



## Herbal preparations use in prevention and treatment of gastrointestinal and hepatic disorders—Data from Vojvodina, Serbia



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### ABSTRACT

**Objective:** Gastrointestinal (GI) disorders are estimated to be frequent among general population. Various types of traditional and complementary therapies, primarily phytotherapy, can be used for prevention and treatment of many diseases and conditions, including GI complaints. Thus, the aim of this study was to investigate the patterns of use of medicinal herbs in treatment and prevention of GI disorders, together with their efficacy and safety.

**Methods:** A prospective, repeated cross-sectional, descriptive study was conducted in the form of a specifically created questionnaire, filled in by consumers and/or patients in pharmacies on the territory of Autonomous Province of Vojvodina, Republic of Serbia. All data were statistically analyzed in Microsoft Excel 2007.

**Results:** In the total number of 1137 patients, 10.4% declared themselves as consumers of phytopreparations for GI disorders. The most common diseases were constipation (44%) and dyspepsia (23%). The most frequently used preparations contained laxatives (with both anthraquinones and dietary fibers), artichoke and silymarin. Iberogast® was also frequently used. Pharmacists were the main source of recommendation for the most adequate herbal remedies. At the same time, phytopreparations were well tolerated, with no major side effects, and were evidently or presumably effective.

**Conclusions:** Some mild and moderate GI disorders seem to be treated frequently with phytopreparations. Various herbal remedies are well accepted by patients, and the phytopreparations seem to have favorable ratio of safety and efficacy. Further integration into conventional medicine will improve the quality of the products used and provide a rational plan of use of medicinal plants.

### 1. Introduction

Gastrointestinal (GI) tract represents a system of various organs from the mouth to the anus, primarily responsible for processes of food digestion, absorption of nutrients, vitamins and minerals, and excretion of waste material together with metabolic products. It is closely associated with other organs involved in these processes, such as salivary glands, the pancreas and hepatobiliary tree.<sup>1</sup> Due to the large contact area (approx. 400 m<sup>2</sup>), the long time of contact and direct exposure of the GI tract to food and beverages, but also to food contaminants, drugs (both active compounds and vehicles) and various xenobiotics, there is

a potential for the development of various disorders.<sup>2</sup> These can be divided according to the location of the disorder (e.g. the diseases of esophagus, stomach, colon) or according to the type of disorder: 1. organic (structural) (e.g. peptic ulcer, colon cancer), 2. motility (e.g. gastroparesis, intestinal pseudo-obstruction) and 3. functional (e.g. functional dyspepsia, functional constipation).<sup>3</sup> Due to the relatively large number of organs in the GI tract and a wide spectrum of potential disorders, it is hard to estimate the global prevalence of these disorders; however, it is most likely that this number is quite high.

Traditional and complementary medicines (TCMs) are a set of skills and practices used in the maintenance of health as well as in

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prevention, diagnosis, improvement or treatment of physical and mental illness. Although not fully integrated into the dominant health care system, TCMs of proven quality, safety and efficacy contribute to the goal of ensuring that all people have access to health care. Major advantages of TCMs are that they are accessible, affordable, culturally acceptable and trusted by a large number of people. TCMs also stand out as a way of coping with the relentless rise of chronic, non-communicable diseases. Among the TCM practices, phytotherapy or herbal medicine is possibly one of the most famous and the most frequently used one.<sup>4</sup> TCM products include herbs, herbal materials, herbal preparations and finished herbal products that contain plant parts, other plant material or combinations of active ingredients. In EU, these products can be registered either as herbal medicines (HM), or medical devices (herbal dietary supplements (HDS), cosmetics or biocidal products), and the distinguishing between them varies from country to country. The delimitation of borderline products could be based on the content ( $n$ ) of the previously mentioned herbal ingredients, which should be  $n \geq 65\%$  and  $15\% < n < 65\%$  of the therapeutic daily dose of the herbal ingredient for HM and HDS, respectively. However, another type of categorization is also used, from case to case, and is applied in UK.<sup>5</sup> Data from 2012 suggest that prevalence of HM and HDS users varies from 5.9 to 48.3% in Europe.<sup>6</sup> It is estimated that the market value of natural products in many developed and developing countries is worth up to several billions of dollars,<sup>4</sup> again showing both interest in this type of treatment and potential for further development in this area.

It appears that the use of various TCMs is prevalent among patients with GI diseases.<sup>7</sup> Some of these include phytotherapy, nutraceuticals, hypnosis, acupuncture and many others.<sup>8</sup> Evidence based, rational phytotherapy plays an important segment in the treatment of (primarily functional) GI disorders, where phytopreparations are used for achieving the therapeutic effect. Also, the use of multi-herbal preparations can be suggested if there is a possibility of achieving synergistic and additive effects, as well as if side effects can be reduced or eliminated completely.<sup>9</sup>

As these diseases are versatile (from mild to serious symptoms, an acute and chronic course etc.) it is reasonable to assume that many different herbal products can be used in their prevention and treatment. Thus, the aim of this study was to investigate the use of HM and HDS for GI disorders in Vojvodina, Serbia- the frequency and indications of use, the most frequently used herbs, as well as their safety and efficacy.

## 2. Material and methods

The research was conducted as prospective, repeated cross-sectional, descriptive study. A questionnaire was specifically created for the purposes of this research. The questions in the survey included questions of demographic and socio-economic status. Out of the anthropometrics, the patients' heights and weights were later used to calculate their body mass index (BMI), using the following equation:  $BMI = \text{weight [kg]} / \text{height}^2 [\text{m}^2]$ . According to the calculated BMI value, patients were classified in the following groups: underweight ( $< 18.5 \text{ kg/m}^2$ ), normal ( $18.5\text{--}24.99 \text{ kg/m}^2$ ), overweight ( $25\text{--}30 \text{ kg/m}^2$ ) and obese ( $\geq 30 \text{ kg/m}^2$ ).<sup>10</sup> Regarding the use of HM and HDS, healthy ways of living were investigated on one side, as well as the use

of alcohol beverages, coffee and tobacco products on the other side. Further questions concerning GI problems included questions about the type of those problems, the type of phytopreparations used for treatment/prevention, the reasons for their use and the efficacy and safety of the used preparations. The questions in survey were closed or semi-open. All data were statistically analyzed and presented using Microsoft Excel 2007.

Participation in this survey was voluntary and consumers asked to participate were chosen randomly. The patients filled in the survey by themselves, and parents filled it in for under-age children ( $< 18$  years). All of the patients visiting the pharmacies and willing to participate in the study were included. Informed consent was obtained from the patients. Exclusion criteria were the inability to communicate (due to any reason) and the refusal of participation. Due to the fact that data was gathered in the same pharmacies over an extended period of time, patients were asked whether they had previously participated; the same patients were not included multiple times. The survey was conducted in pharmacies on the territory of The Autonomous Province of Vojvodina, Republic of Serbia, during a 5 year period (2010–2015). The questionnaire and the protocol of study were approved by The Board of Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Serbia.

## 3. Results

### 3.1. General data about patients

The survey included 1137 questionnaires that were completed by consumers who purchased HM or HDS in pharmacies. Out of them, 10.4% (118/1137) declared themselves as consumers of phytopreparations in therapy/prevention of gastrointestinal and hepatic disorders.

Demographic data showed that the survey successfully included consumers of HM or HDS in therapy/prevention of gastrointestinal and hepatic disorders of various categories. Concerning the sex of the patients, the majority of them were women (62.7%). The age distribution of the patients showed that most of them are in the category of 41–60 years (35.6%). The category with the fewest declared consumers was the group of underage children (0.9%). Using the data of the patient's height and weight, a BMI was calculated, according to the previously provided formula. Most of the consumers (58.5%) had normal a BMI value and 29.7% of them were overweight. The patients gave their personal opinion about their socio-economic status, and about half of them declared themselves as satisfied (50.8%) followed by 34% of them who said their status was bearable. All the data are presented in Table 1.

The consumption of products that can potentially trigger GI problems was varying: about a quarter of the consumers were consuming tobacco products (24.6%), a third of them consumed alcoholic beverages (34.7%), and approximately 4 out of 5 of them consumed coffee (81.4%). All the data are presented in Fig. 1.

### 3.2. Data about phytopreparations consumption

Out of 118 investigated patients who consumed phytopreparations

**Table 1**  
Detailed data about patients consuming phytopreparations for digestive disorders.

demographic data	sex	women			men		
		62.7% (74/118)			37.3% (44/118)		
age		< 18	18-25	26-40	41-60	> 60	
		0.9% (1/118)	22.9% (27/118)	22% (26/118)	35.6% (42/118)	18.6% (22/118)	
anthropometrics	BMI	underweight		normal	overweight		
		3.4% (4/118)	58.5% (69/118)	29.7% (35/118)	8.4% (10/118)		
socio-economic status	self-declared opinion	extremely unsatisfied	unsatisfied	bearable	relatively satisfied	satisfied	extremely satisfied
		3.4% (4/118)	5.9% (7/118)	34% (40/118)	1.7% (2/118)	50.8% (60/118)	4.2% (5/118)

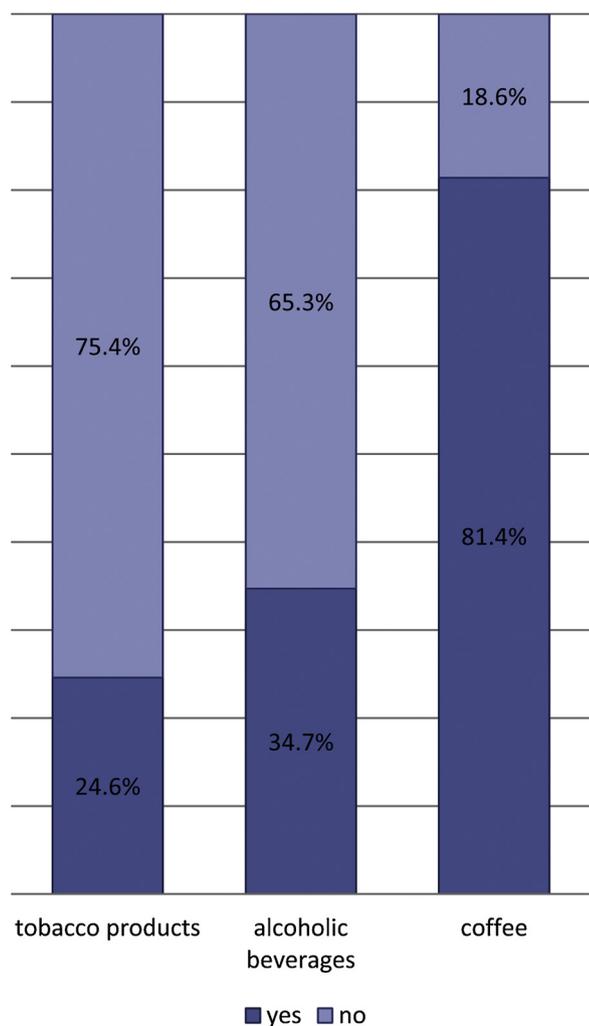


Fig. 1. Consumption of potential triggers of gastrointestinal disorders.

for various GI ailments, only about a quarter of them (26.3%, 31/118) had the diagnosis of the GI or hepatic disorder confirmed by their doctor, while others believed to be or were experiencing symptoms of these disorders.

The most frequent disorder being treated was constipation (44%), followed by dyspepsia (23%) (Fig. 2.)

The most frequently used HM and HDS are presented in Fig. 3. The preparations contained buckthorn (*Rhamnus frangula*, Rhamnaceae) (16.1%), senna (*Cassia* sp., Fabaceae) (8.5%) or dietary fibers (6%) for constipation, artichoke (*Cynara scolymus*, Asteraceae) (11%) and silymarin (from *Silybum marianum*, Asteraceae) (9.3%) for hepatic disorders. Iberogast® (10.2%) was also a widely used herbal medicine in various digestive disorders.

Phytopreparations were most frequently used based on the recommendation of pharmacists (35.6%, 42/118) or on the own initiative of the consumer (32.2%, 38/118), and rarely on the advice of a doctor or another person (Fig. 4).

The tolerability of the preparations used was generally positive - good (52.6%) or excellent (39.2%). Only one patient reported a side effect (without providing details on this matter); others experienced no side effects (90.7%) or were unaware of them (8.4%). Finally, patients gave their opinion on the efficacy of the used phytotherapy. In this survey, 72.2% consumers stated that there was a change since the start of usage; however, only about a fifth of them (18.6%) had confirmation from a doctor or relevant laboratory testing. All the data are presented in Table 2.

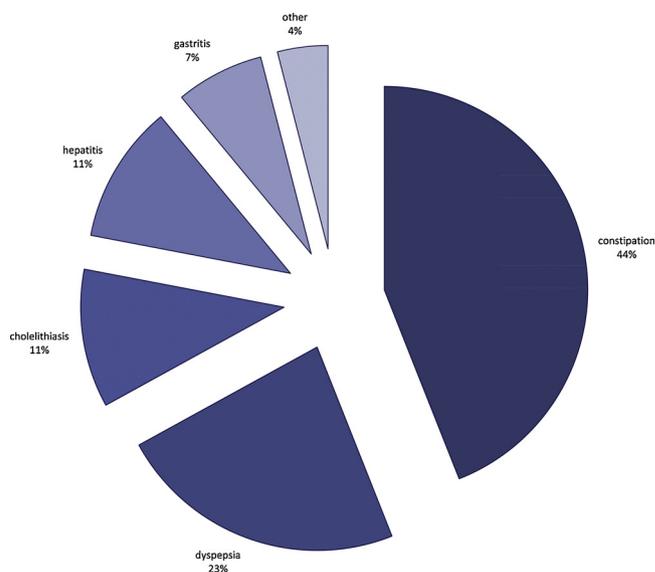


Fig. 2. Medical conditions treated with phytopreparations.

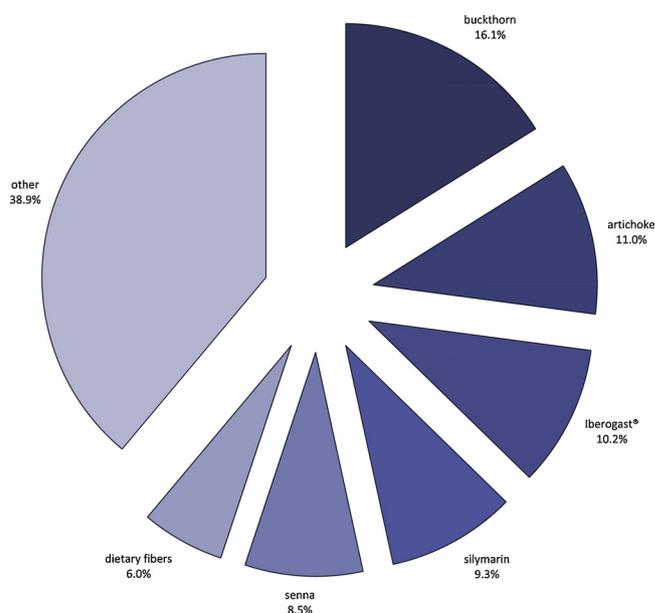


Fig. 3. The most frequently used plants or phytopreparations.

#### 4. Discussion

Previous researches, conducted in the mountain regions of Serbia, found that gastrointestinal ailments were one of the conditions most frequently treated with phytotherapy.<sup>11–14</sup> Some differences between these surveys and current research can be noticed. These investigations were conducted among a predominantly older population, and their emphasis was on the traditional knowledge and application of medicinal plants. Our study was conducted in various age groups and in pharmacies, so there is no surprise that the use of commercially available phytopreparations is detected. A previous study, by Samojlik *et al.*,<sup>15</sup> also investigated the use of HMs and HDSs in Vojvodina. Herbs for prevention/treatment of GI disorders were among the most frequently used ones practically in all age groups. Another study, conducted in patients with GI malignancies in Vojvodina, stated that approximately two thirds of them used additional herbal therapy.<sup>16</sup>

Users are more frequently women (62.7%), which is in accordance with the results of other studies where the use of TCMs was investigated.<sup>6,7,17</sup> Also, it seems that consumers of TCM are more

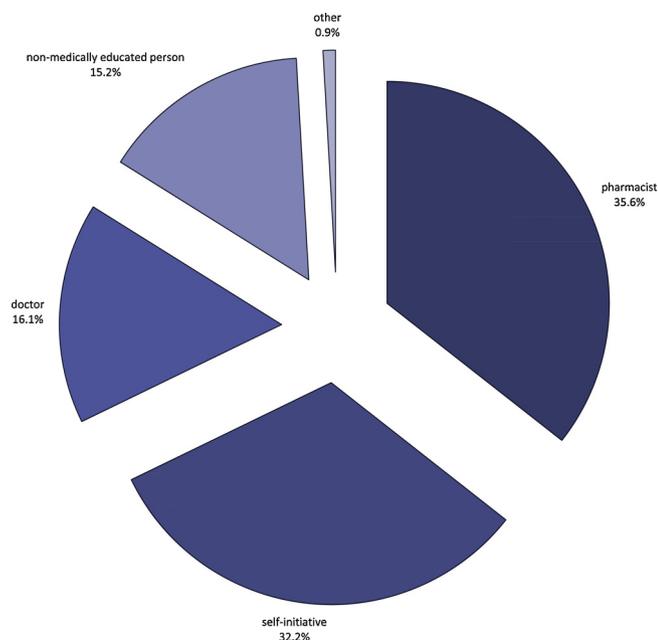


Fig. 4. Source of recommendation for phytopreparation use.

frequently in the age group above 40 or 45 years<sup>7,17</sup> as it is the case in the present study (35.6% in the age group 41–60 years). Concerning BMI, patients with normal and slightly increased BMI are the ones most often seeking aid in TCM,<sup>17</sup> again in consistency with our results.

Some of the products often declared as triggers of GI disorders are coffee, alcohol and tobacco. However, a single agent cannot be considered the sole cause of a disease, as it is more likely that gastrointestinal disorders are caused by a complex interaction of entities of several etiologies. As a result of the recorded usage of products that are described as triggers of GI disorders, it would be advisable to promote healthy living habits through the public health care system.

Our survey detected a high usage of coffee (81.4%). This beverage is often associated with heartburn, as caffeine present in coffee is considered responsible for increased gastric secretion<sup>18</sup> and coffee intake is associated with an increased risk for *Helicobacter pylori* infections, a causative agent of infectious gastritis.<sup>19</sup> However, a large study conducted in Japan found no evidence of gastric and duodenal ulcers or reflux diseases in consumers of coffee.<sup>20</sup>

Ethanol in alcoholic beverages shows harmful effects on several organ systems, including the GI tract. A direct effect on the mucous tissue and modifications of motility and gastric secretion are supposed mechanisms of harmful activity in the GI tract. Since ethanol is mainly metabolised in the liver, this organ is the most affected by alcohol consumption; chronic intake leads to cirrhosis and fibrosis.<sup>21</sup> A third of our patients declared themselves as alcohol consumers, however, without data on the quality and quantity of the consumed liquor.

A quarter of our patients declared themselves as smokers. Nicotine (the main alkaloid in cigarettes) is proven to be one of the causes of peptic ulcer and various cancers of the GI tract. Besides the worsening of the current health status, it is believed that it has the potential to

induce such diseases.<sup>22</sup>

Only about a quarter of our patients (26.3%) who used phytopreparations had a diagnosis from a medical doctor. This result is not surprising, as some disorders have mild symptoms and can be of an acute course. However, there is always a danger that phytotherapy can be used to mask the symptoms, sometimes of more serious diseases, which require medical interventions and/or treatment.

Nearly half of the interviewed patients reported having constipation. This is a problem often associated with a modern lifestyle and irregular diet. A previously conducted survey on the territory of Vojvodina also detected a use of laxatives in various age groups.<sup>15</sup>

A high usage of potent herbal laxatives can be noticed. Buckthorn (*Rhamnus frangula*, Rhamnaceae) and senna (*Cassia* sp., Fabaceae) were used by a quarter of patients (16.1% and 8.5%, respectively). Both plants contain anthraquinones as active principles; their mechanism of activity is associated with the release of prostaglandins and the inhibition of NaCl absorption and additional chloride secretion.<sup>23</sup> These compounds are often associated with safety concerns, as numerous morphological and functional side effects are reported.<sup>24</sup> However, there is a question in the scientific community whether these side effects are exaggerated. Serious adverse effects are mainly recorded in the cases of chronic use and abuse of these laxatives. When used correctly (in purified form, in adequate doses, and for acute, short-term conditions), these phytopreparations are extremely effective and generally safe for application, and should not be disregarded easily.<sup>23,24</sup>

Dietary fibers have many beneficial effects, not only in the GI tract, but in general, concerning the human health.<sup>25</sup> One of their potential uses is for the treatment and prevention of constipation. Fibers increase the fecal mass, and in that manner, promote the motility of the terminal parts of the digestive path.<sup>26</sup> This mechanism of activity makes products containing dietary fibers a safer alternative to phytopreparations with anthraquinone compounds. This also makes them the preferred type of laxative in underage children; e.g. prunes and figs<sup>15</sup> are believed to have this mechanism of activity and their pleasant organoleptic features cannot be disregarded.<sup>27,28</sup>

Artichoke (*Cynara scolymus*, Asteraceae) is a plant world-wide known and used for both its nutritional and medical properties.<sup>29</sup> Modern research confirmed that active compounds from the artichoke exhibit hypoglycemic, cholesterol lowering, choleric, anticholestatic, hepatoprotective and antioxidative properties.<sup>29,30</sup> Bearing in mind that the disorders of the hepatobiliary tract are detected in approximately a quarter of interviewed consumers (hepatitis 11% and cholelithiasis 11%), it is no surprise that artichoke is the second most used plant. Previous research in Vojvodina detected the use of artichoke in the elderly population (> 60 years) for hypolipemic purposes.<sup>15</sup>

Iberogast® is a registered commercial phytopreparation which contains extracts of nine herbal drugs (*Iberis amarae fructus*, *Chelidonium herba*, *Cardui mariae fructus*, *Melissae folium*, *Carvi fructus*, *Liquiritiae radix*, *Angelicae radix*, *Matricariae flos*, *Menthae piperitae folium*). This product is used for various gastrointestinal disorders, as its activity includes antispasmodic, anti-inflammatory and antioxidative effects.<sup>31</sup> Several studies demonstrated its positive effects in the treatment of functional dyspepsia,<sup>32</sup> a disorder recorded in nearly a quarter (23%) of our patients, suggesting its use for these purposes.

*Silybum marianum*, Asteraceae, also known as milk thistle, is the

Table 2 Safety and efficacy of used phytopreparations.

safety	tolerability				
		excellent	good	neutral	poor
		39.8% (47/118)	52.6% (62/118)	5.1% (6/118)	2.5% (3/118)
	side effects				
		yes	unaware of them	no	
		0.9% (1/118)	8.4% (10/118)	90.7% (107/118)	
efficacy	change since start of usage	yes	he/she believes there is	maybe	no
		72% (85/118)	20.4% (24/118)	3.4% (4/118)	4.2% (5/118)
		confirmation of change (by doctor or laboratory testing)			
		yes	no		
		18.6% (22/118)	81.4% (96/118)		

biological source of silymarin. Although several activities are documented (including hypoglycemic, reno-protective, anti-cancer), this plant is most commonly used for its hepatoprotective properties.<sup>33</sup> Positive effects on the liver are achieved via the antioxidant, anti-inflammatory and anti-fibrotic activities of silymarin. Disorders of various etiologies, including steatosis (both ethanol and non-ethanol induced), hepatitis (commonly viral), cirrhosis and carcinoma, as well as some exposure to toxins (fungal *Amanita* spp., carbon tetrachloride, tetrachloromethane etc.) can be treated with silymarin.<sup>33,34</sup> In our study, 11% of patients used products with silymarin, suggesting that this is a widely-recognized herbal therapy.

The integration process of TCM services into primary healthcare systems (as one of the World Health Organization Traditional Medicine Strategy 2014–2023 strategic objectives) could, among others, enable better communication between health care professionals and patients on the TCM matter. This would also lead to the promotion of safe and effective TCM products and practices of high quality.<sup>4</sup> A systematic review of the general TCM use in Europe found dissatisfaction with conventional medicine as one of the primary reasons for turning to TCMs. This dissatisfaction includes the unpleasant side-effects of conventional drugs, as well as a bad communication with a medical doctor, while the communication with a TCM practitioner is a better one.<sup>6</sup> This also appears to be the main reason for TCM use in patients with GI disorders.<sup>7</sup> A survey conducted in the United States among users of TCM for GI disorders found that this type of therapy is also used for achieving a general well-being, preventing a disease and because of the convenience of self-practice.<sup>17</sup>

Patients in Europe believe that their medical professionals (doctors, but also pharmacists, nurses, physiotherapists etc.) should be better informed about TCMs. A negative attitude towards these therapies seems to hold the patients back from using them.<sup>35</sup> A study conducted in the United States declared that 70% of patients discussed their TCM use for GI disorders with medical doctors, where doctor's opinion was generally neutral or positive towards TCMs.<sup>7</sup> In our research, medical doctors were listed as the third most frequently used source of information (16.1%) of used phytopreparations. The main source of information were pharmacists (35.6%), which is a positive aspect of the use of phytopreparations and other over-the-counter drugs, as pharmacists are viewed as the final link in a chain which ensures that a patient's treatment is effective, safe and of high quality.<sup>36</sup> Furthermore, the role of the pharmacist in the education of patients on the TCM matter should be emphasized since they are the only health care professionals who receive formal education on phytotherapy through their compulsory curriculum.<sup>37</sup>

The claim that these therapies are natural is often emphasized by patients.<sup>6,17</sup> Interestingly, TCMs (especially phytotherapy) are frequently perceived as completely safe and non-harmful by users.<sup>15</sup> Terms natural (or herbal) and safe are often used synonymously by patients.<sup>35</sup> Unfortunately, they are also unaware that phytopreparations have a great potential for exhibiting both side effects and interactions with conventional drugs.

Most of our patients had no side effects (90.7%) and the tolerability is declared as excellent (39.8%) or good (52.6%). The use of TCMs for GI disorders was believed to have had no side effects in 75% of patients, in a survey conducted in the United States.<sup>7</sup>

Concerning efficacy of used phytopreparations, the majority of users noticed or believed that there was a positive change in their post-treatment health status (72% and 20.3%, respectively). Other studies also found similar results, where over 80–96% of TCM users (phytotherapy included) perceived them as helpful.<sup>7,17</sup> Specifically, 62% of patients in one survey said that there was an improvement of their GI symptoms.<sup>7</sup> However, only about a fifth of our patients had confirmation of their improvement, which is consistent with the percent of patients that went to the doctor's office for a diagnosis in the first place.

This study has several limitations. Due to the fact that this survey was performed using questionnaire, the research was limited to literate

patients, without communication difficulties, and to those who understand Serbian language. As patients filled out the surveys themselves, it is possible that some of them had memory bias. As the study was conducted in pharmacies, it is possible that some patients not visiting them were excluded. On the other hand, the study has several advantages. A relatively high number of patients was included in the preliminary search for patients with GI complaints. As shown in Table 1, relatively heterogeneous population was included. This research was conducted throughout Vojvodina, successfully including both urban and rural located pharmacies (as opposed to frequent single center studies).

## 5. Conclusion

Phytopreparations play an important role in the prevention and treatment of various digestive diseases, constipation and dyspepsia being the most frequent in our study. Accordingly, laxatives (with various herbs as active principles), artichoke, Iberogast® and silymarin were commonly used HM and HDS. Used phytotherapy is well tolerated, with no major side effects, and at the same time, patients are satisfied with evident or presumed changes. In order to experience the full benefit of TCM usage in patients with GI disorders, it is necessary to enable the integration of TCM within the national health care system and to promote the safety, efficacy and quality of TCMs.

## Conflict of interests

The authors declare that they have no conflict of interest.

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