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The role of nutrivigilance for consumer safety

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Abstract. In the current global conditions, of intense pollution, daily stress or sedentary lifestyle, many consumers choose to improve their quality of life, consuming more and more food supplements. We mention that some of the supplements may have unwanted effects, as a result of consumption in excessive doses, inadequate properties of the active compounds, either due to drug-food supplement interactions or falsifications. Today there are few countries (France, Czech Republic, Italy, Slovenia, USA) that have implemented Nutrivigilance - a new science and activity that detects, evaluates and understands the interactions produced by food supplements, with the aim of increasing consumer safety.
In the present work, we aim to present the risks of the uncontrolled consumption of some food supplements and to raise awareness of the importance of developing nutrivigilance in all countries, especially in those where it has not been implemented at all. In this context, we want nutrivigilance to be implemented in our country, as is pharmacovigilance for the use of medicines and medical devices

Keywords. food supplements, nutrivigilance, consumer safety, uncontrolled consumption, national legislation

1. Introduction

In the last 20 years, we have witnessed an increase in the global market of food supplements (FS) in the USA and Western countries (Italy, Germany, Great Britain and France), followed by Eastern Europe (Romania, Turkey, Macedonia, Czech Republic, Bulgaria, Albania, Bosnia and Herzegovina) [1].

Food supplements contain vitamins, minerals and over 400 substances with nutritional and physiological effect (amino acids, enzymes, essential fatty acids, pre- and probiotics, lycopene, lutein, coenzyme Q10, taurine, carnitine, inositol, glucosamine, chitosan, spirulina, soy isoflavones, medicinal plants and plant extracts), according to EC Directive 46/2002 [2, 3]**.** Supplements complement the balanced diet and the consumer should not exceed the recommended portion on the label/package leaflet. In the current conditions of: intense pollution, daily stress, eating habits, metabolic imbalances and intense sports activities, many consumers choose to improve their quality of life by consuming dietary supplements [4, 5]. Many are determined to consume natural ones as an alternative to adjuvant therapy in certain pathologies or to prevent and correct biological imbalances [6, 7]. Inadequate consumption, properties of some active compounds, drug-dietary supplement interactions can be multiple causes of adverse reactions of these FS.

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The decision to use FS must be taken at the recommendation and under the supervision of the doctor, pharmacist, nutritionist, so as to ensure health and quality of life. The choice of an FS is made after verifying that it has been notified by the competent authorities, that the manufacturer complies with the norms of good manufacturing practice and quality standards of the pharmaceutical industry.

An analysis at European Union (EU) level shows a balance between the share of supplements containing vitamins and minerals - 50%, with those containing other substances with nutritional and physiological effect - 43% (these are not legally harmonised in all countries, even at this time) [1].

Our country has stood out since 2010 with the highest increase in FS, especially for those containing vegetable extracts -51% and respectively 36% contain medicinal and aromatic plants, being approved 80 plant species [8]. The average annual sales volume has progressively increased, which also explains the continuous increase in the number of operators occupying this market niche. Economic agents on the Romanian dietary supplements market are represented by micro-enterprises (40%), small and medium-sized enterprises (45%), authorized individuals and individual enterprises (10%), large companies representing only 5% of the total. Generally, domestic producers use their own recipes, domestic or imported raw materials, and the distribution of products is carried out through their own chains of warehouses and stores or turn to third parties [1].

Increasing consumption of FS increases the unknown risks to consumers as a result of many possible interactions between supplement, food and drugs. It is necessary for the authorities to implement nutrivigilance regulations for the use of FS, just as pharmacovigilance regulations for the use of drugs and medical devices are established.

Therefore, in this paper we intend to present the risks of uncontrolled consumption of FS and to bring to attention the importance of developing nutrivigilance in all countries, especially in those where it has not been implemented at all.

2. Material and Methods

For the study, the main Regulations of the EU, France and Romania, some FS Guides, online newsletters, as well as recent articles published in MDPI/ PubMed open access journals were used and analyzed.

3. Discussions

A drug in therapeutic circulation must be effective and safe for the user, with fewer side effects. New, suspected adverse reactions with undesirable effects, other than those which are known and listed in the package leaflet for consumer information, must be urgently reported to the competent authorities. In this context, the European Medicines Agency (EMA) and the Scientific Committee for Pharmacovigilance Risk Assessment (SCPRA) operate at European Union level, which ensure the pharmacovigilance of the consumption of medicinal products. Directive 2010/84/EU and EU Regulation no. 1235/2010 define the pharmacovigilance system as "the system for reporting suspected adverse reactions, necessary for the protection of public health, allowing the prevention, detection and evaluation of adverse reactions to medicinal products placed on the Union market" [9, 10, 11, 12].

In Romania, pharmacovigilance is monitored by the Romanian National Agency for Medicines and Medical Devices (NAMMD), which strives to collect and analyse reports of suspected adverse reactions to medicinal products, taking measures to minimise risks. A new and important element of the legislation in force is to allow the reporting of adverse reactions, not only by healthcare professionals (doctors, pharmacists, pharmacy assistants, nutritionists),

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but also by patients. Thus, for patients or their legal guardians, special reporting forms were developed, in physical and electronic format (at the end of 2016), available on the NAMMD website under the section *Report an adverse reaction* [13].

Finally, after assessing the reports, the information is communicated superiorly in the database managed by EMA, called Eudravigilance. Along with 81 countries, the NAMMD was involved in the MedSafetyWeek 2022 Global Campaign, led by the Uppsala Monitoring Centre (UMC), the World Health Organisation's Collaborating Centre for International Medicines Monitoring and supported by members of the International Medicines Regulatory Coalition (IMRC). Obtaining more information about these side effects helps to take measures to reduce the risks of medicines, which leads to improved health of patients [14].

If the pharmacovigilance system is today regulated and functional on a global scale and monitors the safety of the medicine, we cannot say the same about Nutrivigilance [15]. In recent years, few countries (USA, France, Czech Republic) have introduced Nutrivigilance – a safety activity of authorized dietary supplements and to detect changes in risk-benefit ratio. The World Health Organization – WHO, has adapted the definition of Nutrivigilance from the definition of pharmacovigilance, as "The science relating to the detection, evaluation, understanding and prevention of adverse reactions produced by common foods, food supplements, novel foods, fortified foods, including energy drinks (ED), medicinal plants and algae" [15].

In France, responsible for nutrivigilance is the French Agency for Food, Environment, Health and Safety Optional – ANSES, established in 2009, with the objective of collecting reports on adverse effects of FS or as a result of their interactions with medicines or food, some beverages enriched with vitamins, minerals or plant extracts. Adverse effects of FS can be reported by healthcare professionals, but also by individuals through online forms on the ANSES website [16]. The reports are evaluated and attempts are made to establish the cause of undesirable adverse effects reported by consumers. If the ANSES agency finds adverse effects of varying degrees of severity, it signals to the public authorities and appropriate measures are taken (FS labelling may be modified, withdrawn from the market or regulations may be amended). Between 13.11.2009 and 31.12.2018 ANSES received 4312 reports of adverse effects [16].

In the Netherlands, the statutory responsible for pharmacovigilance activities is the independent foundation - The Netherlands Pharmacovigilance Centre (LAREB), funded by the Ministry of Health and the Dutch Committee for the Evaluation of Medicines. Over the past 10 years, there have been more spontaneous reports of adverse effects attributed to unregistered health-enhancing products (such as those with vitamin B6, melatonin or *Hypericum perforatum* extract) that the LAREB Foundation takes them up for evaluation. There is currently no other authority that is focused on a structural vigilance approach. Official data record 33 cases reported in 2013 and 133 reported reports in 2018 [17].

In order to be something unitary at European level, France brings together European countries and encourages the configuration of the similar Nutrivigilance scheme. France also joined Italy, Belgium, Czech Republic, Greece, Slovenia, Ireland, Brazil, USA. Among the other European and non-European countries that are beginning to regulate nutrivigilance are Romania, along with the Netherlands, Denmark, Croatia, Poland, Canada, Singapore, India [16].

In our country – Romania, it is a beginning of applying nutrivigilance. In this context, the Romanian Association of Manufacturers of Over-the-Counter Medicines, Food Supplements and Medical Devices (RASCI), which trains specialists in the field, is responsible. In volunteer activities, future pharmacists – students, organized in associations of pharmacy

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students, are affirmed in the online environment and in university centers. They initiated the MedAccess campaign, supported by the pharmaceutical company Worwag Pharma, promoting the administration of dietary supplements with great responsibility [18].

In the following, we present some of the numerous risk assessments for FS and ED, published by ANSES.

In 2018, melatonin supplements were flagged as unsafe. In 2017, some FS containing spirulina were questioned, some recommended for consumption in sports activities or in special physiological states (pregnancy). Spirulina was at risk of contamination with cyanotoxins, bacteria or metal trace elements. ANSES recommends a threshold set for microcystines that does not exceed the tolerable daily intake (TDI) of 0.04 µg/kg/day (established by WHO). Spirulina consumed in the amount of 5 g/day provides 7 and 8.5 mg of beta-carotene, while the maximum daily intake of beta-carotene from FS has been estimated at 7 mg/day. It is not recommended for those suffering from phenylketonuria.

Regarding supplements for athletes, ANSES warns athletes to use supplements at the direction of a sports nutrition professional, in cooperation with the fitness coach. There are many cases of recording reactions with cardiovascular and muscular effect. Since 2013, ANSES receives 25 reports of adverse reactions related to the consumption of food supplements containing red yeast rice, for which reason it will notify the European Union to take appropriate measures. These supplements contain monacolin K, similar to statins in cholesterol-lowering drugs, causing muscle and liver disorders. The risks are higher for pregnant women, the elderly over 70 years, children and adolescents, people with renal/hepatic insufficiency, as well as for people who use cholesterol-lowering drugs or who consume large amounts of grapefruit [16].

Regarding ED, based on reports of nutrivigilance cases monitored by ANSES, caffeine was considered to be the main factor, especially if consumed together with alcohol [19]. Among the adverse reactions caused by caffeine, consumers reported cardiovascular disorders (chest pain, tachycardia, hypertension), psycho-comparative or neurological disorders (anxiety, nervousness, panic attacks, hallucinations, sleep disorders) [20]. There are numerous data in the literature that draw attention to the uncontrolled consumption among young people of these ED, having consequences on health, especially since the effect of caffeine is cumulated with taurine, glucoronolactone [21, 22, 23]. Some may also contain preservatives or dyes, which can act synergistically in potentiating the ADHD syndrome (benzoate in combination with tartrazine, carmoisine or yellow orange G is responsible for this synergy) [24].

The European Food Safety Authority (EFSA) recommends caffeine intake below 400 mg/day for general consumers (70 kg body weight), and for taurine, it has established a daily reference intake of 1400 mg taurine/day [21, 25]. Following studies conducted in Germany and Denmark, standardization of BE with a maximum caffeine content of 32 mg/100 mL is promoted, along with a wide variety of other active components, such as taurine (usually 4000 mg/L) and D-glucuronolactone (generally 2400 mg/L) [26]. The authors of the US study believe that this public health problem, caused by abuse of ED, can be reduced by regulating the establishment of an evidence-based upper limit for caffeine, restricting sales and regulating marketing strategies [22].

Given the abundance of complaints to undesirable reactions of many FS, it is desirable that nutrivigilance be consistently active in all countries and that competent professional agencies adopt appropriate regulations. Thus, the costs of patients' health problems and the national health system will be reduced, and control of marketed dietary supplements can be improved.

4. Conclusions

By encouraging consumers of food supplements/energy drinks to send to the competent authorities, reports on adverse reactions associated with the consumption of these FS/ED, consumer-professional cooperation and implicitly the quality of life will increase.

We hope that, by disseminating this informative material, we will contribute to informing, warning, educating and protecting consumers, but also to empowering operators who place FS, sometimes even non-compliant, on the market. In this context, we want to develop sectoral strategies and improve the legislative framework in the country and worldwide.

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