https://doi.org/10.31925/farmacia.2019.3.24 **ORIGINAL ARTICLE**

NUTRIVIGILANCE: A NEW ACTIVITY IN THE FIELD OF DIETARY SUPPLEMENTS

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Abstract

Dietary supplements (DS) used to improve the quality of life, can produce adverse events, either as a result of inappropriate consumption, or as the intrinsic properties of active compounds, either as drug-dietary supplement interactions or due to contaminations or adulterations. The European legislation, including the Romanian legislation doesn't refer to all types of DS, and even more it doesn't contain any regulations regarding detecting, monitoring or reporting adverse events. In the last years, some countries (USA, France, Czech Republic) started the nutrivigilance, a scientific support in order to identify the possible adverse effects of DS and to enhance consumer safety, necessary for detection, understanding and prevention of adverse events related to the use of DS, a major public health risk, which can lead to an inappropriate practice and may eventually be harmful to patients' lives. This study highlights the necessity to introduce the nutrivigilance as a habitual practice and activity of all authorities and actors from the Romanian dietary supplements' market, due the increase of dietary supplements consumption and their risks for the people's health.

Rezumat

Utilizate cu scopul de a creşte calitatea vieţii, suplimentele alimentare pot cauza reacţii adverse, fie ca urmare a consumului inadecvat sau din cauza proprietăţilor intrinseci ale compuşilor activi conţinuţi, fie datorită interacţiunilor medicament – supliment alimentar, sau chiar a contaminării sau falsificării lor. Legislaţia europeană, inclusiv cea românească, nu reglementează toate categoriile de suplimente, şi cu atât mai mult nu conţine aspecte privind detectarea, monitorizarea şi raportarea reacţiilor adverse cauzate de acestea. In ultimii ani, câteva state (SUA, Franţa, Cehia etc.) au introdus nutrivigilenţa, o nouă ştiinţă şi activitate necesară pentru detectarea, evaluarea, înţelegerea şi prevenirea efectelor adverse produse de suplimentele alimentare. Lucrarea de faţă doreşte să evidenţieze necesitatea introducerii nutrivigilenţei ca o practică şi activitate permanentă a tuturor autorităţilor şi actorilor implicaţi în piaţa suplimentelor alimentare din România, ca urmare a tendinţei de creştere accelerată a consumului acestora, dar şi a riscurilor pe care aceste produse le pot avea pentru sănătatea populaţiei.

Keywords: nutrivigilance, dietary supplements, adverse events, legislation and regulations

Introduction

Nowadays, the modern human being has new standards regarding their personal life, like having good health status or increasing their quality of life. The daily stress, food habits, sedentary lifestyle and the pollution are the main factors which can lead to a suboptimal state of health. This can be attenuated or reduced by the use of dietary supplements (DS) [10, 60]. The demand for these products shows an increasing trend all over the world. The DS market makes a fast development, so, drugs manufacturers identified a good opportunity for their business, in this segment. The increasing prevalence of different pathologies such as cardiovascular diseases, cancers, diabetes, epilepsy, respiratory or digestive disease etc. [20, 34, 36, 62] determined people to use more and more natural products as adjuvant therapy, or for prevention or correction of some biological imbalances. In some cases, the DS can partially replace the high amount of prescribed drugs (non-steroidal anti-inflammatory drugs, antihypertensive drugs, statins, oral antidiabetics, gastrointestinal agents etc.) [1, 5, 6, 22, 59], for limiting the risks of drugs adverse reactions. Today, when the pharmaceutical market registers a lot of tensions, the development of the health products trade (drugs, DS, cosmetics, medical devices etc.) is a good opportunity to improve the economic efficacy of the pharmacies. Thus, this business determines an

increase in the turnover, in the net profit and also in the cash flow obtained by pharmacies [35].

Materials and Methods

In this study there were analysed the main regulations about DS from European Union (EU) and Romania: a) Directive 2002/46 EC; b) Regulation (EU) no. 432/2012; c) Law 491/2003 republished in 2011; d) Joint Order no. 244/401/2005 of Ministry of Agriculture, Forests and Rural Development and Ministry of Health; e) Joint Order no. 1228/2005/ 63/244/2006 of the Ministry of Agriculture, President of the National Sanitary Veterinary and Food Safety Authority and Ministry of Health; f) Order no. 1069/ 2007 of the Ministry of Health; g) Order no. 1946/ 2014 of Ministry of Agricultures and Rural Development [15, 30, 40-43, 48]. This research has been carried out employing the comparative method and interpretation method [9, 10] of the regulations from this field.

Results and Discussion

Regulations regarding the dietary-supplement activity

The first regulation regarding DS was introduced in 1994, in the US. In this regard, the "Dietary Supplement Health and Education Act of 1994" stipulates that DS are foodstuffs, not drugs [57]. Following this regulation, the EU authorities have tried to implement some rules for the DS field. Despite all EU Commission's and the professionals' efforts from over the last 25 years, the field of dietary supplements is not yet entirely covered by a unitary legislation to this day. In this regard, the Directive 2002/46/EC, approximates the laws of the Member States relating to DS. According to this Directive, the dietary supplements mean foodstuffs used to supplement the normal diet. Moreover, DS "are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose forms", meaning capsules, pastilles, tablets, pills and other similar forms, sachets with powder, ampoules with liquids, drops in dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small-unit quantities [15]. The DS contain a wide range of nutrients or other ingredients: vitamins, minerals, amino acids, enzymes, essential fatty acids, prebiotics, probiotics, botanicals and botanical extracts, as: Q10 coenzyme, lycopene, inositol, glucosamine, spirulina etc. [15, 18].

These products started to gain market share in the EU over the last twenty years, after the recognition of their nutritional role [18]. At the moment, there is a unitary EU legislation regarding the DS with vitamins and minerals. This establishes: 1) the vitamins and minerals that can be used as DS and their maximal quantities; 2) the wording of health-related claims that can be written on the packages respectively; 3) the products' authorization procedure by a notification [15, 16, 47]. It should be mentioned that even if DS are foodstuffs, the specific legislation regarding the food labelling or advertising [46] doesn't refer entirely to DS. The EU authorities launched a process evaluation of all possible foodstuffs components, in order to establish which kind of health-related claims can be approved to be written on the products' labels. The result of this process was the issue of a new EU Regulation (432/2012) that established the wording of the health claims for all vitamins and minerals and respectively for a few other usual nutrients [48]. At the same time, this process has shown how difficult it is to evaluate the botanicals, from the same point of view as the vitamins and minerals. However, we are still missing a unitary legislation or requirements for botanical-origin DS.

At the moment, in Romania, the specific legislation of DS includes many normative acts (Table I). Thus, the legislative aspects referring to DS from medicinal plants and hive products was regulated through the republished Law no. 491/2003 [30] and through the Joint Order of Ministry of Agriculture, Forests and Rural Development and Ministry of Health no. 244/ 401 from 2005 [40]. The Joint Order no. 1228/2005/ 63/244/2006 contains regulations regarding the DS of animal, plant origin and/or their mixtures with vitamins, minerals or other nutritive substances. In this Order, there are established: 1) the DS categories; 2) the authorization procedure; 3) the labelling and advertising rules adopted from the foods legislation which shouldn't overlap with regulations of drugs [10, 41]. The legislation regarding DS with minerals and/or vitamins was adopted in Romania by the Health Minister's Order no. 1069 from 2007. The Romanian legislation also specifies that a DS is a product which supplements the normal diet, taken orally by a healthy person which needs an increase in nutrients exogenous intake [42].

In the last few years it was introduced the term of "novel food" to cover the possibility of introducing new food ingredients that are not recognized at this moment as foodstuffs. The new EU and Romanian regulations in this field has the aim to request from the manufacturers more proofs regarding the safety and efficacy of these kind of food ingredients before they are introduced in usual foods or are marketed as they are [26].

The Romanian DS legislation respects two essential principles: 1) the consumer has not been misled or exposed to aggressive trade techniques; 2) any affirmation must be clear, exact and justified, and must allow the consumer to choose the desired and appropriate product [10, 37, 40-43]. The DS label is not mandatory to contain information referring to the prevention, treatment or cure of any pathology [42, 43].

Table I

Romanian legal background for dietary supplements

Regulatory approach	Year	Description
Law no. 491 [30]	2003 (republished in 2011)	– rules for manufacturing of medicinal plants and hive products – medicinal plants or hive products must be notified at the Institute for Food Bio-Resources Bucharest or at Regional Centre of Public Health from Cluj-Napoca, Iaşi or Timişoara
Joint Order of Ministry of Agriculture, Forests and Rural Development and Ministry of Health no. 401/244 [40]	2005	– list of botanicals that can be used in DS – list of herbs and plants prohibited to use in DS – list of cultivated and wild mushrooms that can be used in DS
Joint Order no. 1228/63/244 of the Ministry of Agriculture, President of the National Sanitary Veterinary and Food Safety Authority and Ministry of Health [41]	2005	– trade in DS which contain animal or herbal products (extracts) or in combination with vitamins and minerals – dosage forms of DS and authorization, packing, labelling and advertising rules – the animal or herbal DS must be notified at the Institute for Food Bio-Resources Bucharest or at the Regional Centre of Public Health from Cluj-Napoca, Iaşi or Timişoara
Order of Ministry of Health no. 1069 [42]	2007	– notification of DS consisting exclusively of nutrients (such as vitamins and minerals), such nutrients being synthetically obtained. – rules regarding DS authorization, packing, labelling and advertising – DS (exclusively vitamins or minerals) must be notified at the Ministry of Health
Order of Ministry of Agricultures and Rural Development no. 1946 [43]	2014	– the notification procedure of DS which contain animal or herbal products (extracts), or in combination with vitamins and minerals (including external products, hive products, cosmetics etc.) – the content of the safety report on DS
Government Decision no. 590 [26]	2018	– the procedural steps of the consultation process for establishing the status of novel food

According to Order no. 1946/2014 the notification file has to contain a Product Safety Report filled by a qualified person in pharmacy, toxicology, medicine or other related field [43]. Even if DS are not drugs, the Romanian regulations allow the writing of short health claims on products, but there is no regulation to force manufacturers to demonstrate the efficacy of DS, claimed on the labels or leaflets. As a result, due to the lax manner of notification on these products, their efficacy and safety are exclusively the producers' responsibility. There are some situations, when the inefficient, low-quality or unsafe (counterfeited or contaminated) products appeared on the market. Also, in Romania, several instances in which DS advertising was misleading have been identified [10].

The evolution of dietary supplements market

The request for DS has been registering a significant growth during the last years, which determined more and more producers to enter in this segment. The results of different studies have shown a continuous increasing of the number of healthcare products such as drugs, DS, medical devices, cosmetics etc., on the pharmaceutical market [11, 18, 19, 28, 35]. The magazine articles, TV shows, advertising, online forums, blogs or websites, celebrities etc., all offer information about DS. All these media increase the credibility of DS, about their role in the preventive or curative healthcare and also the DS consumption [56].

In 2012, the worldwide market was valued at $82 billion (US ~ 28%, Europe ~ 10%). It was estimated that the annual growth would be 5 - 6% [56]. In the US, there are more than 85,000 products with vitamins, minerals, botanicals, amino acids, probiotics etc. [8]. In 2013, in US, vitamins (32.2%) and botanicals (17.1%) were the best-selling DS [19]. More than 36% American DS consumers were over 65 years old [56].

In 2015, the value of DS market in Europe was over 7.1 billion euros, and in 2020, it is projected to grow by around 9.5% (at 7.9 billion euros). Following the international trend, the DS Romanian market has been developing over the past years (72.2 million euros, in 2015). The Eastern European countries are projected to be the top fastest-growing markets: Romania (+41%), Turkey (+27%), Bosnia-Herzegovina (+23%), Russia (+21.5%) and Macedonia (+19%) [64]. Thus, the Romania represents the most attractive market, with the greatest potential. Several factors are contributing to this evolution. For example, the people's attitude towards adopting a healthy life-style has improved due to the increase in the level of education and degree of information. Other causes are the developing of distribution channels and the expansion of DS advertising [10, 56, 60]. The DS can be procured from pharmacies, drugstores, super-markets, specialized shops, the Internet, independent sellers etc. In this context, the pharmacies role in the

DS providing is reduced, although the pharmacists have the competences to offer appropriate information. Thus, a study carried out in the US showed that in 2012 only about 18% of DS were sold in pharmacies, while the rest was sold by supermarkets or hypermarkets, specialized retailers, direct selling, Internet or home-selling [56], possibly due to their easy affordability.

Dietary supplements and adverse events

As it was presented above, DS can be purchased from different unspecialized places including the Internet which represents a comfortable source. Unfortunately, the lack of correct medical information or scientific support for these online-purchased products represents a major public health risk, which can lead to an inappropriate practice and may eventually be harmful to patients' lives. The main problems of DS intake are represented by several adverse events (e.g.: hepatic, cardiac, renal, metabolic disorders, neurotoxicity, teratogenicity etc.). An adverse event is defined as "any health-related event associated with the use of a dietary supplement that is adverse" [51]. The adverse event can be determined by: a) the intrinsic adverse effects of DS induced by the active substances or b) the interactions between dietary supplements and drugs (Table II).

Other adverse events of DS can be determined by the adulteration to improving their activity (e.g.: improve the sexual activity, reduce the articular or neck pain, lose body weight, improve the athletic performances etc.) with pharmacological active substances such as steroids, antidepressants, neurostimulants (sibutramine, a methamphetamine analogue), phenolphthalein, sildenafil analogues etc. [8, 21, 32, 52]. On the other hand, the involuntary or incorrect administration of some DS which contain prohibited substances (with stimulant, doping effects etc.) may cause disqualification of the athletes from various competitions [32]. For example, three athletes were disqualified from the 2014 Winter Olympic Games because they used DS contaminated with 1,3-dimethylamylamin - a sympathomimetic substance withdrawn from the market in 1983 [8]. Although the DS are efficient and easily affordable, they can have negative consequences on health, as it was mentioned above. Because of this, it is necessary to implement a system to prevent and monitore the adverse events of DS.

Table II

Adverse effects and drug interactions of some dietary supplement

Substance Medicinal plant	**Current use**	**Adverse event**	**Interactions with drugs**
Aloe vera [1, 7, 33]	immunomodulatory, antioxidant, antibacterial, laxative	gastrointestinal complaints, arrhythmias, nephropathies, oedema	+ antidiabetics → hypoglycaemia
Aristolochic acids *Aristolochia sp.* [25, 52, 53]	joint pain, stomach ache, malaria	Nephropathy	
Chelidonium majus [21, 54, 63]	dyspepsia, irritable bowel syndrome	Hepatitis	+ hormones, anti-inflammatories
Citrus sp. [7, 14, 38]	antioxidant, anti-tumoural, anti-inflammatory, anti-atherosclerotic, natural preservative	Hyperacidity	enzyme inhibitor, acting on CYP3A4 and P-glycoprotein Interacts with calcium channel blockers, sedatives etc. Inhibits the intestinal organic anion transporting polypeptides (OATPs) that facilitate the drugs absorption
Cytisus sp. [21, 63]	antioxidant, diuretic, anxiolytic, antidiabetic, antiparasitic	dizziness, headache, heartbeat changes, leg weakness, sweating, sleepiness, mydriasis	
Echinacea purpurea [1, 13, 24, 31]	antioxidant, immunostimulant, anti-inflamatory, anti-bacterial, antifungal, antiviral	rash, headache, drowsiness	+ lorazepam, pantoprazole → hallucinations
Ginkgo biloba [1, 3, 12, 24, 58]	ischemic protective antioxidant	gastrointestinal complaints, allergic reactions, hypotension	+ amitriptyline, and acetaminophen–hydrocodone → seizure + warfarin use→ increased risk of bleeding
Green tea extract *Camellia sinensis* [4, 7, 38, 45, 54]	body weight loss	liver injury	+ warfarin, anti-hypertensives → reduces drug effects
Hypericin St. John's wort *Hypericum perforatum* [1, 3, 7, 12, 13, 29, 58]	antidepressant, anxiolytic	diarrhoea, vomiting, drowsiness, agitation, rash, photosensitization	+ oral contraceptives, warfarin, omeprazole, amiodarone, carbamazepine, alprazolam → reduces the clinical efficiency of drugs + fluoxetine, paroxetine, sertraline, triptans → serotonin syndrome

Substance Medicinal plant	Current use	Adverse event	Interactions with drugs
Kava extract *Piper methysticum* [3, 7, 13, 24, 29]	anxiolytic	hepatitis, headache, nausea, drowsiness, dyspnoea, pruritus	+ alprazolam → increases drug effect + levodopa → decreases drug effect
Lamiaceae sp. With high contents in rosmarinic acid [21, 39]	Antioxidant, hepatoprotective, antibacterial	Hypertension	inhibits the organic anions transporters SLC22A6 and SLC22A8, inhibiting some drugs absorption
Milk thistle *Silybum marianum* [3, 21, 55]	hepatoprotection protein synthesis	headache, dizziness, pruritus, laxative effect	+ antiretrovirals, warfarin, diazepam → decreases drug effect
Passiflora incarnate [7, 21]	anxiolytic, antihypertensive	dizziness, confusion drowsiness	+ warfarin, antiepileptics → increases drug effect
Saw palmetto extract *Seronoa repens* [7, 8, 13, 24]	used in benign prostatic hyperplasia	pruritus, tingling of extremities, nausea dizziness, vomiting	+ hormone therapy → decreases drug effect
Senna *Cassia angustifolia* [21, 54]	laxative	hepatitis	+ digitalis glycosides → increases digitalis toxicity + antiarrhythmic → arrhythmias + indomethacin → decreases the therapeutic effect of Senna
Usnic acid (a secondary lichen metabolite) [4, 54]	antimicrobial	local irritation, contact dermatitis, liver injury	+ rifampicin → increase drug effect
Valeriana officinalis [7, 13, 29]	anxiolytic-sedative-hypnotic	vomiting, nausea, agitation, dizziness, drowsiness, headache	+ antiepileptics, barbiturates → increases drug effect
Creatine [13]	metabolism of skeletal muscle	proteinuria, agitation, vomiting	+ glucose → increase total muscle mass
Lysine (partial 5HT4 receptor antagonist) [49]	anxiolytic	diarrhoea, abdominal pain	
Omega-3 fatty acids (fish oil, linseed) [6, 12, 29]	prevention of cardio-vascular diseases, reduces the production of PGE_2, antidepressant	gastrointestinal reactions, dysgeusia	+ anticoagulants → bleeding, bruising + antidepressant → increases drugs effect
Melatonin [7, 23, 29]	regulates the circadian rhythm	nausea, headache, dizziness	+ antidepressants → decreases drug effect
Magnesium [7, 17]	anxiolytic, involves in metabolic reactions	abdominal pain, diarrhoea	+ quinolones, tetracycline, nitrofurantoin → decreased antibiotic absorption.
Zinc [13, 29]	relieves symptoms of common colds, CNS functioning	nausea, vomiting, metallic taste, sideroblastic anaemia	+ quinolones, tetracycline → decreased antibiotic absorption.
Vitamin D3 and calcium phosphate [50]	bone metabolism	constipating, bloating, metallic taste, thirst, tiredness, weakness, loss of appetite, muscle pain	Ca^{2+} + quinolones, tetracycline → decreased antibiotic absorption
Vitamin C [6, 49, 58]	antioxidant	nausea, pyrosis, diarrhoea, renal calculi	+ co-trimoxazole → increases drug absorption
Vitamin A [7, 49]	well-functioning of skin antioxidant	general weakness, dizziness, headache, intracranial pressure, nausea, vomiting	+ isotretinoin, valproic acid → increase drug effect
β-caroten (provitamin A) [49]	inhibits proliferation of cells	yellowish skin tinge, slight diarrhoea	+ simvastatin, niacin → decreases drugs effect
Vitamin E (α-tocopherol) [7, 49, 58]	stimulation of fertility, activation of immune system	gastric pain, vomiting and diarrhoea, muscular weakness, rashes, skin inflammations	+ oral anticoagulants, oestrogens → bleedings + antidiabetics → hypoglycaemia

The nutrivigilance activity

In US, the herbal products are marked as dietary supplements or botanicals. The law covers aspects regarding the reporting of adverse events to FDA MedWatch scheme, by consumers, manufacturers, distributors, pharmacists etc. [51]. In EU, some herbal products can be included on the drugs list, requiring safety and quality standards, and having the obligation to report adverse events. Unlike drugs, DS authorization does not require any safety studies (preclinical, clinical or toxicological). The European legislation (including the Romanian legislation) refers only to their processing, preparing, authorising, trading, advertising and labelling.

In 2012, Palet *et al*., proposed that the adverse events' reporting system must be strongly encouraged all over the world [44]. This system represents the first main step for developing a new domain, Nutrivigilance**,** which is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse events related to the use of a food, dietary supplement, or medical food" [51]. The term "nutrivigilance" is not used within the DS legislation framework, except in France, where *Agence Nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* (ANSES) has been working since 2009 on this field, seeking to identify the adverse events of consuming DS [2, 61]. Over the last few years, the European Food-Safety Authority's Advisory Forum has been trying to create a nutri-vigilance network, following France's example. At the moment, many EU countries agreed to discuss the issue with ANSES [61]. Concretely, the Czech Republic has started too, the nutrivigilance activity in 2015 at the Centre for Health, Nutrition and Food in Brno. Several solutions to improving DS safe use have been identified by Cohen: a) reforming the legislation; b) founding centres to monitor DS adverse events; c) creating a database of all DS adverse events; d) requiring rigorous quality-control tests in order to authorize DS etc. [8]. The evaluation of intake risks can be achieved employing some models used for drugs, but adapted to DS: WHO scale, FDA algorithm, the Narnajo scale, Kramer scale or Liverpool scale [4, 19, 52, 53]. Ide *et al*. have adapted the FDA algorithm to estimate a causality relationship between adverse events and DS usage [27].

Because of its importance to people's life, nutri-vigilance had been sustained by authorities. For example, in US, FDA together with the National Health Institute and The Dietary Supplements Office are continually financing research in this field in order to extend the scientific knowledge regarding DS efficacy and safety (more than 855 million USD during 2009 - 2011) [23, 24, 58]. Most of these funds were directed to projects for studying plants (22%), vitamins (20%), lipids (14%), minerals and trace elements (10%). The targeted research fields were oncology, cardiology, and women's reproductive health [24].

Conclusions

This study presents some aspects that encourage the development of nutrivigilance as a main activity in the dietary supplements field. Its main object is "to detect, assess, understand or prevent the adverse events of food, dietary supplements or medical foods". In EU, including Romania, there are some regulations regarding dietary supplements which have been changed and improved during the time. However, these don't refer to the detecting, monitoring or collecting the dietary supplements adverse reactions. Taking into account of these aspects, the Romanian authorities should start the activity of nutrivigilance, following the example other countries. Thus, a major decrease in the risks related to dietary supplement adverse-events can be achieved with a better involvement of the pharmacists.

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