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Patient's knowledge and awareness about the effect of the over-the-counter (OTC) drugs and dietary supplements on laboratory test results: a survey in 18 European countries

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Abstract

Background: Nowadays over-the-counter (OTC) drugs and dietary supplements are widely used. Their use can have a significant impact on the validity of laboratory results. The aim of this multicenter European study was to determine the frequency of consumption of various dietary products and OTC drugs among patients and explore their level of knowledge and awareness about the potential impact of various products on laboratory test results.

Methods: Eighteen European countries participated in this study. The survey was carried out anonymously on a subsequent series of outpatients (n = 200) in each participating country. Included were patients who were referred to the laboratory for blood sampling and who voluntarily agreed to participate in the study. The survey included questions about the frequency of consumption of various products, awareness of the importance of informing physicians and laboratory staff about it and information about influence of preanalytical factors in general on laboratory test results.

Results: In total, 68% of patients were regularly taking at least one OTC drug or dietary supplement. The frequency of patients consuming at least one OTC drug or dietary supplement differed between countries (p = 0.001). Vitamins (38%), minerals (34%), cranberry juice (20%), acetylsalicylic acid (ASA) (17%) and omega fatty acids (17%) were the most commonly used in our study.

Conclusions: The use of various OTC drugs and dietary supplements is highly prevalent in Europe and patients are often not willing to disclose this information to the laboratory staff and ordering physician. The education of both patients and healthcare staff is needed.

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Keywords: diagnostic errors; dietary supplements; over-the-counter drugs; preanalytical phase; preanalytical variability.

Introduction

There is ample evidence in the literature confirming the effect many of over-the-counter (OTC) drugs, dietary supplements (juices, various herbal preparations) and other preanalytical factors on laboratory test results [1–4]. These effects are exerted through direct (e.g. consumption of minerals) and indirect (e.g. induction or inhibition of various enzymes) mechanisms and may be divided into acute (e.g. increase of glucose concentration after coffee consumption) and chronic (e.g. increase of liver enzymes as a consequence of alcohol consumption) [5].

Many OTC drugs and dietary supplements are widely used by patients (e.g. ginkgo extracts for dementia and memory loss, *Sylibum marianum* for improved liver function, garlic for atherosclerosis and lipid reduction, herbal remedies to complement conventional therapy, etc.), healthy adults (vitamins, minerals, proteins, non-steroidal anti-inflammatory drugs, vinegar, etc.) and even children [6–9]. Their use can have a significant impact on the metabolic processes, the effect of simultaneously used drugs prescribed by the physician and the validity of the laboratory results.

On average, an American household annually spends 338 US dollars on OTC products (drugs and dietary supplements) [10]. According to German Federal Health Reporting, OTC self-medication in Germany in 2006 represented a market with an annual sale of over 5.4 billion Euros, whereas the annual expenditure in USA on more than 85,000 different combinations of vitamins, minerals, botanicals, amino acids, probiotics and other supplement ingredients rose to nearly 32 billion US dollars [11, 12]. Obviously, OTC products are considered as an attractive medical alternative due to their affordability and accessibility, but also because it is generally believed that OTC products are safe and healthy.

Unfortunately, despite such prevalent use of OTC drugs, herbal medicines and dietary supplements in the general population, users are mostly uninformed about how they affect their health, metabolism, drug interactions and possible effect on the results of blood tests. One recent study in Australia showed that pharmacy staff often fail to provide sufficient spoken information to OTC users. Furthermore, in the same study consumers tended not to read OTC labels or leaflets, especially if they were familiar with the product [13]. Moreover, as was nicely demonstrated by a recent Israeli study on children aged 0–18 years, although the use of complementary and alternative medicine was common among hospitalized pediatric patients, it was very often undocumented in medical records and commonly overlooked by the medical staff [14].

There is not much data in the literature about the frequency of consumption of various dietary products, vitamins or OTC drugs among the users of laboratory services. Their awareness and opinions about the potential impact of various products on laboratory test results is also unknown. Failure to share this information with the laboratory staff may cause erroneous and misleading results and lead to diagnostic errors.

Our hypothesis was that the users of laboratory services very commonly consume self-prescribed OTC drugs and/or other dietary supplements. We also hypothesized that they are unaware of the effect such products have on laboratory test results. Finally, it was our belief that they are neither reporting the use of such products to their physician nor to the laboratory staff.

The aim of this multicenter European study was therefore to:

(i) determine the frequency of consumption of various dietary products, vitamins or medicaments among the users of laboratory services.
(ii) determine the level of knowledge, awareness and opinion of users of laboratory services about the potential impact of various products on laboratory test results.

Materials and methods

This study was conducted in the period of January 2015–October 2015. An invitation was sent to 18 randomly selected European countries of which 17 agreed to participate. In total 18 countries participated in this study (Croatia and 17 other European countries).

The list of participating laboratories is presented in Table 1.

All participating countries received detailed instructions on how to perform the survey. In terms of epidemiology, age groups as well as the gender of participants were registered. The survey was carried out anonymously on a subsequent series of outpatients who were referred to laboratory for blood sampling and who voluntarily agreed to participate in the study. Details about the Institution where the survey was conducted were collected for each participating country.

The survey was translated into the local language of each participating country. If required by the local institutional policy, ethical approval was granted for the study by the respective Institutional Ethical Committee (Portugal, Turkey and Bosnia and Herzegovina). The survey included questions about the frequency of consumption of various products, awareness of the importance of informing physicians and laboratory staff about it and information about influence of preanalytical factors in general on laboratory test results (Figure 1). Each country was asked to collect 200 surveys. Raw data were sent to the team in Croatia, for data entry and analysis.

Table 1: The list of participating laboratories.

	Country	Details about the institution		
		Laboratory	Hospital (city)	Number of beds
1.	Albania	Laboratory Department, Clinical Biochemistry Laboratory	University Hospital Center "Mother Teresa", Tirana	1600
2.	Austria	Department of Laboratory Medicine	University Hospital Salzburg/ Landeskrankenhaus	1143
3.	Bosnia and Herzegovina	Department for Laboratory Diagnostics	University Clinical Centre of the Republic of Srpska	1000
4.	Croatia	University Department of Chemistry	Clinical Hospital Center "Sestre milosrdnice", Zagreb	863
5.	Denmark	Department of Clinical Biochemistry and Pharmacology	Odense University Hospital	1225
6.	Hungary	Department of Laboratory Diagnostics	Szabolcs -Szatmár- Bereg County Hospitals and University Teaching Hospital, Nyíregyháza	2979
7.	Lithuania	Centre of Laboratory Medicine	Vilnius University Hospital Santaros Klinikos	1200
8.	Macedonia	Avicena Laboratory Skopje[a]	Private Diagnostic Laboratory-laboratory on field	n/a
9.	Montenegro	Center for Clinical-Laboratory Diagnostic	Clinical Center of Montenegro	800–1000
10.	Poland	Department of Laboratory Medicine	Antoni Jurasz University Hospital No. 1, Bydgoszcz	900
11.	Portugal	Department of Clinical Pathology, São João Hospital Center	University Hospital Centre	1100
12.	Russia	Clinical Diagostic Laboratory	Clinical Hospital Saint Luke	374
13.	Serbia	Policlinic Laboratory Diagnostics Department, Center for Medical Biochemistry	Clinical Center of Serbia	3600
14.	Slovakia	synlab slovakia s.r.o. Prešov	Private Diagnostic Laboratory, Prešov	1248
15.	Slovenia	Department for Laboratory Diagnostics	University Clinical Centre Maribor	1311
16.	Spain	Clinical Laboratory	University Hospital Arnau de Vilanova, Lleida	600
17.	The Netherlands	Department of Clinical Chemistry	Academic Medical Center, Amsterdam	1000
18.	Turkey	Central Laboratory	Umraniye Research and Training Hospital, Istanbul	326

[a]400–500 patients per day.

Statistical analysis

Statistical analysis was performed using EXCEL (Microsoft, Redmond, WA, USA) and MedCalc statistical software 12.7.2.0 (MedCalc Software, Ostend, Belgium). Data are presented as counts/numbers and percentages. χ^2- and z-Tests were used to compare frequencies and proportions between categories. Level of significance was set at 0.05.

Results

Two-hundred patients were surveyed in each participating country (n = 18). With the exception of four countries, patients were always interviewed by the laboratory staff. In Austria and Slovenia patients filled out the form themselves, whereas in Bosnia and Herzegovina and Lithuania surveys were collected in a combined manner (some patients filled questionnaires themselves, while some were assisted by the laboratory team).

Out of 3600 patients who participated in this study, 2238 (62%) were females. Most of the participants (68%) were in the age ranges 26–45 and 46–65 years (35% and 33%, respectively), whereas only a minority was under the age of 25 (13%) or above 65 years (19%). In the entire group, 68% of patients were regularly taking at least one OTC drug or dietary supplement. The frequency of patients consuming at least one OTC drug or dietary supplement differed significantly between countries ($p = 0.001$, Figure 2).

In the entire group of patients, women were more likely to take at least one OTC drug or dietary supplement than men (71% vs. 62%, $p < 0.001$). Patients in the age of

Institution: Interviewed by: Questionnaire Nº:

Date:

Patient age (years):

☐ ≤ 25 ☐ 26 - 45 ☐ 46 – 65 ☐ ≥ 65

Gender:

☐ male ☐ female

1) Are you taking regularly any of the following products? If yes, please state for how long?

Products	≤ 7 days	8-30 days	≥ 30 days	No
1. Acetylsalicylic acid (Aspirin) (not ordered by physician)				
2. Aloe vera (Aloe Barbadensis Miller)				
3. Cranberry (tea, capsules)				
4. Red yeast rice				
5. Ginkgo Biloba				
6. Minerals (Ca, Mg, Zn, Se, Fe, etc.)				
7. Noni juice				
8. Omega-3 fatty acids				
9. Propolis				
10. Caraway oil (Carum carvi)				
11. Silymarin (Silybum marianum)				
12. Vitamins (A, B, C, D, E, etc.)				
13. Green coffee bean extract				
14. Weight loss supplements				
15. other (please specify):*				

** other: apple cider vinegar (capsules), guarana (Paullinia cupana), royal jelly, papaya enzyme (chewable tablets) echinacea, Green magma (Hordeum vulgare) beta-glucan, hyaluronic acid, garlic capsules, evening primrose oil (Oenothera biennis), neem (Azadirachta indica) etc.*

2) Does your physician know that you take these products?

☐ yes ☐ no ☐ not applicable

3) Is it important to inform your physician that you are taking* some of the listed products?
(*patients who are not taking any of the listed products should simply give their opinion about the statement)

☐ yes ☐ no

4) Is it important to inform the laboratory staff that you are taking* some of the listed products?
(*patients who are not taking any of the listed products should simply give their opinion about the statement)

☐ yes ☐ no

5) What do you think, could the below listed factors affect the laboratory tests results?

Factor	yes	no	I don't know
Intense physical activity on the day before the blood sampling**			
Alcohol consumption on the day before the blood sampling			
Consumption of coffee on the day before the blood sampling			
Consumption of grapefruit on the day before the blood sampling			
Consumption of broccoli 3 days before the blood sampling			
Consumption of any of the products from the Table 1.			

*** cycling, tennis, running*

Figure 1: Survey used in this study (in 18 laboratories, on 3600 patients).

46–65 were most likely to take at least one OTC drug or dietary supplement, relative to younger and older patients ($p < 0.001$).

Most commonly used drugs and dietary supplements in our study were vitamins (38%), minerals (34%), cranberry juice (20%), acetylsalicylic acid (ASA) (17%) and omega fatty acids (17%) (Figure 3). The category *Other* contained OTC drugs and dietary supplements which were not included in the questionnaire, such as hyaluronic acid, aronia juice, chia seeds, echinacea, proteins and carnitine,

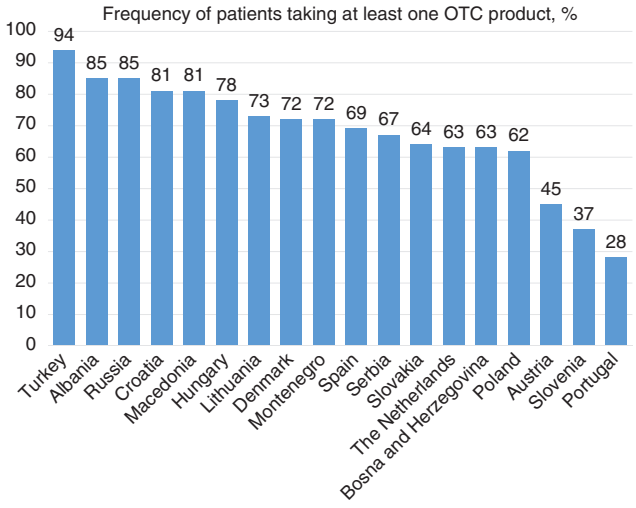

Figure 2: Distribution of countries (n = 18) relative to the frequency of patients (n = 3600) taking at least one OTC drug or dietary supplement.

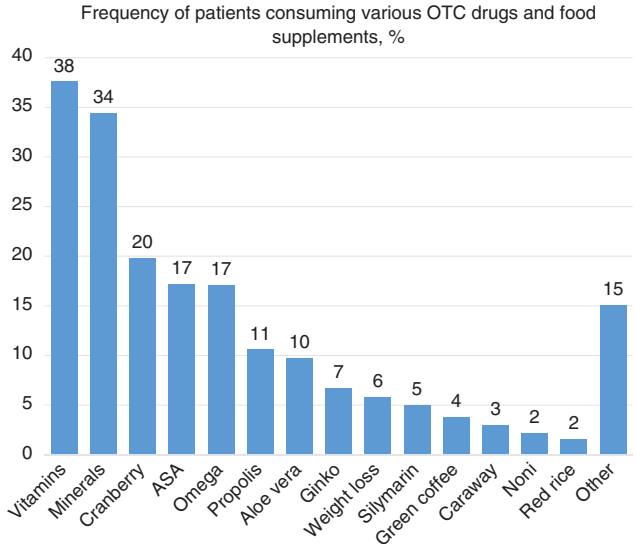

Figure 3: Frequency of consumption of OTC drugs or dietary supplements by all patients in this study (n = 3600).

apple cider vinegar capsules, garlic capsules, guarana, green magma and some other, none of them presented in the entire survey population with a frequency of use >1%.

The frequency of the most commonly used OTC drugs and dietary supplements differed significantly between countries ($p < 0.001$, Table 2).

Countries with the highest overall rate of consumption of individual OTC products and dietary supplements were Turkey, Russia, Hungary and Croatia. Slovenia, Austria and Portugal had the lowest frequency of OTC and dietary supplements use among the surveyed populations. There was a ten-fold or even greater difference between the frequency of the use of some individual OTC products and dietary supplements (e.g. 3% vs. 60.5% for ASA, 1.5% vs. 36% for weight loss products, in Slovenia and Turkey, respectively) between Slovenia and Turkey.

Informing the physician and laboratory staff

Replies to questions 2–5 are presented in Tables 3 and 4. In those patients who were taking at least one OTC drug or dietary supplement (n = 2429), 49% replied negatively when asked if their physician knew about it. Countries where most patients did not share this information with their physician were Turkey (82%) and Albania (65%), whereas countries where most patients had disclosed this information with their physician were Denmark (73%), Lithuania (70%), Austria (63%) and Macedonia (63%).

When asked whether it is important to inform their physician, 70% of surveyed patients (n = 3600) replied positively. The frequency of positive response to this question ranged from 55% (Russia) to 82% (Lithuania). Interestingly, although patients predominantly did not share the information about their consumption of OTC drugs or dietary supplements with their physician in Turkey and Albania, the majority of them still believed that it is important to inform their physician about it (63% and 73%, in Turkey and Albania, respectively).

Patients across all age groups were equally likely to inform their physician ($p = 0.373$), whereas women were more likely to inform their physician about the use of various OTC drugs and dietary supplements than men ($p = 0.001$).

Only 55% of participants considered it important to inform the laboratory staff about their consumption of OTC drugs and dietary supplements. More patients felt that they should share this information with their physician rather than with the laboratory staff (70% vs. 55%, $p < 0.001$). Out of those who considered they should inform their physician about their consumption of OTC drugs and dietary supplements, 30% did not consider it important to disclose this information to the laboratory staff.

Countries where more than 2/3 of patients considered they should inform the laboratory staff about their consumption of OTC drugs and dietary supplements were Macedonia (79%), Slovenia (70%), Bosnia and Herzegovina (67%) and Poland (67%). Countries where the lowest proportion of patients felt they should share this information with the laboratory staff were Denmark (43%), Hungary (43%), Spain (40%) and Slovakia (37%).

Table 2: Frequency of patients (n = 3600) regularly taking various OTC drugs and dietary supplements, in 18 countries participating in this study.

	ASA, %	Aloe vera, %	Cranberry, %	Red rice, %	Ginko, %	Minerals, %	Noni, %	Omega, %	Propolis, %	Caraway, %	Silymarin, %	Vitamins, %	Green coffee, %	Weight loss, %	Other, %
Albania	34.5	11	38	0	1.5	17	0	13	2	0	0	22	0	3.5	24
Austria	14.5	2.5	6	0	2	19	0.5	4.5	2	0	0	23.5	0	0.5	5.5
Bosnia and Herzegovina	13.5	2	18.5	0	4.5	21.5	2.5	10.5	19.5	3.5	1.5	31.5	2	3	6.5
Croatia	17	6.5	32.5	12.5	7	50	0.5	24	11.5	0.5	3	47	0.5	1.5	25.5
Denmark	17.5	5.5	8	2.5	2.5	38	2.5	23	1.5	0.5	1.5	51	0	2	6.5
Hungary	33	23.5	11.5	0.5	8.5	63.5	1	7.5	6	1	13	49	7.5	9.5	21
Lithuania	13.5	4	15.5	0	6	41	1.5	35	10	1	13	44.5	1.5	1	4
Macedonia	12.5	14	5	0.5	9.5	26.5	2.5	21	10	0	1	39.5	3.5	5.5	5.5
Montenegro	11	9.5	42.5	4	6	44	1	16	28.5	3	0.5	41.5	0	3.5	17
Poland	6	7	14	1	6	37	3.5	18.5	5	6.5	4	35	2	5.5	6
Portugal	3.5	0.5	10.5	3	3	16	2	10	0	0	0	20	4.5	9	4.5
Russia	32	5	45	2.5	5	42	3	24	16	2.5	12	50.5	7.5	4.5	9.5
Serbia	10	5	7	0.5	5	39.5	1	10.5	14	0.5	1	44.5	0.5	3	11
Slovakia	7.5	9	14	0.5	12.5	33	1	12	15	2.5	5.5	32.5	1	7.5	5.5
Slovenia	3	2	4.5	0.5	0.5	17	2.5	5	5.5	1	2.5	20	1	1.5	8
Spain	14	14.5	19.5	0.5	1	29.5	1	16.5	8.5	0	0	27.5	1.5	7	36
The Netherlands	5.5	3.5	15	0.5	1	26.5	0	17.5	0.5	0	0	39.5	0.5	1	10
Turkey	60.5	49	49	0.5	39.5	58.5	14	39	35.5	32	32	58	34	36	66

Table 3: Replies to the questions 2–4 of the questionnaire (n = 3600).

	Country	Are you taking at least one OTC drug or dietary supplement? Yes; n (%)	Does your physician know? Yes; n (%)	Is it important to inform your physician about it? Yes; n (%)	Is it important to inform laboratory staff about it? Yes; n (%)
1.	Albania	169 (85%)	59 (35%)	146 (73%)	125 (63%)
2.	Austria	90 (45%)	57 (63%)	134 (67%)	129 (65%)
3.	Bosnia and Herzegovina	125 (63%)	66 (53%)	141 (70%)	134 (67%)
4.	Croatia	161 (81%)	85 (53%)	140 (70%)	96 (48%)
5.	Denmark	144 (72%)	105 (73%)	134 (67%)	85 (43%)
6.	Hungary	155 (78%)	92 (59%)	139 (70%)	85 (43%)
7.	Lithuania	145 (73%)	101 (70%)	165 (82%)	99 (50%)
8.	Macedonia	161 (81%)	101 (63%)	163 (82%)	158 (79%)
9.	Montenegro	144 (72%)	65 (45%)	144 (72%)	123 (62%)
10.	Poland	124 (62%)	51 (41%)	148 (74%)	133 (67%)
11.	Portugal	56 (28%)	27 (48%)	150 (75%)	104 (52%)
12.	Russia	170 (85%)	80 (47%)	109 (55%)	91 (46%)
13.	Serbia	133 (67%)	80 (60%)	148 (74%)	101 (50%)
14.	Slovakia	127 (64%)	58 (46%)	118 (59%)	74 (37%)
15.	Slovenia	74 (37%)	39 (53%)	149 (74%)	139 (70%)
16.	Spain	138 (69%)	70 (51%)	143 (71%)	83 (40%)
17.	The Netherlands	126 (63%)	64 (51%)	123 (62%)	96 (48%)
18.	Turkey	187 (94%)	34 (18%)	126 (63%)	118 (59%)
	Total	2429 (68%)	1234 (51%)	2520 (70%)	1973 (55%)

The effects of preanalytical factors on test results

When asked if intense physical activity or consumption of alcohol, coffee, grapefruit and any of the products from Table 1 in the questionnaire on the day before the blood sampling, or broccoli 3 days before the blood sampling, may affect laboratory test results, surveyed patients were most concerned with alcohol (76%) and intense physical activity (52%), whereas they were least concerned with the consumption of grapefruit (30%) and broccoli (20%). Spain was the country with the highest level of awareness among patients about the effect of consumption of some products from Table 1 on the day before the blood sampling (89%) and intense physical activity (74%) on laboratory test results. Patients in Denmark (38%), Hungary (38%) and Slovenia (36%) were least aware of the effect of the intense physical activity the day prior to blood sampling could have on laboratory test results.

Less than half of the surveyed patients knew that some OTC drugs and dietary supplements could affect laboratory test results (47%). Especially low awareness about it was observed in Turkey (26%), Slovakia (27%), Macedonia (28%), Russia (30%), Austria (31%) and Albania (32%).

A high proportion of patients in the entire group considered that consumption of coffee on the day before the blood sampling may affect the results of laboratory testing (41%) with additional 18% of participants who stated they were unsure about this matter.

Discussion

Key observations of our study are as follows: a substantial number of the users of laboratory services in 18 European countries are taking different dietary supplements and various OTC drugs and a large proportion of these patients do not consider they should disclose this information with the laboratory staff and/or responsible physician. Moreover, these patients are not aware of the potential effect various dietary supplements, OTC drugs, coffee, alcohol and physical activity may have on the laboratory test results.

Our observations indicate that dietary supplements and OTC drugs are more frequently used by middle aged patients and that women are more frequent consumers than men, which is in line with other similar reports in the literature. According to the National Health and Nutrition Examination Survey (NHANES) data, the use of dietary supplements in USA is widespread among US adults (53% in 2003–2006) and is increasing over time [15]. USA women are more commonly consuming dietary supplements than men and most common dietary supplements used are multivitamins and multiminerals. This is in line

Table 4: Replies to the question 5 of the questionnaire (n = 3600).

	Country	Is the below listed factor affecting laboratory tests results?																	
		Intense physical activity (e.g. cycling, tennis, running)[a]			Alcohol[a]			Coffee[a]			Grape fruit[a]			Broccoli 3 days before the blood sampling			Any of the products from the Table 1[a]		
		Yes n (%)	No n (%)	DN n (%)	Yes n (%)	No n (%)	DN n (%)	Yes n (%)	No n (%)	DN n (%)	Yes n (%)	No n (%)	DN n (%)	Yes n (%)	No n (%)	DN n (%)	Yes n (%)	No n (%)	DN n (%)
1.	Albania	87 (44.5%)	34 (17%)	79 (39.5%)	159 (79.5%)	17 (8.5%)	24 (12%)	107 (53.5%)	48 (24%)	45 (22.5%)	43 (21.5%)	61 (30.5%)	96 (48%)	45 (22.5%)	75 (37.5%)	80 (40%)	65 (32%)	23 (12)	112 (56%)
2.	Austria	95 (47.7%)	61 (30.5%)	44 (22%)	56 (28%)	127 (63.5%)	17 (8.5%)	98 (49%)	59 (29.5%)	43 (21.5%)	107 (53.5%)	37 (18.5%)	56 (28%)	121 (60.5%)	21 (10.5%)	58 (29%)	63 (31%)	53 (27%)	84 (42%)
3.	Bosnia and Herzegovina	99 (49.5%)	63 (31.5%)	38 (19%)	139 (69.5%)	46 (23%)	15 (7.5%)	79 (39.5%)	84 (42%)	37 (18.5%)	44 (22%)	87 (43.5%)	69 (34.5%)	22 (11%)	96 (48%)	82 (41%)	81 (40%)	56 (28%)	63 (32%)
4.	Croatia	88 (44%)	62 (31%)	50 (25%)	165 (82.5%)	22 (11%)	13 (6.5%)	93 (46.5%)	67 (33.5%)	40 (20%)	46 (23%)	64 (32%)	90 (45%)	23 (11.5%)	65 (32.5%)	112 (56%)	95 (47%)	52 (26%)	53 (27%)
5.	Denmark	76 (38%)	89 (44.5%)	35 (17.5%)	150 (75%)	35 (17.5%)	15 (7.5%)	62 (31%)	109 (54.5%)	29 (14.5%)	53 (26.5%)	108 (54%)	39 (19.5%)	43 (21.5%)	106 (53%)	51 (25.5%)	84 (42%)	66 (33%)	50 (25%)
6.	Hungary	77 (38%)	81 (41%)	42 (21%)	180 (90%)	10 (5%)	10 (5%)	89 (44.5%)	75 (37.5%)	36 (18%)	36 (18%)	70 (35%)	94 (47%)	27 (13.5%)	70 (35%)	103 (51.5%)	125 (62%)	29 (15%)	46 (23%)
7.	Lithuania	106 (53%)	54 (27%)	40 (20%)	181 (90.5%)	10 (5%)	9 (4.5%)	83 (41.5%)	86 (43%)	31 (15.5%)	59 (29.5%)	85 (42.5%)	56 (28%)	23 (11.5%)	101 (50.5%)	76 (38%)	116 (58%)	39 (20%)	45 (22%)
8.	Macedonia	130 (65%)	47 (24%)	23 (11%)	160 (80%)	31 (15.5%)	9 (4.5%)	105 (52.5%)	77 (38.5%)	18 (9%)	62 (31%)	87 (43.5%)	51 (25.5%)	31 (15.5%)	89 (44.5%)	80 (40%)	56 (28%)	45 (22%)	99 (50%)
9.	Montenegro	133 (67%)	32 (16%)	35 (17%)	175 (87.5%)	9 (4.5%)	16 (8%)	74 (37%)	86 (43%)	40 (20%)	89 (44.5%)	61 (30.5%)	50 (25%)	45 (22.5%)	73 (36.5%)	82 (41%)	120 (60%)	20 (10%)	60 (30%)
10.	Poland	129 (65%)	38 (19%)	33 (16%)	173 (86.5%)	15 (7.5%)	12 (6%)	53 (26.5%)	111 (55.5%)	36 (18%)	71 (35.5%)	65 (32.5%)	64 (32%)	29 (14.5%)	90 (45%)	81 (40.5%)	104 (52%)	29 (15%)	67 (33%)
11.	Portugal	86 (43%)	65 (33%)	49 (24%)	139 (69.5%)	41 (20.5%)	20 (10%)	69 (34.5%)	89 (44.5%)	42 (21%)	39 (19.5%)	84 (42%)	77 (38.5%)	39 (19.5%)	92 (46%)	69 (34.5%)	83 (41%)	46 (23%)	71 (36%)
12.	Russia	108 (54%)	59 (30%)	33 (16%)	163 (81.5%)	18 (9%)	19 (9.5%)	115 (57.5%)	42 (21%)	43 (21.5%)	65 (32.5%)	56 (28%)	79 (39.5%)	35 (17.5%)	76 (38%)	89 (44.5%)	60 (30%)	35 (18%)	105 (52%)
13.	Serbia	98 (49%)	=35 (17%)	67 (34%)	163 (81.5%)	21 (10.5%)	16 (8%)	79 (39.5%)	75 (37.5%)	46 (23%)	90 (45%)	=39 (19.5%)	=71 (35.5%)	43 (21.5%)	48 (24%)	109 (54.5%)	130 (65%)	22 (11%)	48 (24%)
14.	Slovakia	109 (55%)	54 (27%)	37 (18%)	165 (82.5%)	27 (13.5%)	8 (4%)	46 (23%)	121 (60.5%)	33 (16.5%)	33 (16.5%)	91 (45.5%)	76 (38%)	26 (13%)	91 (45.5%)	83 (41.5%)	55 (27%)	68 (34%)	77 (39%)
15.	Slovenia	72 (36%)	57 (28%)	71 (34%)	137 (68.5%)	37 (18.5%)	26 (13%)	88 (44%)	65 (32.5%)	47 (23.5%)	48 (24%)	77 (38.5%)	75 (37.5%)	31 (15.5%)	83 (41.5%)	86 (43%)	89 (44%)	43 (25%)	68 (34%)
16.	Spain	148 (74%)	37 (18%)	15 (8%)	183 (91.5%)	13 (6.5%)	4 (2%)	70 (35%)	104 (52%)	26 (13%)	36 (18%)	78 (39%)	86 (43%)	33 (16.5%)	97 (48.5%)	70 (35%)	177 (89%)	14 (7%)	9 (4%)
17.	The Netherlands	99 (49%)	61 (31%)	40 (20%)	160 (80%)	25 (12.5%)	15 (7.5%)	75 (37.5%)	93 (46.5%)	32 (16%)	80 (40%)	71 (35.5%)	49 (24.5%)	29 (14.5%)	106 (53%)	65 (32.5%)	120 (60%)	39 (19.5%)	41 (20.5%)
18.	Turkey	130 (65%)	64 (32%)	6 (3%)	94 (47%)	99 (49.5%)	7 (3.5%)	95 (47.5%)	92 (46%)	13 (6.5%)	72 (36%)	103 (51.5%)	25 (12.5%)	65 (32.5%)	102 (51%)	33 (16.5%)	53 (26%)	95 (47.5%)	52 (26%)
19.		1870 (52%)	993 (28%)	737 (20%)	2742 (76%)	603 (17%)	255 (7%)	1480 (41%)	1483 (41%)	637 (18%)	1073 (30%)	1324 (37%)	1203 (33%)	710 (20%)	1481 (41%)	1409 (39%)	1676 (47%)	805 (22%)	1119 (31%)

[a]On the day before the blood sampling. NA, not applicable; DN, I don't know.

with our data, which indicate that vitamins and minerals are the most frequent dietary supplements among the users of laboratory services in most European countries, with some exceptions (cranberry and ASA were more prevalent than minerals and/or vitamins in some countries, e.g. Albania, Russia, Turkey and Montenegro).

Proper patient preparation is of great importance for achieving accurate and reliable test results as well as for their appropriate interpretation. As proposed by the Working Group for Preanalytical Phase (WG-PRE) of the European Federation for Clinical Chemistry and Laboratory Medicine (EFLM) blood for all blood tests should be taken preferably in the morning (7:00–9:00), after an overnight fast (12 h). During that time, water consumption is permitted, but consumption of alcohol should be avoided for 24 h before blood sampling. Also, in the morning on the day of the blood sampling, patients should refrain from cigarette smoking, tea, coffee and other caffeine containing drinks [16].

Besides being in a fasting state, patients should make sure to avoid any extraordinary or unusual physical activity (marathon running, cold water swimming, etc.) as well as sporadic consumption of any compound which may have an effect on laboratory test results, in the days preceding the blood sampling. Many of the compounds (cinnamon, red rice, cranberry, bitter orange, cayenne pepper, broccoli, grapefruit, etc.) which are known to affect laboratory test results are nowadays widely available as OTC products and dietary supplements.

The list is long and potential effects range from mild to serious. For example, cinnamon ingestion 12 h before the blood sampling or even simultaneous with blood sampling causes a significant decrease of blood glucose and improves insulin sensitivity [17]. Weight loss pills containing cayenne pepper, bitter orange and amphetamine have been demonstrated to lead to myocardial injury accompanied by an increase in concentrations of troponin and CK-MB through the activation of the sympathetic nervous system [18–21]. Consumption of red rice and green tea extract have been associated with liver enzyme abnormalities [22–24]. Red rice is also known to inhibit the HMG-CoA reductase, enzyme involved in the cholesterol synthesis and thus lead to decrease of cholesterol concentration [25]. Cranberry has been reported to increase the activity of paraoxonase, lower PSA and regulate the expression of androgen-responsive genes [26, 27]. Grapefruit and clementine juice may lead to increased tacrolimus trough concentrations in renal transplant patients due to induction of several drug transporters and drug metabolizing enzymes [28]. *Gingko biloba* and *Sylibum marianum* are known to modify the activity of microsomal enzymes and through this mechanism affect the metabolism of many drugs [29, 30]. Broccoli is a potent enzyme inductor, highly effective in protecting the liver from various xenobiotic substances through the induction of detoxification enzymes, glutathione synthesis thus reducing the oxidative stress level [31, 32]. The effects of some dietary supplements and dietary products have been studied in animals but not yet on humans, like the effect of propolis on hematological and serum biochemical parameters in birds and on dementia in rats [33, 34].

Due to all the mentioned issues the self-prescribed use of various OTC drugs, herbal medicines and dietary supplements obviously raises some patient safety concerns. If consumed within the short period before blood sampling, the above listed compounds may cause changes in laboratory test results. Such test results are very difficult to interpret if information about the consumption of the substance underlying or causing these changes is not disclosed to the laboratory staff and ordering physician.

Our study shows that patients are not aware of the need to inform their physician and laboratory staff about the OTC products they are using. This finding is also in line with other findings in the literature: in a study by Tarn and colleagues, only 46% of patients disclosed the use of dietary products to their healthcare provider [35]. This study also suggested that education of healthcare providers might increase the rate of patient disclosure of dietary supplements to the healthcare staff. Another study in Serbia on 288 patients who were taking some herbal medicines or dietary supplements found that even 88.9% of the study participants did not consider it necessary to inform a physician or a pharmacist about their use of herbal medicines or dietary supplements during their therapy with a conventional drug [36]. This study also confirmed that the use of herbal medicines or dietary supplements was more common among middle-aged women, which is fully in line with our observations.

The fact that our study participants were more likely to disclose their use of OTC products to their physician than to the laboratory staff indicates a low level of awareness of laboratory users about the potential effect of various OTC products on laboratory test results.

There are many reasons due to which patients may not be willing to share the information about their use of non-prescribed medicines and dietary supplements to the healthcare staff: lack of understanding of the potential effects of the OTC product, low perception of potential risk associated with OTC products, negative attitude of healthcare professionals about complementary medicine, lack of awareness by hospital staff regarding such practice being the main ones [37].

A multifaceted approach is necessary to address this problem. Educational interventions targeting both healthcare professionals and patients seems like an obvious remedy to this problem. Moreover, clinicians ordering the tests and laboratory staff should be more engaged with patients by asking them direct questions about the use of various self-prescribed products. Educational posters in the waiting areas is another good way to inform patients about the importance of disclosing relevant information to the laboratory staff prior to blood sampling. A standardized questionnaire to be fulfilled before phlebotomy, regarding some most frequent preanalytical factors (including OTC products) which influence laboratory test results, could be one good solution.

Finally, it is up to the regulatory agencies to implement more stringent rules of approval for OTC products which certainly need to include the list of potential side-effects as well as list of potential laboratory abnormalities. New compounds surface every day, and the number of new tests is also increasing. As stated clearly earlier in the discussion, the number of different compounds to interact with the test results are vast. So, how do we keep up our knowledge on this? One potential solution might be an international OTC library, which may be interconnected with our laboratory information systems.

Our study has some limitations. Although we included a large group of patients, the number of patients per each country is rather small. Due to the limited number of participants per country, the respective sample size might not be representative of the entire population of that country. However, even if small by a single country, the overall number of patients included in this study is significant, just as significant is the territorial representation. The overall picture definitely points to the underestimation of the problem. As already stated in the Introduction, there is not much data in the literature about the frequency of consumption of various dietary products, vitamins or OTC drugs among the users of laboratory services, so we hope that this paper could help in improving the awareness about the issue among laboratory professionals. One might also argue that at least in some large European countries large differences in the use of OTC drugs might exist between urban and rural areas. This issue certainly deserves to be addressed in some further studies.

Also, we are aware that our sample might not be representative of a general population. The enrolment of the outpatients in our study might be a source of bias, as we have only included patients who were visiting a laboratory at the time of the study, instead of recruiting randomly recruited individuals from a general population. Nevertheless, we hope that our results provide at least some preliminary insight into the issue, pointing to the need for more extensive work in this field. Obviously, further well-designed studies with a larger number of patients are needed to confirm our observations.

Although all countries were given instructions on the recommended way to perform the survey, there were differences in the way patients were providing their responses. These differences might have influenced the results of our study. Moreover, the observed differences between countries relative to their rate of consumption of OTC products are difficult to interpret without more demographic data. Some future studies will hopefully address this issue and explore whether there are some cultural, socio-demographic reasons underlying these possible differences.

Conclusions

There is a high prevalence of the use of various OTC drugs and dietary supplements among the users of laboratory services in Europe. This fact is easily overlooked, as patients are often not willing to disclose this information to the laboratory staff. It is important to note that the patients are neither sufficiently informed nor aware about the potential impact of these compounds on the laboratory test results. Education of both patients and healthcare staff is warranted to improve this situation in order to minimize the risk of preanalytical errors and ensure quality of laboratory and health service in general.

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References

1. Kaneko R, Ohishi C, Kim M, Shiina M, Kusayanagi S, Ogawa M, et al. Two cases of food additive-induced severe liver damage associated with positive results on lymphocyte stimulation test and for antinuclear antibodies. Clin J Gastroenterol 2012; 5:268–74.
2. Catlin DH, Leder BZ, Ahrens B, Starcevic B, Hatton CK, Green GA, et al. Trace contamination of over-the-counter androstenedione and positive urine test results for a nandrolone metabolite. J Am Med Assoc 2000;284:2618–21.
3. Reyes MA, Actor JK, Risin SA, Dasgupta A. Effect of Chinese medicines Chan Su and Lu-Shen-Wan on serum digoxin measurement by Digoxin III, a new digoxin immunoassay. Ther Drug Monit 2008;30:95–9.
4. Nishiguchi M, Kinoshita H, Higasa K, Taniguchi T, Ouchi H, Minami T, et al. The false positive reaction of the Triage panel drug-of-abuse by herbal drugs ma-huang (Ephedra sinica (Ephedraceae)). Nihon Hoigaku Zasshi 2001;55:331–8.
5. Simundic AM, Nikolac N, Guder WG. Preanalytical variation and preexamination processes. In: Rifai N, Horvath R, Wittwer C, editors. Tietz textbook of clinical chemistry and molecular diagnostics, 6th ed. St. Louis, Missouri, USA: Elsevier, 2017.
6. Nayir T, Okyay RA, Yesilyurt H, Akbaba M, Nazlıcan E, Acık Y, et al. Assessment of rational use of drugs and self-medication in Turkey: a pilot study from Elazıg and its suburbs. Pak J Pharm Sci 2016;29(4 Suppl):1429–35.
7. Brigden M, Smith RE. Acetylsalicylic-acid-containing drugs and nonsteroidal anti-inflammatory drugs available in Canada. Can Med Assoc J 1997;156:1025–8.
8. Cooper RJ. 'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study. BMJ Open 2013;3:e002913. doi:10.1136/bmjopen-2013–002913.
9. Håkonsen H, Hedenrud T. A population-based study of risk perceptions of paracetamol use among Swedes-with a special focus on young adults. Pharmacoepidemiol Drug Saf 2017;26:992–7.
10. Hanson GR, Venturelli PJ, Fleckenstein AE. Drugs and society. Burlington, MA, USA: Jones & Bartlett Learning, 2017.
11. Cohen PA. Hazards of hindsight — monitoring the safety of nutritional supplements. N Engl J Med 2014;370:1277–80.
12. Du Y, Knopf H. Self-medication among children and adolescents in Germany: results of the National Health Survey for Children and Adolescents (KiGGS). Br J Clin Pharmacol 2009;68:599–608.
13. Tong V, Raynor DK, Aslani P. Receipt and use of spoken and written over-the-counter medicine information: insights into Australian and UK consumers' experiences. Int J Pharm Pract 2018;26:129–37.
14. Oren-Amit A, Berkovitch M, Bahat H, Goldman M, Kozer E, Ziv-Baran T, et al. Complementary and alternative medicine among hospitalized pediatric patients. Complement Ther Med 2017;31:49–52.
15. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, et al. Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994). NCHS data brief, no 61. Hyattsville, MD: National Center for Health Statistics; 2011.
16. Simundic AM, Cornes M, Grankvist K, Lippi G, Nybo M. Standardization of collection requirements for fasting samples: for the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chim Acta 2014;432:33–7.
17. Hlebowicz J, Hlebowicz A, Lindstedt S, Bjorgell O, Hoglund P, Holst JJ, et al. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagonlike peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr 2009;89:815–21.
18. Sogut O, Kaya H, Gokdemir MT, Sezen Y. Acute myocardial infarction and coronary vasospasm associated with the ingestion of cayenne pepper pills in a 25-year-old male. Int J Emerg Med 2012;5:5.
19. Sayin MR, Karabag T, Dogan SM, Akpinar I, Aydin M. A case of acute myocardial infarction due to the use of cayenne pepper pills. Wien Klin Wochenschr 2012;124:285–7.
20. Nykamp DL, Fackih MN, Compton AL. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. Ann Pharmacother 2004;38:812–6.
21. Perez-Downes J, Hritani A, Baldeo C, Antoun P. Amphetamine containing dietary supplements and acute myocardial infarction. Case Rep Cardiol 2016;2016:6404856.
22. Patel SS, Beer S, Kearney DL, Phillips G, Carter BA. Green tea extract: a potential cause of acute liver failure. World J Gastroenterol 2013;19:5174–7.
23. De Backer GG. Food supplements with red yeast rice: more regulations are needed. Eur J Prev Cardiol 2017;24:1429–30.
24. García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. Int J Mol Sci 2016;17:537.
25. Patrick L, Uzick M. Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha-tocopherol, red yeast rice, and olive oil polyphenols. A review of the literature. Altern Med Rev 2001;6:248–71.
26. Begcevic I, Simundic AM, Nikolac N, Dobrijevic S, Rajkovic MG, Tesija-Kuna A. Can cranberry extract and vitamin C + Zn supplements affect the in vivo activity of paraoxonase 1, antioxidant potential, and lipid status? Clin Lab 2013;59:1053–60.
27. Student V, Vidlar A, Bouchal J, Vrbkova J, Kolar Z, Kral M, et al. Cranberry intervention in patients with prostate cancer prior to radical prostatectomy. Clinical, pathological and laboratory findings. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016;160:559–65.
28. Theile D, Hohmann N, Kiemel D, Gattuso G, Barreca D, Mikus G, et al. Clementine juice has the potential for drug interactions – in vitro comparison with grapefruit and mandarin juice. Eur J Pharm Sci 2017;97:247–56.
29. Umegaki K, Taki Y, Endoh K, Taku K, Tanabe H, Shinozuka K, et al. Bilobalide in Ginkgo biloba extract is a major substance inducing hepatic CYPs. J Pharm Pharmacol 2007;59:871–7.
30. Zuber R, Modrianský M, Dvorák Z, Rohovský P, Ulrichová J, Simánek V, et al. Effect of silybin and its congeners on human liver microsomal cytochrome P450 activities. Phytother Res 2002;16:632–8.
31. Yoshida K, Ushida Y, Ishijima T, Suganuma H, Inakuma T, Yajima N, et al. Broccoli sprout extract induces detoxification-related gene expression and attenuates acute liver injury. World J Gastroenterol 2015;21:10091–103.
32. Kikuchi M, Ushida Y, Shiozawa H, Umeda R, Tsuruya K, Aoki Y, et al. Sulforaphane-rich broccoli sprout extract improves hepatic abnormalities in male subjects. World J Gastroenterol 2015;21:12457–67.

33. Silva CR, Putarov TC, Fruhvald E, Destro FC, Marques Filho WC, Thomazini CM, et al. Action of Brazilian propolis on hematological and serum biochemical parameters of Blue-fronted Amazons (Amazona aestiva, Linnaeus, 1758) in captivity. Poult Sci 2014;93:1688–94.
34. Nanaware S, Shelar M, Sinnathambi A, Mahadik KR, Lohidasan S. Neuroprotective effect of Indian propolis in β-amyloid induced memory deficit: impact on behavioral and biochemical parameters in rats. Biomed Pharmacother 2017;93:543–53.
35. Tarn DM, Karlamangla A, Coulter ID, Paterniti DA, Knox L, Khang PS, et al. A cross-sectional study of provider and patient characteristics associated with outpatient disclosures of dietary supplement use. Patient Educ Couns 2015;98:830–6.
36. 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. Int J Clin Pharm 2013;35:835–40.
37. Samuels N, Zisk-Rony RY, Zevin S, Becker EL, Yinnon AM, Oberbaum M. Use of non-vitamin, non-mineral (NVNM) supplements by hospitalized internal medicine patients and doctor-patient communication. Patient Educ Couns 2012;89:392–8.