

PROBIOTICS: RATIONAL APPLICATIONS, PATIENTS' OPINION AND HEALTHCARE PROFESSIONALS' ROLE IN THEIR PROPER SELECTION AND USE

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Probiotics have gained worldwide use in great spectrum of indications. The aim of this study was to analyze the current market of probiotic-enhanced dietary supplements and fortified foods alongside patient's awareness of probiotic use. In addition, this work reviews contemporary knowledge on rational probiotic application in regard to recommendations from 1-4th Yale/Harvard workshop on probiotic use. Structured questionnaire was used to determine the attitude, knowledge level and habits of consumers in Niš, Serbia, in relation to products containing probiotics. A total of 363 individuals (age 18 - 80; 187 female and 160 male) responded to questionnaire which, in addition to the items of attitude, also assessed the health of consumers and acceptance and frequency of consumption of these products. In general, the attitude of respondents was positive and main named indications were different gastrointestinal disorders. Our results show that further information on rational use and potential positive health of probiotics. The healthcare professionals, especially physicians and pharmacists, should play the key role in patients' education.

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Key words: probiotics, respondents' attitude, health benefits

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Introduction

"Probiotics will be to medicine in the twenty-first century as antibiotics and microbiology were in the twentieth century." (As Dr. Michael McCann, MD, physician and researcher)

According to currently widely accepted definition, probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host (1). Probiotics and fermented foods (specifically fermented milks that are usually easily digestible) have a long history of safe use; they provide beneficial microorganisms to the human diet and may benefit human health in many ways (2). Probiotic microbial strains directly isolated from

the fermented foods and beverages are shown to have anti *Helicobacter pylori* activity. Nair et al. Hypothesized that regular consumptions of these probiotics may have protective effect against peptic ulcer and gastric cancer for some populations (3). Since resident microbiota from mouth to rectum is an important factor for homeostasis and for the pathophysiological course of events, probiotics are reasonable and promising means of intervention (4).

The panel of International Scientific Association of Probiotics and Prebiotics recommended that the term "probiotic" should be used only for products that deliver live microorganisms with a suitable viable count of well-defined strains with a reasonable expectation of delivering benefits for the wellbeing of the host (2, 5).

Multi-strain probiotics appear to show greater efficacy than single strains, including strains that are components of the mixtures themselves. However, it is still unclear whether this is due to synergistic interactions between strains or a consequence of the higher probiotic dose used in some studies (6).

Each probiotic strain is a unique organism itself with specific properties that cannot be extrapolated from other, even closely related, strains (7). There are extremely large variations between the most popular taxa used as probiotics: *Lactobacillus* and *Bifidobacterium*. But the phylogenetical differences are also substantial between many of the different Lacto-

bacillus spp. (i.e. between *L. acidophilus*, *L. Fermentum*, *L. reuteri*, *L. plantarum*) (4). Thus, probiotic performance of strains differs and host-related factors also have a great influence on overall health outcomes (7).

The applications of probiotics among others are: childhood and adult diarrhea, systemic immunomodulation, prevention of eczema in infants, the metabolic syndrome, liver injury, inflammatory bowel disorders, irritable bowel syndrome, management of side effects from antibiotics, colorectal cancer and radiation-induced enteritis (4, 5, 8). Bearing in mind huge differences between different types of probiotics, it is to be expected that the human body can respond differently to the different species and strains of probiotics (4).

In order to make recommendations for probiotics clinical use the first workshop meeting at Yale University (in conjunction with Harvard University), which included experts in the field of probiotic orga-

nisms, occurred in 2006. Second Yale/ Harvard workshop was held two years later, third in 2011 and fourth in March 2015 (9-12). At the last meeting the liver disease was included in to recommendations for the first time.

Since decision which probiotic to use in which clinical condition has remained confusing in some clinical conditions even for healthcare professionals, in this article we adopted and listed recommendations from these workshops on probiotic use (Table 1.) alongside brief overview of probiotic containing products from Serbian market (Table 2.).

The aim of this study was to analyze the market of probiotic-enhanced dietary supplements and fortified foods alongside patient's awareness and attitudes on probiotic use. In addition, this work reviews contemporary knowledge on rational probiotic application alongside recommendations from 1-4th Yale / Harvard workshop on probiotic use.

Table 1. Yale/ Harvard workshop recommendations for probiotic use (9 - 12)

Clinical Condition	No*	Specific probiotic strain
DIARRHEA		
Infectious childhood—treatment	1	<i>Lactobacillus</i> GG (LGG), <i>Saccharomyces boulardii</i> , <i>Lactobacillus reuteri</i> SD2112
Prevention of infection	2	<i>S. boulardii</i> , LGG
Prophylaxis of antibiotic-associated diarrhea	1	<i>S. boulardii</i> , LGG, combination of <i>L. casei</i> DN114 G01, <i>L. bulgaricus</i> , <i>Streptococcus thermophilus</i>
Prevention of <i>Clostridium difficile</i> associated diarrhea	2/3	LGG, <i>S. boulardii</i>
Prevention of recurrent <i>Clostridium difficile</i> associated diarrhea	2/3	<i>S. boulardii</i> , LGG, fecal microbiota transplant
INFLAMMATORY BOWEL DISEASE		
Pouchitis	1/3	VSL#3
Ulcerative colitis	2	<i>Escherichia coli</i> Nissle, VSL#3
• Inducing remission	1	<i>E. coli</i> Nissle, VSL#3
• Maintenance	3	<i>E. coli</i> Nissle, <i>S. boulardii</i> , LGG
• Crohn's	2	<i>Bifidobacterium infantis</i> B5624, VSL#3
IRRITABLE BOWEL SYNDROME	3	<i>B. animalis</i> , <i>L. plantarum</i> 299V
NECROTIZING ENTEROCOLITIS	2/3	<i>L. acidophilus</i> NCD01748, <i>B. bifidum</i> NCD01453
IMMUNE RESPONSE	1	<i>L. rhamnosus</i> GG, <i>L. acidophilus</i> LAFT1, <i>L. plantarum</i> , <i>B. lactis</i> , <i>L. johnsonii</i>
ATOPIC ECZEMA ASSOCIATED WITH COW'S MILK ALLERGY	1	LGG, <i>B. lactis</i>
RADIATION ENTERITIS	3	VSL#3, <i>L. acidophilus</i>
VAGINOSIS AND VAGINITIS	3	<i>L. acidophilus</i> , <i>L. rhamnosus</i> GR-1, <i>L. reuteri</i> RC14
LIVER DISEASE		
Hepatic encephalopathy	1	VSL#3
Nonalcoholic fatty liver disease	3	VSL#3, combinations of <i>L. plantarum</i> , <i>L. delbrueckii</i> , <i>L. bulgaricus</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>B. bifidum</i> , <i>S. thermophilus</i> , <i>B. longum</i>
Nonalcoholic fatty liver disease in children	3	VSL#3, LGG
Alcoholic liver disease	3	VSL#3, LGG, <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>B. bifidum</i> , <i>B. longum</i> with oligosaccharides

* No. 1 - effectiveness denotes recommendation based on strong, positive, well-conducted, controlled studies;

No. 2 - positive, controlled studies but also the presence of some negative studies and

No. 3 - some positive studies but clearly an inadequate amount of work to establish the certainty of 1 or 2.

Examinees and methods

This study was conducted in a territory of Niš, Serbia by recording products from market and using face-to-face interview. Our 10 minute, 17-item questionnaire, inspired by similar research of Chin-Lee et al. (13), was designed in order to assess the knowledge, attitude and experience of patients towards probiotics use. The questionnaire consisted of three sections, containing both open and closed forms of questions. The first part consisted of questions related to the socio-demographic characteristics of each individual, while the second one comprised questions dealing with the knowledge on probiotic term and composition, (possible) usage of probiotics and symptomatology indications for probiotic use. The third group of questions dealt with the source of information/ recommendation and the origin of probiotic product; this part also revealed patients previous experience and attitudes towards the usage of probiotics and the data about the effects observed

during its consumption. A total of 363 examinees patients (randomly chosen individuals from 18 to 80 years of age) were invited to complete a questionnaire while waiting in the community pharmacy. All questionnaires were completed anonymously, on a voluntary basis, and individual responses were not linked to specific patients. Patients were able to skip questions they did not wish to answer although its consequences exclusion from the study. Data obtained by filling out the questionnaire were statistically analyzed by SPSS software, 10th version. A probability value of $p < 0.05$ or less was deemed of significance.

Results

Analysis of marketed products (probiotic-enhanced dietary supplements and fortified foods) showed different content of broad spectrum of bacterial and yeast strains (Table 2.).

Table 2. Overview of probiotic containing products (dietary supplements and food) on Serbian market

Product	<i>Lactobacillus helveticus</i>	<i>Lactobacillus rhamnosus</i>	<i>Lactobacillus casei</i>	<i>Lactobacillus plantarum</i>	<i>Lactobacillus acidophilus</i>	<i>Lactobacillus salivarius</i>	<i>Lactobacillus bulgaricus</i>	<i>Lactobacillus reuteri</i>	<i>Lactococcus lactis</i>	<i>Lactobacillus paracasei</i>	<i>Bifidobacterium infantis</i>	<i>Bifidobacterium longum</i>	<i>Bifidobacterium breve</i>	<i>Bifidobacterium lactis</i>	<i>Bifidobacterium bifidum</i>	<i>Pedococcus pentosecans</i>	<i>Streptococcus thermophilus</i>	<i>Saccharomyces boulardii</i>	<i>Bacillus subtilis</i>	CFU per dose
Biogaia protectis®								+												$1 \cdot 10^8$
Bulacol®250																		+		$5 \cdot 10^9$
Esenbak kolic®												+				+				$3 \cdot 10^{11}$
Fermental®		+			+		+								+		+			$> 2 \cdot 10^9$
Flobian®				+																$20 \cdot 10^9$
Medicobiotic		+			+							+						+		$5 \cdot 10^9$
Multilac®	+	+	+	+					+			+	+		+		+			$4,5 \cdot 10^9$
Multilac® Baby		+	+	+	+	+			+	+		+			+					$1 \cdot 10^9$
Probiotic®		+			+							+								$5 \cdot 10^9$
Probalans imuno®*																			+	$2 \cdot 10^9$
Probiochocco+Zn**					+										+					10^9
Probiodrops®	+	+																		$15 \cdot 10^9$
Prolife®					+		+								+		+			$2,1 \cdot 10^9$
ProbioKid immuno®					+						+				+					$5 \cdot 10^9$
Food																				per 100 ml
AB jogurt					+										+					min 10^8
Balans +					+										+					min 10^8
Probiotik jogurt KPlus					+										+					min 10^8

A total of 363 individuals (age from 18 to 80) responded to questionnaires. Since 16 questionnaires were incomplete and excluded from study, investigation included 347 examinees. Socio-demographic data are presented in Table 3. There were more female than male examinees (187 versus 160)

and most (40%) participants were in the age group from 26 to 55. The most common education level was Bachelor's /Master's degree and only 9% (31) of examinees were medical professionals. According to our results there were no gender differences in probiotics use.

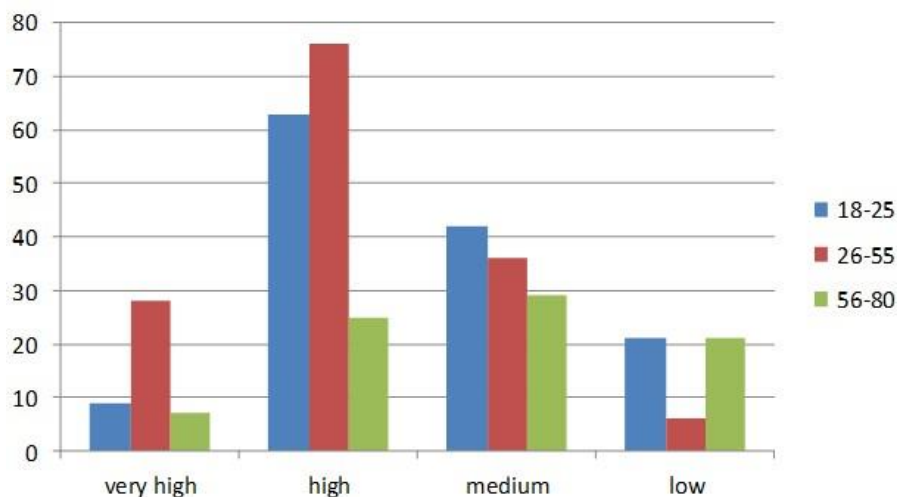
Table 3. Demographics of population – examinees

Demographic characteristic	% (n)
Age	44*
18-25	38 (132)
26-55	40 (139)
56-80	22 (76)
Female	54 (187)
Male	46 (160)
Education level	
High school diploma	15 (52)
Bachelor's /Master's degree	63 (219)
Doctorate or professional degree	22 (76)
Profession	
Pupils/students	33 (115)
Medicinal professionals	9 (31)
Non-medicinal professions	58 (201)

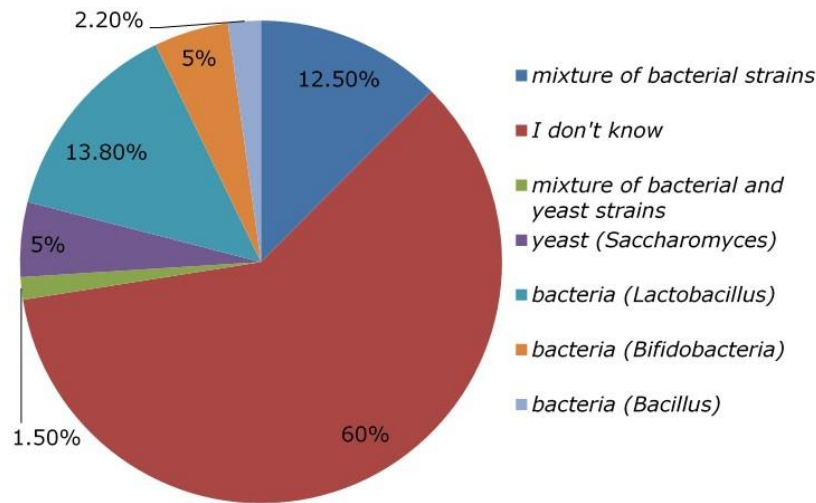
* - mean value of examinees age

On Graphs 1 and 2 are presented main results of questions concerning overall knowledge on term

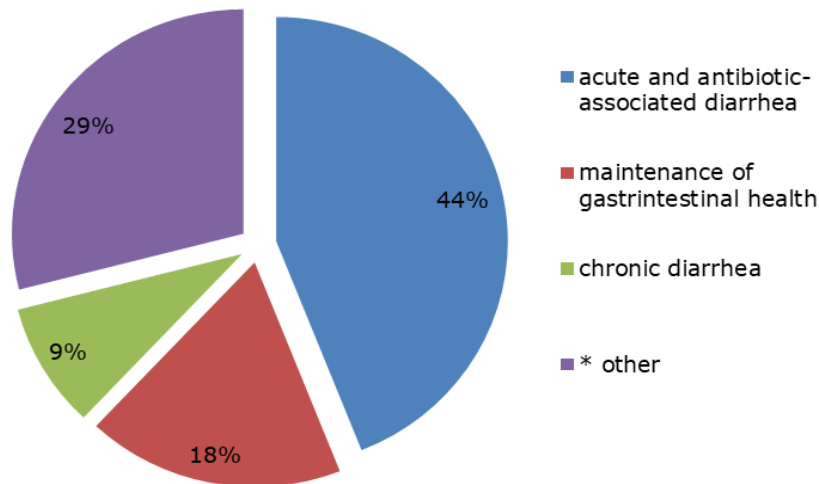
probiotic. Indications for probiotic use according to our examinees are shown on Graph 3.



Graph 1. Level of specific knowledge concerning probiotics shown by different examinees age groups



Graph 2. Content of the probiotic products that were used, according to examinees



Graph 3. Indications for probiotics use identified by respondents (*eczema, allergy, low immune function, dyspepsia, high cholesterol levels)

Discussion

Results of our analysis of probiotic containing products from the Serbian market (on the July 2016) that are presented in Table 2, shows that the largest number of products contains few milliards of colony forming units (CFU) per dose. On the other hand, food products with probiotics contains $1 \cdot 10^9$ (one milliard) of CFU in 1 liter. Thus, patient should take more that 1 lit. of probiotic drink instead of 1 dose of probiotic-enhanced dietary supplement in order to obtain equivalent amount of CFU.

Bearing in mind recommendations from Table 1, in order to get the maximal health benefits, specific probiotic strain should be applied in specific medicinal condition.

Although probiotics have a long history of use, and offer a promising strategy for preventing and treating a large number of diseases, there are still doubts about their proper application and choosing the right probiotic preparations. Examinees were divided into four groups based on their personal perceptions on probiotic term knowledge – from low to very high level (Graph 1.). Graph 2 presents patients' specific knowledge on probiotic/prebiotic contents (Graph 2.). Since less than 10% of examinees were medical professionals we believe that our findings reflect real state of average patient awareness on this topic. Statistically significant difference was observed in the awareness of meaning and importance of probiotic use in relation to the education level of examinees ($p < 0.05$). There was no significant difference between knowledge levels of diffe-

rent age groups. From 243 respondents that have ever consumed probiotic products, about 42% were consumed both probiotic-enriched food and supplements while 45% were used only supplements. Most of the examinees that have previously used probiotic preparation didn't know the composition of probiotic products they used: even 60% answered "I don't know". Recognized probiotic strains were: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium* and *Bacillus*. Around a quarter of respondents was familiar with named bacterial strains and believed that one of them is unique one used in probiotics formulation. Despite the result of our study that less than a half of examinees get familiar with term and use of probiotics through TV or internet promotion, named strains are frequently present in media and consequently adopted by auditorium. Our survey brings forward conclusion that of those patients with some knowledge of probiotics, the most common source of their information were medicinal professionals (45%) followed by family member or friend recommendation. On the contrary, the similar survey find out that the most popular sources of such data were TV, radio and internet (13).

Although previous investigations showed higher frequency of probiotic and prebiotic use in female population, there was no gender difference in our study. Also, there was no statistical significance in probiotic/prebiotic use experiences among three different age groups of examinees. In their questionnaire-based study, Schultz and al. (14) reported lower rate of previous experiences with probiotic use (around one-third of all respondents) toward our survey (52%). It could be, at least partly, explained by the date their study took place (2011.) and by growing popularity of probiotic applications.

The usually named indications for probiotic use are different gastrointestinal disorders. Probiotics indeed have been used in a variety of gastrointestinal illnesses with varying degrees of success and supporting evidence. Some of the proposed mechanisms of its action are multiple and include suppression or displacement of pathogenic bacteria, enhancement of innate immunity, and promotion of epithelial barrier function (15, 16). Despite the heterogeneity in effectiveness among the patients, the antibiotics, and the probiotic strains or blends, the pooled evidence suggests that adjunct probiotic administration is associated with a reduced risk of antibiotic-associated diarrhea (17).

Patients with inflammatory bowel disease and irritable bowel syndrome (in multicenter study conducted by Mercer et al. in 2012) doubts about the data on probiotics obtained from internet and/or media. They have expressed the need for reliable information from health care professionals (18). Our examinees (around half of all of them) also showed the highest level of trust in the information provided by health professionals. However, Williams et al. (15) tried to determine how perceive and use probiotic-based therapies in practice and concluded that gas-

troenterologists practice patterns did not consistently correlate with published, expert-panel-generated recommendations for evidence based probiotic use.

Only 22 of total 347 examinees linked probiotics and immunology, despite the fact that gut microflora is extremely important for immunological function of GIT (70% of organism's immune cells are located in intestine). In survey of Green et al. (19) respondents were often aware of this probiotic's indication. Since probiotic research is still in its infancy, World Allergy Organization emphasizes that the full implications of probiotic supplementation for the treatment of allergic disease remain to be worked out. Further epidemiologic, immunologic, microbiologic, genetic, and clinical studies are necessary to demonstrate probiotic supplements efficiency in preventing allergy (20).

Probiotics could be locally applied in terms of prevention of recurrent vulvovaginal infections (21). A minority of our female respondents were aware about its positive effects when applied with the antimicrobial treatment in order to prevent vaginal candidiasis.

However, overall findings of this survey suggest that attitude towards probiotics at baseline was positive, as was patient experience with applied preparation. And furthermore, based on the results of our study obtained from voluntary subjects, we can say that average consumer/patient is interested in hearing more about possibilities for rational probiotic application, especially if that information is coming from healthcare professionals.

Conclusion

The great variety of dietary supplements is available today. A growing number of them are probiotic-enriched products. With the right selection and application probiotics could have a health-promoting effect. According to our results there is a certain level of awareness of the population on probiotic supplements and their positive effects, especially those on gastrointestinal health. Of course, this conclusion should be taken with reserve since our examinees were of higher education level than average ones. The healthcare professionals should play the key role in right selection and rational use of probiotics as well as in providing relevant public information on benefits of consuming probiotic products. Since probiotics enriched dietary supplements are over-the-counter products, further education of patients by health care professionals is preferred for recognizing their proper indications and applications.

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PROBIOTICI: RACIONALNA PRIMENA, STAVOVI BOLESNIKA I ULOGA ZDRAVSTVENIH PROFESIONALACA U NJIHOVOJ PRAVILNOJ SELEKCIJI I PRIMENI

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Upotreba probiotičkih dijetetskih preparata je poslednjih godina u porastu, kao i njihova širina indikacijskog područja. Cilj ovog istraživanja bio je analiza postojećih prehrambenih proizvoda i dijetetskih suplemenata koji sadrže probiotike na našem tržištu. Pored toga, rad evaluira nivo znanja i uverenja bolesnika u vezi sa upotrebom probiotika, a u odnosu na postojeće preporuke u literaturi (preporuke radionica o upotrebi probiotika u organizaciji Yale/Harvard). Upitnik je sačinjen sa ciljem spoznaje stavova i nivoa znanja ispitanika o probioticima. Ispitanici koji su birani slučajno na teritoriji grada Niša (187 žena i 160 muškaraca, uzrasta od 18 do 80 godina) odgovarali su na pitanja vezana za učestalost i način upotrebe probiotika i ulogu zdravstvenih profesionalaca u sticanju informacija o mogućim pozitivnim zdravstvenim efektima upotrebe probiotičkih preparata. Uočen je pozitivan stav ispitanika prema upotrebi probiotičkih preparata, a najčešće navođene indikacije za primenu su različiti poremećaji gastrointestinalnog trakta. Rezultati rada ukazuju na potrebu za informisanjem o racionalnoj primeni i mogućim pozitivnim zdravstvenim ishodima upotrebe probiotika. Zdravstveni profesionalci, posebno lekari i farmaceuti, treba da imaju odlučujuću ulogu u podršci i daljoj edukaciji bolesnika.

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Ključne reči: probiotici, stav ispitanika, pozitivni zdravstveni ishodi