš, Serbia^d Clinic for Psychiatry "Gornja Toponica", Clinical Center Niš, 18000 Niš, Serbia^e Department of Chemistry, Faculty of Sciences and Mathematics, University of Niš, Višegradska 33, 18000 Niš, Serbia

ARTICLE INFO

Article history:

Received 26 November 2017

Accepted 22 January 2018

Available online xxxxx

Keywords:

Psychosis

Psychotic symptoms

Plant-derived therapeutics

Ethno-medicines

Side effects

ABSTRACT

Utilization of herbal products (HPs) is a common practice in the traditional medicine of people from southeastern Serbia. In this study, we focused on the usage of HPs as a self-medication practice among patients diagnosed with a mental illness, by aiming to ascertain the usage prevalence, the identity of the main plant taxa utilized, their formulations and target symptoms. This was accomplished through a cross-sectional study of psychiatric outpatients, conducted in the Clinic for Mental Health Protection in Niš, and which included a questionnaire on HP utilization and a non-structured psychiatric interview. Typically, single, middle-aged males, with a secondary education degree, utilized *Matricaria chamomilla* and/or *Melissa officinalis* in a form of an infusion (tea) for relieving anxiety and psychotic symptoms. In some cases, adverse effects were noted when HPs were used in combination with prescribed psychotropic medications. Our and previous results urge a thorough evaluation of possible benefits and/or harmful interactions of HP with standard medication in the treatment of psychiatric patients.

© 2018 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Psychiatric disorders such as schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20–F29), or those possessing some symptoms related to schizophrenia (F31.2 and F31.5), represent the most serious mental disorders that significantly affect all aspects of human consciousness (WHO, 2010; Murray and Lopez, 1996). These are chronic illness, starting during the adolescence or young adulthood, with an acute or gradual beginning and that need to persist for more than 6 months in order to establish the diagnosis of schizophrenia (Ritter et al., 2015; Murray and Lopez, 1996). The treatment with either typical (e.g. chlorpromazine, haloperidol) and atypical (e.g. clozapine, risperi-

done) antipsychotics is quite effective (Ritter et al., 2015). Side effects of antipsychotic drugs are hard to tolerate since after prolonged application they can cause sedation, extrapyramidal reactions, hypotension, metabolic syndrome, sexual dysfunction and constipation (Ritter et al., 2015). The intensity, incidence and severity of side effects is depending on the specific antipsychotic applied (Ritter et al., 2015).

According to the World Health Organization reports, almost 80% of the World's population consumes herbal products (HPs) as a source of primary care (Ekor, 2014). There is a strict definition of HPs brought by the EU commission (65/65/EEC, European Commission, 1965), which is implemented in the national laws of all EU countries and should be of enormous assistance to HP users intending to buy for such commercial products. The data concerning the utilization of HPs in patients suffering from different forms of schizophrenia, and/or some symptoms related to it, are scarce and only several publications dealt with this issue (Ahmed and Azam, 2014; Yadavi et al., 2015; Sarris, 2007). However, due to numerous side effects occurring during the treatment with antipsychotics, there has been an increase in the usage of HPs (together with some other alternative therapies) for the treatment of schizophrenia (Zhang et al., 2011; Xinrong, 2003), especially in the Chinese (traditional) medicine.

* Corresponding author.

E-mail addresses: gordanani@gmail.com (G. Nikolić), nikola.st90@yahoo.com (N. M. Stojanović), pavleus@gmail.com (P.J. Randjelović), nikoradulovic@yahoo.com (N. S. Radulović).

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

<https://doi.org/10.1016/j.jsps.2018.01.009>

1319-0164/© 2018 Production and hosting by Elsevier B.V. on behalf of King Saud University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article in press as: Nikolić, G., et al. An epidemiological study on herbal product self-medication practice among psychotic outpatients from Serbia: A cross-sectional study. Saudi Pharmaceutical Journal (2018), <https://doi.org/10.1016/j.jsps.2018.01.009>

The territory of the Republic of Serbia represents a natural habitat of diverse plant taxa that are being used throughout centuries for self-medication; among them, a significant portion is being utilized for the treatment of different mental disorders (Jarić et al., 2015; Zlatković et al., 2014; Šavikin et al., 2013; Jarić et al., 2007; Stojanović et al., 2017). The ethnopharmacological knowledge on HPs and their specific uses had been systematized during the last century in a single volume (“Herbal therapy”, Tucakov, 1973) and is still regarded as the choice literature of this type in Serbia. A relatively large portion of the book is devoted to plant taxa (HP) used for the treatment of mental disorders of differing severity, where more than 20 species are recognized to beneficially influence the HP-user’s mental health (Tucakov, 1973). However, none of the suggested HPs from this volume is recommended for the treatment of psychotic disorders.

The aim of our study was to determine whether and to what extent patients suffering from psychotic disorders, originating from Serbia (Clinical Center Niš), apply/utilize HPs for the treatment of their disease-related symptoms. We also intended to ascertain the plant taxa identity and their formulations used by these patients since the data concerning the plant species used for the treatment of these disorders is scarce. Additionally, the effect of HP and standard drug combination on the symptoms’ intensity was evaluated.

2. Materials and methods

2.1. Study definition and design

The study included patients originating from the municipal areas of Niš and the surrounding municipalities (population 373,407). The cross-sectional survey was designed as such to acquire the data concerning the usage, formulations and general attitude towards HPs in the selected patient population. The evaluation was done in the Clinic for Mental Health Protection of the Clinical Center Niš. The Ethical Committee of the University of Niš (decision No. 12-3380/6) and the Ethical Committee of the Clinical Center Niš (decision No. 9288) approved the study. A psychiatrist conducted a face-to-face psychiatric interview and a structured questionnaire about HP utilization, during regular checkups in a standard outpatient setting. In total, 106 adult patients, in the remission phase of their psychotic mental disorders (F20-F29, F31.2 and F31.5), were selected by the method of consecutive sampling. The sample was initially divided into users and non-users groups. Users group was afterwards subdivided based on the psychiatric diagnosis to: schizophrenic spectrum (F20; F21; F23 and F25), chronic delusional (F22 and F29) and depressive (F31.2 and F31.5) disorders. Additionally, HP users were divided based on the different symptoms that were treated with specific HP, to those that treated psychosis- (P), anxiety- (A) and depression- (D) related symptoms, as well as insomnia (I).

2.2. Data collection

A trained psychiatrist collected data during regular diagnostic or therapy sessions. The questionnaire consisted of five sections, containing both open and closed forms of questions as previously described in detail (Stojanović et al., 2017). The second part of the questionnaire related to psychosis-related symptoms (e.g. paranoid delusions, delusions of a magical influence, belief of poisoning by other persons, occurrence of voices) and to adverse symptoms, if any occurred during the utilization of HP.

2.3. Statistical analysis

The data collected from 106 subjects were analyzed using GraphPad Prism (version 5.03, San Diego, CA, USA) and SPSS (version 21.0, IBM Corp, 2012) where the sample size and power analysis showed $\beta < 0.2$ for the number of interviewed patients. The data are shown in frequency distribution tables expressed as percentages, which were further analyzed using Fisher’s exact and Chi-squared tests. The adjusted residual was then calculated and the values of the adjusted residual ≥ 2 or ≤ -2 were considered as statistically significant (Tanaka et al., 2007). Some questions allowed more than a single answer, thus the sum was not always 100%. Patient age is presented as mean \pm SD and Student’s *t*-test or One Way ANOVA were used to estimate the statistical difference among the groups. Probability values (*p*) less than or equal to .05 were considered statistically significant.

3. Results

All of the patients asked to participate in study agreed and finalized their interviews. More than a half of the sample, around 60%, used HPs for the treatment of their symptoms, while the rest did not believe in the effectiveness of HPs (Table 1). The patients that did not consume HP were either afraid or ignorant of the existence of HPs used for these purposes. Interestingly, only around 5% answered that the prescribed medication they already use is adequate therapy for them.

The sample, HP users and non-users together, was comprised of predominantly single male (55.7 and 65.1%) patients of different age, which were unemployed (58.5%), with a secondary level of education (69.9%), and living in an urban area (82.1%). Two groups differed in their education levels (Table 2) ($p < .05$), while only one HP user went to primary school alone, where the adjusted *z* value was found to be ≥ 2 for the primary level of education in both HP users and HP non-users ($z = \pm 2.69$).

The group of users was divided according to psychiatric diagnosis and most of them displayed schizophrenic spectrum disorders (around 60%) predominantly abundant in middle-aged males, younger than 40 years. The patients with a depressive disorder were significantly younger ($p = .013$) than the patients from the subgroups with schizophrenic spectrum and chronic delusional disorders.

The largest number of patients used HPs to relieve anxiety symptoms ($\approx 55\%$), while patients that were using HPs due to a psychotic symptomatology (delusions, hallucinations, agitation)

Table 1
HP utilization and frequency of the stated reasons for not utilizing them.

Characteristics	N (%)
<i>Interviews</i>	
Completed	106 (100)
Declined	0 (0)
<i>Used HPs for the treatment of psychiatric symptoms</i>	
Yes	57 (53.8)
No	49 (46.2)
<i>Reason for not consuming HPs</i>	
Do not believe in the effectiveness of HPs	15 (31.2)
Never heard of such HPs	11 (22.9)
Afraid to use HPs	9 (18.8)
Do not need HPs	4 (8.3)
No one had ever suggested the use of HPs	3 (6.2)
Already have adequate medication	2 (4.2)
Does not have the finances for HPs	2 (4.2)
Other ^a	2 (4.2)

^a These include the following answers: have not thought about HP or do not like to take HPs.

Table 2
Socio-demographic characteristics of the sample.

Characteristics	Total n = 106 (100%)	HP users n = 57 (53.8%)	HP non-users n = 49 (46.2%)	p value
Mean age	43.3 ± 14.9	42.1 ± 14.9	44.7 ± 15.0	>.05
Gender				>.05
Male	59 (55.7)	34 (59.6)	26 (53.1)	
Female	47 (44.3)	23 (40.4)	23 (46.9)	
Age groups				>.05
<30	24 (22.6)	15 (27.1)	9 (18.4)	
30–39	21 (19.8)	12 (21.0)	9 (18.4)	
40–49	20 (18.9)	10 (17.4)	10 (20.4)	
50–59	24 (22.6)	11 (19.2)	13 (26.5)	
60–69	13 (12.3)	6 (10.5)	7 (14.3)	
>70	4 (3.8)	3 (5.2)	1 (2)	
Marital status				>.05
Single	69 (65.1)	42 (73.7)	27 (55.1)	
Married	32 (32.1)	12 (21.1)	20 (40.8)	
Widowed/separated/divorced	5 (2.8)	3 (5.2)	2 (4.1)	
Level of education				.0372 ^a
Primary	8 (7.5)	1 (1.8) ^b	7 (14.3) ^c	
Secondary	74 (69.9)	44 (77.2)	30 (61.2)	
Post-secondary and tertiary	24 (22.6)	12 (21)	12 (24.5)	
Employment status				>.05
Employed	19 (17.9)	10 (17.5)	9 (18.4)	
Unemployed	62 (58.5)	34 (59.6)	28 (57.1)	
Retired	25 (23.6)	13 (22.9)	12 (24.5)	
Place of residence				>.05
Urban area	87 (82.1)	47 (82.5)	39 (79.6)	
Rural area	19 (17.9)	10 (17.5)	10 (20.4)	

^a Existence of statistically significant differences between HP and non-HP users found in Fisher's/ χ^2 analysis.

^b Adjusted residual ≤ -2 .

^c Adjusted residual ≥ 2 .

were the second largest group with around 20% of all HP users. Here again, the statistically significant difference ($p = .024$) was found for the level of education and the adjusted z value was ≥ 2 in patients, belonging to the subgroup that used HP for the treatment of anxiety symptoms, than the others had with higher educational levels. Thus, an HP user utilizing selected HPs for psychotic symptoms treatment could be a single unemployed male person, aged 50–59, with a secondary level of education, and living in an urban area.

The predominant source of information on HP utilization were family members, followed by the internet (Table 3). However, no statistically significant differences were found between the groups of patients with different psychiatric diagnosis, nor between the patients characterized by certain symptoms utilizing HPs and a specific information source (Table 3).

No statistically significant differences were found between patients with different diagnoses, or treated symptoms compared to the origin of HPs (Table 4). Most of the patients obtained their HPs from the pharmacy or herbal pharmacy shops, while the least number of them collected HPs personally (Table 4).

Table 5 contains identity data of HPs that were used in the treatment of both psychotic and non-psychotic symptoms, where the two most commonly used plants were found to be *Valeriana officinalis* and *Melissa officinalis*. For the treatment of psychotic symptoms patients utilized *Matricaria chamomilla* (3), *Melissa officinalis* (3), *Valeriana officinalis* (1), *Mentha x piperita* (1), *Salvia officinalis* (1) and *Allium cepa* (1), as well as some herbal mixtures and honey based products (2 in total) (Table 6).

The herein reported HPs were mainly used in the form of an infusion (tea) while in the case of *H. perforatum* and *V. officinalis* in the form of oil/tincture drops, the essential oil of *S. officinalis* was used, while *C. longa* was added to lemonades and *A. cepa* was consumed fresh (Table 6). Most frequently, these HP preparations were consumed only once daily at different times of the day and that was depended on the group of symptoms targeted with each HP.

Amongst the patients that used HPs, more than 50% reported HP co-usage with standard therapy (Table 7). Some of the patients experienced mild to moderate side effects, which included shivering, numbness, nausea and an increase in anxiety level (Table 7).

Table 3
Comparison of HP utilization information source among HP users with different diagnosis and symptoms targeted by the HPs.

Characteristics	Total number (%)	Family	Friends	Internet	Literature	Radio/TV	Physician	Shop or pharmacy	p-value
Schizophrenic spectrum	34 (59.6)	13 (38.2)	4 (11.8)	5 (14.7)	4 (11.8)	3 (8.8)	2 (5.9)	3 (8.8)	>.05
Chronic delusional disorder	15 (26.3)	7 (46.7)	1 (6.7)	3 (20)	0 (0)	1 (6.7)	3 (20)	0 (0)	
Depressive disorders	8 (14.1)	2 (25)	0 (0)	3 (37.5)	0 (0)	1 (12.5)	1 (12.5)	1 (12.5)	
Psychotic symptoms	10 (17.5)	2 (20)	1 (10)	2 (20)	1 (10)	1 (10)	2 (20)	1 (10)	>.05
Anxiety symptoms	40 (70.3)	15 (48.2)	3 (9.7)	3 (9.7)	2 (6.5)	3 (9.7)	3 (9.7)	2 (6.5)	
Depression symptoms	8 (14.1)	2 (25)	0 (0)	4 (50)	0 (0)	1 (12.5)	1 (12.5)	0 (0)	
Insomnia	8 (14.1)	3 (37.5)	1 (12.5)	2 (25)	1 (12.5)	0 (0)	0 (0)	1 (12.5)	

Table 4
Origin of HPs according to the diagnosis and treated symptoms.

Origin of HPs	Total number (%)	Pharmacy	Herbal pharmacy	Amateur herbalist	Collect HPs personally	Multiple answers ^a	p-value
Schizophrenic spectrum	34 (61.8)	15 (44.1)	14 (41.2)	4 (11.8)	1 (2.9)	0 (0)	>.05
Chronic delusional disorder	3 (5.45)	5 (33.3)	4 (26.7)	4 (26.7)	1 (6.7)	1 (6.7)	
Depressive disorders	14 (24.45)	3 (37.5)	2 (25)	1 (12.5)	1 (12.5)	1 (12.5)	
Psychotic symptoms	10 (17.5)	2 (20)	2 (20)	4 (40)	1 (10)	1 (10)	>.05
Anxiety symptoms	40 (70.3)	13 (41.9)	11 (35.5)	5 (33.3)	2 (6.5)	0 (0)	
Depression symptoms	8 (14.1)	2 (25)	5 (62.5)	0 (0)	0 (0)	1 (12.5)	
Insomnia	8 (14.1)	6 (75)	2 (25)	0 (0)	0 (0)	0 (0)	

^a Some of the subjects gave more than one answer to this question.

Table 5
HPs used for the treatment of different groups of symptoms.

Latin binominal	Plant family	Common name	Treated symptoms (N° of users)	Total N° of users ^a
<i>Valeriana officinalis</i>	Caprifoliaceae	Valerian	A/I/D/P (7/7/2/1)	17
<i>Melissa officinalis</i>	Lamiaceae	Lemon balm	A/P/D/I (9/3/2/1)	15
<i>Matricaria chamomilla</i>	Asteraceae	Chamomile	A/P/I (5/3/1)	9
<i>Mentha x piperita</i>	Lamiaceae	Peppermint	A/D/P (5/2/1)	8
<i>Hypericum perforatum</i>	Hypericaceae	St. John's wort	A/D (2/2)	4
Herbal mixtures ^c	/	/	A/D/I/P (1/1/1/1)	4
<i>Thymus vulgaris</i>	Lamiaceae	Thyme	A/D (3/1)	4
<i>Urtica dioica</i>	Urticaceae	Common nettle	A (3)	3
<i>Achillea millefolium</i>	Asteraceae	Yarrow	A (2)	2
Commercial tablets ^b	/	/	A/D (1/1)	2
<i>Salvia officinalis</i>	Lamiaceae	Salvia	P/D (1/1)	2
<i>Tilia cordata</i>	Malvaceae	Small-leaved lime	A/I (1/1)	2
A cactus extract	/	/	A (1)	1
<i>Allium cepa</i>	Amaryllidaceae	Red onion	P (1)	1
<i>Curcuma longa</i>	Zingiberaceae	Turmeric	D (1)	1
<i>Ginkgo biloba</i>	Ginkgoaceae	Ginkgo	D (1)	1
Honey based product	/	/	P (1)	1
<i>Melilotus officinalis</i>	Fabaceae	Yellow melilot	I (1)	1
<i>Panax sp.</i>	Araliaceae	Ginseng	D (1)	1
<i>Ocimum basilicum</i>	Lamiaceae	Basil	A (1)	1

^a Some of the subjects used more than one HP.

^b The plant mixture consisted of *Valeriana officinalis* and *Passiflora incarnata*.

^c An unknown mixture of herbs; Symptoms of: A – anxiety, D – depression, I – insomnia and P – psychosis.

Table 6
Reported formulations, doses and time schedules of HP utilization.

Plant name	Formulation	Amount of the herbal drug per dose	Dosage	N° of applications per day	Preferred time of the day for the application
<i>Achillea millefolium</i>	Infusion	1 tea spoons	1–2 tea cups	1–2	Morning
<i>Matricaria chamomilla</i>	Infusion	1–2 tea spoons	1–2 tea cups	2	Evening
<i>Valeriana officinalis</i>	Infusion/tincture drops	1–2 tea spoons/10–30 drops	1–2 tea cups/10–30 drops	1–3	Morning and evening
<i>Hypericum perforatum</i>	Infusion	1 tea spoon	1–2 tea cups	2–3	Morning and evening
<i>Melissa officinalis</i>	Infusion	1–2 tea spoons	2–3 tea cups	1–3	Any time of the day
<i>Mentha x piperita</i>	Infusion	1–2 tea spoons	1–2 tea cups	1–2	Morning and evening
<i>Ocimum basilicum</i>	Infusion	1–2 tea spoons	3 tea cups	3	Morning, midday, evening
<i>Salvia officinalis</i>	Infusion/essential oil	1 tea spoon/20 drops	1 tea cup/20 drops	3	Morning, midday, evening
<i>Thymus vulgaris</i>	Infusion	1–2 tea spoons	1–2 tea cups	1	Evening
<i>Tilia cordata</i>	Infusion	1 tea spoons	1 tea cup	1	Evening
<i>Urtica dioica</i>	Infusion	1–2 tea spoons	1 tea cup	1–3	Morning and evening
<i>Melilotus officinalis</i>	Infusion	1 tea spoon	1–2 tea cups	3	Morning, midday, evening
<i>Allium cepa</i>	Fresh	1–2 bulbs	Medium size	3	When needed
<i>Panax sp.</i>	Infusion	1 tea spoon	1 tea cup	3	Morning, midday, evening
<i>Ginkgo biloba</i>	Capsules	Commercial	1 capsule	1	Morning
<i>Curcuma longa</i>	Lemonade	1 tea spoon	1–2 glasses	2–3	When needed
Cactus extract	Drops	3 drops	3 drops	3	Morning, midday, evening

Patients that co-used *V. officinalis* and atypical antipsychotic drug (risperidone) or *M. officinalis* and clozapine experienced nausea, while the one that used simultaneously *V. officinalis* and haloperidol experienced shivering and numbness. Interestingly, the patient that used *M. chamomilla* in combination with fluphenazine reported an increase in anxiety.

4. Discussion

The study revealed that more than 50% of patients with psychotic disorders in our sample used HPs for the treatment of different disease-related symptoms (Table 2). From the remaining patients, HP non-users, one third believed that HPs cannot be

Table 7

Usage of HP in combination with standard therapy, and the noted side effects.

Herbal product used	The total number of users ^a	Co-used with standard therapy	Changes in symptom intensity observed during co-usage (N ^o)	Side effects observed (N ^o)
<i>Valeriana officinalis</i>	17	6	Decreased (6)	Shivering and numbness (1)/Nausea (1)
<i>Melissa officinalis</i>	15	8	No change (5)/Decreased (3)	Nausea (1)
<i>Matricaria chamomilla</i>	9	6	Decreased (3)/No change (3)	Increase in anxiety (1)
<i>Mentha x piperita</i>	8	7	Decreased (5)/No change (2)	None
<i>Hypericum perforatum</i>	4	3	No change (2)/Decreased (1)	None
<i>Thymus vulgaris</i>	4	4	Decreased (3)/No change (1)	None
<i>Urtica dioica</i>	3	1	No change (1)	None
<i>Salvia officinalis</i>	2	1	No change (1)	None
<i>Tilia cordata</i>	2	2	No change (2)	None
<i>Ocimum basilicum</i>	1	1	Decreased (1)	None
Cactus extract	1	1	No change (1)	None
Honey based product	1	1	No change (1)	None
Herbal mixtures	4	3	No change (3)	Nausea (1)

^a Some of the subjects used more than one HP.

effective or never heard of such possibility (HP) (Table 1), indicating that among most HP non-users exists a negative attitude towards this kind of treatment. A similar finding was reported in an Asian survey, while in some Western societies, such as USA, psychiatrists informed patients on HP utilization as a potential treatment (Zhang et al., 2011).

The majority of the patients included in this study, both HP users and non-users, were males, which is generally in accordance with the higher prevalence of schizophrenia in males (Abel et al., 2010). On the other hand, females are more frequently diagnosed with schizoaffective disorders (Bardenstein and McGlashan, 1990) and depression, as was in our sample. Patients' age might affect the obtained results only if cognitive functions were damaged, after a long-standing mental illness (e.g. decrease in IQ or memory). In our sample only few patients were older than 70, while only 15% were older than 60 (Table 2). In the HP users group, 15% of the subjects were older than 60, while the majority of them were younger than 30 years. At the time of the assessment, there were no cognitive impairments noted in the interviewed patients and all of them were in stabile remission of the illness.

Generally, more patients from the HP users group lived in a city (Table 2) and claimed to use different HPs in comparison to the interviewed subjects living in the country sides of different regions of Serbia (Jarić et al., 2015; Zlatković et al., 2014; Šavikin et al., 2013; Jarić et al., 2007). The same findings, although statistically significant, were detected in our previous study where patients with non-psychotic disorders that lived in a city consumed more HPs than those living in county sides (Stojanović et al., 2017). Also, some of the plants mentioned by our HP users overlapped with those previously reported for the same study area (Stojanović et al., 2017) or within the same country (Zlatković et al., 2014; Šavikin et al., 2013; Jarić et al., 2007). These differences in HP intake by urban residence patients can be partially due to much larger access to unconventional and/or conventional treatment options than those living in rural areas (Stojanović et al., 2017; Zhang et al., 2011).

The majority of HP users acquired their knowledge on HP utilization from their families (Table 3), although this kind of information source is considered unreliable and lacking any scientific background. On the other hand, traditional Chinese medicine is significantly based on the knowledge of HP utilization originating from family members (Xinrong, 2003), thus one cannot claim that this type of source of information is completely unreliable. It is also noteworthy to mention that none of the non-HP users had any knowledge on HP utilization for the treatment of their disease-related symptoms or were not ready to speak freely. Also, the internet is reported to be the second most common source of infor-

mation on HP utilization (Table 3), which could possibly be explained by the fact that a larger percent of interviewed patients: (i) lived in cities, (ii) were younger than 60 years, (iii) had an education degree higher than primary level (Table 2). Additionally, one might speculate that the people in need (psychiatric patients) are more familiar with such HPs than the rest of the population, thus possessing more information concerning HPs for a particular usage. Patients seeking HPs were predominantly oriented towards pharmacy and/or herbal pharmacy shops, and rarely turned to herbalists, or to identify/collect plant material by themselves (Table 4).

The usage of HPs for the treatment of psychotic symptoms is a relatively uninvestigated area and psychiatrists do not recommend HPs as the first choice therapy, but it certainly could be an adjunctive treatment influencing the therapeutic outcome (Sarris, 2007). The patients targeting psychotic symptoms with HPs used them in order to suppress different manifestations of psychosis such as auditory hallucinations and/or delusions (thought disorder). Previous ethno-botanical surveys conducted on the area of the Balkan Peninsula, amongst the people of Serbia, did not reveal any HPs used for the management of psychotic symptoms (Stojanović et al., 2017; Jarić et al., 2015; Zlatković et al., 2014; Šavikin et al., 2013; Jarić et al., 2007). Sedative properties of HPs could possibly interpret their usage for psychosis-related symptoms, since being agitated is one of the symptoms strongly related to psychosis, as well as with insomnia. In the mountainous region of Suva planina, plant species such as *Matricaria chamomilla*, *Melissa officinalis*, *Thlaspi praecox*, *Tilia cordata* and *Tilia platyphyllos* found their application as sedatives for anxiety, agitation and insomnia (Zlatković et al., 2014). Other mental disorder-related symptoms (non-psychotic) were abundant and they included anxiety/tension management, insomnia, sedation, mood improvement and migraine treatment (Stojanović et al., 2017; Jarić et al., 2015). Most frequently used plants for the treatment of mental illness-related symptoms included: *M. officinalis*, *M. piperita*, *V. officinalis* and *H. perforatum* (Stojanović et al., 2017; Jarić et al., 2015), while a number of them were reported to be used for the management of psychosis-related symptoms by some patients from our study (Table 6), as well. The two mentioned plant species (*M. officinalis* and *V. officinalis*) have been recognized by the European Medical Agency as those traditionally applied for the treatment of mental disorders and to aid sleep (EMA, 2013, 2016). Additionally, there are well-established effects of *V. officinalis* root extract in relieving mild nervous tension and sleep disorders (EMA, 2016). We noticed that some HPs reported here have been used for the treatment of both psychotic and non-psychotic symptoms, while some HPs, such as *A. cepa*, were exclusively stated to be applied for psychotic symptoms (Table 5).

Some plant species that are believed to reduce psychotic and/or depressive symptoms, such as red onion (*A. cepa*), salvia (*S. officinalis*) and turmeric (*C. longa*), as well as honey-based products, are also used as an everyday foodstuff (Table 5). It is not uncommon that people utilize foodstuff (e.g. different types of wild berries) as a source of remedies, for different health disturbances, especially those that are readily available in their surroundings (Zlatković et al., 2014; Šavikin et al., 2013; Jarić et al., 2007). In the traditional Chinese medicine, the treatment of psychosis is one among a great number of indications for turmeric usage (Xinrong, 2003). Also, there are some animal studies showing anti-psychotic effects of turmeric, as well as *A. cepa* extracts on haloperidol-induced catalepsy in rats (Kadian and Parle, 2014; Bishnoi et al., 2008); however, up to now there are no studies reporting human usage of onion for the treatment of psychosis. A local HP used for psychosis management in Bangladesh is a species of pepper (*Piper retrofractum*) consumed with a rice meal (Ahmed and Azam, 2014). One may ask oneself whether the special food intake really reduces the psychosis symptoms intensity at all, or if that is just a placebo effect in patients with impaired cognition. Cultural attitudes towards health and illness influence the predominant way of maintaining the symptoms, as well as tolerability towards mental disorders. Long-standing tradition of certain HPs utilization all over the world is a starting point for a scientific evaluation of their healing potentials.

More than 50% of the interviewed HP users co-used HPs with standard antipsychotics prescribed by a psychiatrist (Table 7) and reported no serious side effects related to this combination. The combination of HP with antipsychotic drugs could produce either a positive or a negative effect on the patient's mental status; thus, it is important to note changes following the start of usage of such combinations. Previous studies report that the incidence of the HPs-antipsychotics interaction probably depends on the combination itself (Zhang et al., 2011), i.e. that each combination represents a case for itself. For example, some HP containing higher amounts of caffeine can decrease clozapine metabolism through a competing for the same CYP isoforms (Bleakley, 2012), while ginseng in combination with phenelzine caused a broad spectrum of side effects in schizophrenic patients (Zhang et al., 2011). Among the studied HP users, only one patient reported using ginseng for the management of depression-related symptoms, however no combination of ginseng with antipsychotics/antidepressants was reported by this user (Tables 5 and 7). In addition, a preadministration of *H. perforatum* is known to inhibit clozapine metabolizing CYP450 enzymes, thus causing a statistically significant decrease in stable plasma level of clozapine from 0.46 to 0.57 mg/L to 0.19 mg/L (van Strater and Bogers, 2012). On the other hand, in a recent meta-analysis that included 1033 patients with chronic schizophrenia, the authors revealed that *G. biloba* extract significantly ameliorates total and negative symptoms (Chen et al., 2015) and this might imply a possible co-administration of this extract with standard therapy. The combination of standard drugs with a *G. biloba* extract could result in both increase/decrease in the drugs' activity or cause some undesired side effects. *G. biloba* extract is known to enhance haloperidol activity, potentially by scavenging free radicals produced by hyperdopaminergic activity (Chavez et al., 2006). However, there are single cases where *G. biloba* extract in combination with risperidone caused priapism (Lin et al., 2007). In our study, only one patient used commercial *G. biloba* extract, but not in combination with his standard medications, for the treatment of depression (Tables 5–7).

The reported side effects related to the HP consumption by psychotic patients could be considered as mild, and only 3 forms of side effects were reported (Table 7). This could be connected to the limited sample of HP users and we can assume that in a

greater number of consumers, more adverse effects would appear. Our findings indicated that *M. chamomilla*, frequently used for non-psychotic symptoms (Stojanović et al., 2017), was associated with a self-reported increase in anxiety when combined with the typical antipsychotic fluphenazine (Table 7). Other side effects, related to the usage of *M. officinalis* and *V. officinalis* included nausea, shivering and numbness, which could be a non-specific side effect connected to the HP intake or the interaction with prescribed antipsychotics. The two plant species (*M. officinalis* and *V. officinalis*) are known to cause serious health disturbances such as hypotension, tachycardia, hepatotoxicity, etc. (Cuzzolin and Benon, 2009; Di Lorenzo et al., 2015), and these were not observed in/mentioned by our patients. A careful utilization of HP with psychotropic medications is necessary, since according to the literature, some HPs in combination with drugs, e.g. *V. officinalis* and fluoxetine (Ernst, 2007), or a plant alone, *H. perforatum* (Sarris, 2007), can induce psychotic symptoms.

5. Strength and limitations of the study

The study group consisted of psychiatric outpatients in the remission phase of their psychosis, at the Clinic for Mental Health Protection, Clinical Center Niš, where the majority of people from several districts are gravitating towards; thus, we can say that the sample of 106 patients could be adequate in size for this type of study (power analysis showed $\beta < 0.2$). This is the first study conducted on patients with the diagnosis of psychosis and their HP utilization in this region. A single psychiatrist interviewed the patients, reducing the interference or differences between interviews.

One of the limitations of the study is the self-reported data, where one can only rely on the patient's memory from the time of HP consumption. This study group is quite delicate, since we were working with patients suffering from psychotic disorders, where several issues, which can affect data reliability, have to be considered. Quality of the remission is usually connected with the motivation for giving precise answers to questions, difficulties to reproduce earlier experiences in HP utilization, also readiness to speak freely, downplay of HP use, self-reporting, etc., and these can possibly lead to some inaccuracies in their answers.

6. Conclusions

Patients diagnosed with a psychiatric chronic illness, HP users in southeastern Serbia, are dominantly single men, of secondary level of education, mostly unemployed, living in an urban area. They used HPs for relieving anxiety and psychotic symptoms and were informed by their family members and/or the internet about the HPs. *Matricaria chamomilla* and *Melissa officinalis* were mostly commonly consumed and in the form of an infusion (tea), once daily. Some of the users experienced side effect symptoms during a combined usage of HPs and their prescribed psychotropic medication, without a relapse of the mental illness. Nonetheless, there is a necessity of a thorough investigation of the traditional knowledge on HPs in the treatment of psychiatric patients, and especially of their possible benefits and/or harmful interaction with standard medication.

Acknowledgment

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 172061).

References

- Abel, K.M., Drake, R., Goldstein, J.M., 2010. Sex differences in schizophrenia. *Int. Rev. Psychiatry* 22, 417–428.
- Ahmed, N., Azam, N.K., 2014. Traditional knowledge and formulations of medicinal plants used by the traditional medical practitioners of Bangladesh to treat schizophrenia like psychosis. *Schizophr. Res. Treatmen.* 2014, 679810.
- Bardenstein, K.K., McGlashan, T.H., 1990. Gender differences in affective, schizoaffective, and schizophrenic disorders. A review. *Schizophr. Res.* 3, 159–172.
- Bishnoi, M., Chopra, K., Kulkarni, S.K., 2008. Protective effect of Curcumin, the active principle of turmeric (*Curcuma longa*) in haloperidol-induced orofacial dyskinesia and associated behavioural, biochemical and neurochemical changes in rat brain. *Pharmacol. Biochem. Behav.* 88, 511–522.
- Bleakley, S., 2012. Identifying and reducing the risk of antipsychotic drug interactions. *Prog. Neurol. Psychiatry.* 16, 20–24.
- Chavez, M.L., Jordan, M.A., Chavez, P.I., 2006. Evidence-based drug-herbal interactions. *Life Sci.* 78, 2146–2157.
- Chen, X., Hong, Y., Zheng, P., 2015. Efficacy and safety of extract of *Ginkgo biloba* as an adjunct therapy in chronic schizophrenia: A systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. *Psychiatry Res.* 228, 121–127.
- Cuzzolin, L., Benon, G., 2009. Attitudes and knowledge toward natural products safety in the pharmacy setting: an Italian study. *Phytother. Res.* 23, 1018–1023.
- Di Lorenzo, C., Ceschi, A., Kupferschmidt, H., Lüde, S., De Souza Nascimento, E., Dos Santos, A., Colombo, F., Frigerio, G., Nørby, K., Plumb, J., Finglas, P., Restani, P., 2015. Adverse effects of plant food supplements and botanical preparations: a systematic review with critical evaluation of causality. *Br. J. Clin. Pharmacol.* 79, 578–592.
- Ekor, M., 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front. Pharmacol.* 4, 1–10.
- Ernst, E., 2007. Herbal remedies for depression and anxiety. *Adv. Psychiatr. Treat.* 13, 312–316.
- Commission, European, 1965. Council Directive 65/65/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relation to proprietary medicinal products. *Off. J. P22*, 369–373.
- European Medicines Agency (EMA), 2013. Community herbal monograph on *Melissa officinalis* L., folium.
- European Medicines Agency (EMA), 2016. European Union herbal monograph on *Valeriana officinalis* L., radix.
- Jarić, S., Maćukanović-Jocić, M., Djurdjević, L., Mitrović, M., Kostić, O., Karadžić, B., Pavlović, P., 2015. An ethnobotanical survey of traditionally used plants on Suva planina mountain (south-eastern Serbia). *J. Ethnopharmacol.* 175, 93–108.
- Jarić, S., Popović, Z., Macukanović-Jocić, M., Djurdjević, L., Mijatović, M., Karadžić, B., Mitrović, M., Pavlović, P., 2007. An ethnobotanical study on the usage of wild medicinal herbs from Kopaonik Mountain (Central Serbia). *J. Ethnopharmacol.* 111, 160–175.
- Kadian, R., Parle, M., 2014. Evaluation of anti-psychotic effect of *Allium cepa*. *World. J. Pharm. Pharm. Sci.* 3, 1146–1159.
- Lin, Y.Y., Chu, S.J., Tsaim, S.H., 2007. Association between priapism and concurrent use of risperidone and *Ginkgo biloba*. *Mayo Clin. Proc.* 82, 1289–1290.
- Murray, C.J.L., Lopez, A.D., 1996. *The Global Burden of Disease*. Harvard University Press, Cambridge, MA.
- Ritter, J., Flower, R., Henderson, G., Rang, H., 2015. *Rang & Dale's Pharmacology*. Churchill Livingstone, London, UK.
- Sarris, J., 2007. Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother. Res.* 21, 703–716.
- Stojanović, N.M., Samardžić, Lj., Randjelović, P.J., Radulović, N.S., 2017. Prevalence of self-medication practice with herbal products among non-psychotic psychiatric patients from southeastern Serbia: a cross-sectional study. *Saudi Pharm. J.* 25, 884–890.
- Šavikin, K., Zdunić, G., Menković, N., Živković, J., Čujić, N., Tereščenko, M., Bigović, D., 2013. Ethnobotanical study on traditional use of medicinal plants in South-Western Serbia, Zlatibor district. *J. Ethnopharmacol.* 146, 803–810.
- Tanaka, H., Sei, M., Quang Binh, T., Munakata, H., Yuasa, K., Nakahori, Y., 2007. Correlation of month and season of birth with height, weight and degree of obesity of rural Japanese children. *J. Med. Invest.* 54, 133–139.
- Tucakov, J., 1973. *Lečenje Biljem*. Izdavačka Radna Organizacija Rad, Belgrade, Yugoslavia (book written in Serbian).
- van Strater, A.C.P., Bogers, J.P.A.M., 2012. Interaction of St. John's wort (*Hypericum perforatum*) with clozapine. *Int. Clin. Psychopharmacol.* 27, 121–124.
- Xinrong, Y., 2003. *Encyclopedic Reference of Traditional Chinese Medicine*. Springer-Verlag, Berlin Heidelberg, Germany.
- Yadav, M., Parle, M., Kadian, M., Sharma, K., 2015. A review on psychosis and anti-psychotic plants. *Asian J. Pharm. Clin. Res.* 8, 24–28.
- WHO, 2010. *International statistical classification of diseases and related health problems. 10th revision*.
- Zhang, Z.J., Tan, Q.R., Tong, Y., Wang, X.Y., Wang, H.H., Ho, L.M., Wong, H.K., Feng, Y. B., Wang, D., Ng, R., McAlonan, G.M., Wang, C.Y., Wong, V.T., 2011. An epidemiological study of concomitant use of Chinese medicine and antipsychotics in schizophrenic patients: implication for herb-drug interaction. *PLoS ONE* 6, e17239.
- Zlatković, B.K., Bogosavljević, S.S., Radivojević, A.R., Pavlović, M.A., 2014. Traditional use of the native medicinal plant resource of Mt. Rtanj (Eastern Serbia): Ethnobotanical evaluation and comparison. *J. Ethnopharmacol.* 151, 704–713.