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THE WORLD-WIDE SPREAD OF CARBAPENEM-RESISTANT ENTEROBACTERALES

Arjana TAMBIC ANDRASEVIC[1,2], Ivana ANTAL ANTUNOVIC[1]

[1]Department of Clinical Microbiology, University Hospital for Infectious Diseses *Dr. Fran Mihaljevic*, Zagreb, Croatia

[2]University of Zagreb School of Dental Medicine, Zagreb, Croatia

Corresponding author: Ivana Antal Antunovic, e-mail: iantal@bfm.hr

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Introduction*. Gram-negative bacilli belonging to the order Enterobacterales are normal inhabitants of the human gut, which also are the most common causative agents of both nosocomial and community acquired infections in patients of all ages. Although not even a century has passed since Fleming's discovery of penicillin, the scientists have been alarmed by the fact that the "last resort antibiotics" viz. carbapenems have been compromised.* ***Material and methods.*** *The analysis of fifty-two articles and documents regarding this topic was peformed.* ***Results.*** *The main mechanism of resistance to carbapenems in Enterobacterales is production of carbapenemases, being enzymes that destroy all or almost all β-lactam antibiotics including carbapenems. According to Ambler's classification β-lactamases can be distributed into four classes (A, B, C, and D) being based on primary amino acid sequence homology. The most important carbapenemases produced by Enterobacterales belong to class A (KPC), class B (metallo-β-lactamases NDM, VIM, IMP) and class D (OXA-48-like). Unlike other mechanisms of resistance, carbapenemase production is easily spread via plasmids making carbapenemase-producing Enterobacterales (CPE) a global challenge for healthcare providers.* ***Conclusions.*** *CPE are not readily detected in the laboratory but the ability to detect carbapenemase production in Enterobacterales has very important infection control implications and therefore is essential for local infection control programs and national and international surveillance systems. Furthermore, local epidemiology of multidrug resistant organisms has major influence on development of national clinical guidelines for antimicrobial use.*

Cuvinte cheie: *Enterobacterales carbapenem rezistente, Klebsiella pneumoniae carbapenem-rezistentă, carbapeneme, cabapenemaze.*

RĂSPÂNDIREA MONDIALĂ A ENTEROBACTERALES CARBAPENEM-REZISTENTE

Introducere. *Bacilii gramnegativi din ordinul Enterobacterales habitează la nivelul intestinului uman, dar în același timp sunt și cei mai comuni agenți cauzali ai infecțiilor nozocomiale și comunitare la pacienții de toate vârstele. Deși nu a trecut nici măcar un secol de la descoperirea penicilinei de către Fleming, suntem deja într-o situație îngrijorătoare în care „antibioticele de ultimă instanță", carbapenemele, au fost compromise.*

Material și metode. *Au fost analizate cincizeci și două de articole și documente pe tema analizată.* ***Rezultate.*** *Mecanismul principal de rezistență la carbapeneme la Enterobacterales este producerea enzimelor carbapenemaze, care distrug toate sau aproape toate antibioticele β-lactamice, inclusiv carbapenemele. Conform clasificării Ambler, β-lactamazele pot fi distribuite în patru clase (A, B, C și D) pe baza omologiei primare a secvenței aminoacizilor. Cele mai importante carbapenemaze produse de Enterobacterales aparțin clasei A (KPC), clasei B (metallo-β-lactamaze NDM, VIM, IMP) și clasei D (OXA-48-like). Spre deosebire de alte mecanisme de rezistență, producerea de carbapenemaze este ușor răspândită prin intermediul plasmidelor, făcând Enterobacterales (CPE) producătoare de carbapenemază o provocare globală pentru lucrătorii medicali.* ***Concluzii.*** *Nu este ușor de detectat CPE în laborator, dar abilitatea de a detecta producerea de carbapenemaze la Enterobacterales este foarte importantă în control infecției și, prin urmare, este esențială pentru programele locale de control al infecțiilor și sistemele de supraveghere naționale și internaționale. Mai mult, epidemiologia locală a organismelor multirezistente are o influență majoră asupra dezvoltării ghidurilor clinice naționale pentru utilizarea antimicrobienelor.*

INTRODUCTION

Advertising of food supplements on various media channels or in specialty stores with natural products, as well as the lack of information and educational programs of the population, on adverse reactions and interaction of food supplements with food and drugs, have led to uncontrolled development of marketing these products.

Although in the US, the FDA (Food and Drug Administration) only authorizes food and drugs, the 1994 Dietary Supplement Health and Education Act (DSHEA) monitors the side effects (SE) of post-market food supplements (1). Under this law, food supplements are orally ingested foods that include botanical products (such as herbal remedies) and non-botanical substances, such as minerals, amino acids, vitamins and microbial products, and traditional cultural remedies, including Asian plants (2). Although the prohibition on the statement that "food supplement (FS) may be used for the treatment or prevention of a disease" is valid in Romania, in the USA, the mention regarding general well-being and health is allowed provided that on the packaging/label is "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease" (1).

SE has been found and reported in vitamin food supplements:

- doses higher than 500 mg/day pyridoxine (vitamin B_6) – photosensitivity, neurotoxicity,
- chronic sensory polyneuropathy associated with pyridoxine,
- bleeding associated with antiplatelet action at doses 800-1200 mg/day,
- diarrhea, weakness, blurred vision and gonadal dysfunction at doses higher than 1200 mg/day α-tocopherol (vitamin E) and
- increased recurrence of cancer in the first 3.5 years (1).

The "Retinol Efficacy Trial" and "ATBC" studies demonstrated the toxicity of β-carotene (vitamin A) supplements by significantly increasing the risk of lung cancer in male smokers (1). Following the study "Teratogenicity of high vitamin A intake" (1), researchers Rothman KJ, Moore LL, Singer MR et al. suggested the association of dietary supplements containing vitamin A with adverse effects on bone health and decreased bone density, thus increasing the risk of fracture.

Side effects have also been found with mineral supplements, omega 3/fish oil, soy protein, soy protein, plant nutrients, antioxidants, anti-inflammatory, supplements for weight loss or bodybuilding, various botanical supplements (3). Multi-skeletal distortion, fatigue, pain and gastrointestinal symptoms and hepatic adverse events have been reported with the nutraceutical ingredient RYR (red yeast rice) at the doses recommended by EFSA (European Food Safety Authority) (4).

With the exception of "classic" foods (hazelnuts, nuts, eggs, etc.) known to cause certain side effects such as allergies, the development of the food industry has led to the emergence of foods eaten especially by teenagers, such as energy drinks. Frequent consumption of this type of drink (≥7 times a week) was significantly associated with asthma, allergic rhinitis and atopic dermatitis (3), high stress, lack of sleep, poor school performance and suicide attempts in Korean adolescents (5).

This present research is aimed at displaying the algorithms that can be applied to determine adverse reactions caused by the consumption of food supplements and foods in Romania, the need to initiate a legislative project and its implementation regarding the reporting of these adverse reactions and implementation of information/education programs on the population when consuming these products. The implementation of the nutrition surveillance system may be one of the methods of re-evaluation of food additives approved by EFSA and European Commission (EC).

The purpose of this paper was to implement nutrivigilence in Romania.

MATERIAL AND METHODS

The PubMed, ResearchGate and EUR-Lex databases (online portal offering access to EU legislation) were analyzed during 2015-2021, starting from the search criteria like: side effects, new food ingredients, supplements food, algorithms. Herbal resources that may influence the clearance of dermatological drugs metablized by cytochrome P-450 have been identified (enzymes CYP2C9, and CYP3A4).

RESULTS

Of the total of 5696 European Union Regulations and/or Decisions published during this period, 39 refer to the authorization of novel food ingredients in the European Union, which are presented in Tables 1, 2 and 3.

Table 1. Adverse reactions caused by new food ingredients authorized by EFSA in the European Union, in the period 2015-2017.

Ingredient/substance approved as a novel food ingredient in the EU	EU Decision/ Regulation	Category of products for which it has been authorized or action - Maximum dose/day (mg or g/day), according to EU Decision/ Regulation	Adverse reactions/Warnings	Consumption mode (e.g. mono-ingredient)
(6S) -5-methyltetrahydrofolic acid, the glucosamine salt, as a source of folate (6)	Reg. (EU)* no. 414/2015 (6)	FS (6)	SE* reported for patients taking 15 mg folic acid for 1 month: - gastrointestinal: nausea, abdominal distension and flatulence; - nervous system: bitter taste, sleep changes, difficulty concentrating, hyperactivity, impaired thinking; - metabolic: anorexia; - other: decrease in serum diphenylhydantoin in patients taking 5 or 15 mg of folic acid daily (7).	Multi-ingredient (7)
Oil extracted from microalgae *Schizochytrium sp*. (ATCC PTA-9695) (8)	EU Decision no. 545/2015 (8)	FS: • 250 mg DHA* per day, as recommended by the manufacturer for the normal population; • 450 mg DHA per day, as recommended by the manufacturer for pregnant and lactating women. Foods intended for use in low-calorie diets for weight loss within the meaning of Directive 96/8/EC: • 250 mg per meal replacement. Other foodstuffs for particular nutritional uses as defined in Directive 2009/39/EC, with the exception of infant formulas and follow-on formulas: • 200 mg /100 g. Dietary foods for special medical purposes: • according to the specific nutritional needs of the persons for whom the products are intended (8).	Possible side effects: - buckling, slight increase in cholesterol; - pregnant women: dose > 3g/day slowing blood clotting and increasing the chances of bleeding; - respiratory sensitivity, in the case of people sensitive to aspirin; - diabetes: Increased blood sugar before meals in people with type 2 diabetes; - tension: decreased blood pressure (9); - respiratory infection and gastroesophageal reflux (10).	Mono-ingredient (9)

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Oil rich in DHA and EPA, extracted from microalgae *Schizochytrium sp.* (11)	EU Decision no. 546/2015 (11)	FS: •3000 mg as recommended by the manufacturer, for the adult population, except for pregnant and lactating women (11).	Possible SE: - belching, slight increase in cholesterol (9); - pregnant women: dose> 3g/day slowing blood clotting and increasing the chances of bleeding (9); - respiratory sensitivity, in the case of people sensitive to aspirin (9); - diabetes: Increased blood sugar before meals in people with type 2 diabetes (9); - blood pressure: decreased blood pressure (9); - respiratory infection and gastroesophageal reflux (10).	Mono-ingredient (9)
Flavonoids from *Glycyrrhiza glabra L.* (12)	EU decision no. 1213/2015 (12)	Foods intended for use in low-calorie diets for weight loss (only for products presented as a substitute for the whole daily diet): • daily consumption of 120 mg. Dietary foods for special medical purposes: • daily intake of 120 mg (12).	- dose-dependent increase in plasma renin, Na, concomitant decrease in plasma cortisol, ACTH *, aldosterone and K (13); - hipertensiune, hipokalimie, edem (13); - contraindicated with co-administration with laxatives or diuretics (13).	Mono-ingredient (13)
Refined *Buglossoides arvensis* seed oil (14)	EU Decision no. 1290/2015 (14)	FS as defined in Directive 2002/46/EC, with the exception of food supplements for infants and young children: • a daily dose of 500 mg, as recommended by the manufacturer. Foods intended for special medical purposes as defined in Directive 1999/21/EC, with the exception of dietary foods for infants and young children: • in accordance with the specific nutritional needs of the persons for whom the products are intended. Foods intended for use in low-calorie diets for weight loss within the meaning of Directive 96/8/EC: • 250 mg/food substitute (14).	No side effects have been reported (15).	Mono-ingredient (15)

Lacto-N-neotetraosis (16)	EU Decision no. 375/2016 (16)	Dietary foods intended for special medical purposes as defined in Directive 1999/21/EC: • in accordance with the specific nutritional needs of the persons for whom the products are intended. FS, as defined in Directive 2002/46/EC, with the exception of infant food supplements: • 1.5 g/day for the general population 0.6 g/day for young children, etc. (16).	No adverse reactions have been reported (17, 18).	Mono-ingredient (17, 18)
2′-O-fucosyl-lactose (19)	EU decision no. 376/2016 (19)	Dietary foods intended for special medical purposes, as defined in Directive 1999/21/EC: • in accordance with the specific nutritional needs of the persons for whom the products are intended. Foods used in low-calorie diets for weight loss as defined in Directive 96/8/EC (only for products presented as a substitute for the whole daily diet): • 4.8 g/l in beverages and 40 g/kg in bars. FS, as defined in Directive 2002/46/EC, with the exception of infant food supplements: • 3.0 g/day for the general population and 1.2 g/day for young children, etc. (19).	Mild side effects: • flatulence; • stomach ache; • diarrhea. Severe side effects not reported (20).	Mono-ingredient (20).
Trans-resveratrol (21)	EU Decision no. 1190/2016 (21)	FS in the form of tablets or capsules intended adults, in maximum dose: • 150 mg per day (21).	No side effects have been reported (22).	Mono-ingredient (22).
Enzymatic preparation of prolyl-3-oligopeptidase produced with a genetically modified strain of *Aspergillus niger* (23)	EU decision no. 1387/2017 (23)	FS as defined in Directive 2002/46/EC: • 120 PPU*/day (2.7 g of enzyme preparation/day); • (2×106 PPI*/day) for the general adult population (23).	No side effects have been reported (24).	Multi-ingredient (7)
Beta glucans in yeast * (25)	EU Decision no. 2078/2017, for the extension of	FS, as defined in Directive 2002/46/EC, with the exception of food supplements for infants and young children:	Possible side effects: • dermal hypersensitivity (26)	Multi-ingredient (26)

	the field of use according to Decision no. Commission Regulation (EC), no. 762/2011 (25)	• 1,275 g/day for children older than 12 years and the adult population in general; • 0.675 g/day for children under 12 years of age; Substitutes for a total diet for weight control as defined in Regulation (EU), No 182/2011. 609/2013: • 1,275 g/day; Foods intended for special medical purposes, as defined in Regulation (EU), No 182/2011. 609/2013, except for foods intended for special medical purposes for infants and young children: • 1,275 g/day (25).		
Taxifolin Rich Extract * (27, 28)	EU Decision no. 2079/2017 (27, 28)	FS, as defined in Directive 2002/46/EC, with the exception of food supplements for infants and young children, children and adolescents under 14 years of age: • 100 mg/day (27, 28).	No adverse reactions have been reported (29).	Multi-ingredient (29)
2′-fucosyl-lactose * (30)	EU Decision no. 2201/2017 (30)	Starting formulas and follow-on formulas: • 1,2 grams of 2′-fucosyl-lactose per liter of final product, ready to use, marketed as such or reconstituted according to the manufacturer's instructions (30).	Not mentioned	Not mentioned
Calanus finmarchicus oil * (31)	EU Decision no. 2353/2017 (31)	FS as defined in Directive 2002/46/EC: • 2.3 g/day (31)	Mild side effects: - increased incidence of eczema (32). Possible side effects: - gastrointestinal disorders, in case of an amount greater than 2.3 g/day; - intolerance (33).	Mono-ingredient (32)
Chia seeds (*Salvia hispanica*) (34)	EU Decision no. 2354/2017 (34)	Yogurt: • 1.3 g of whole chia seeds per 100 g yogurt; • 4.3 g of whole chia seeds per 330 g of yogurt (portion). Bakery: • 5 g of whole seeds per 100 grams of bak-	No side effects have been reported.	Mono/multi-ingredient (34)

		ery products. Breakfast cereals; mixes of fruits, nuts and seeds, as well as prepacked chia seeds as such: • 5 g of whole seeds per 100 grams of breakfast cereals (34).		
Ultraviolet-treated mushrooms * (*Agaricus bisporus*) (35)	EU Decision no. 2355/2017 (35)	Marketed fresh (35)	Not mentioned	Not mentioned

***SE** - Side effects; **RYR** – Red yeast rice fermented with Monascus purpureus; **monocholine** - monocholine of K, Reg. (UE) - Regulation (EU); **FS** –Food supplements; **DHA** - docosahexaenoic acid; **PPU** - Prolyl peptidase units or proline protease units; **PPI** – Protease Picomole International; **beta glucans in yeast** – human studies are very limited (27); **taxifolin-rich extract** - obtained from Dahurian larch wood [Larix gmelinii (Rupr.) Rupr]; **2'-fucosyl-lactose** - produced with Escherichia coli BL21 strain (31); **Calanus finmarchicus oil** - oil obtained from the shellfish (marine zooplankton) Calanus finmarchicus harvested in the Norwegian Economic Zone, and in the Jan Mayen area (32).*

Table 2. Adverse reactions caused by new food ingredients authorized by EFSA in the European Union during 2018.

Ingredient/substance approved as a novel food ingredient in EU	EU Decision/ Regulation	Category of products for which it has been authorized or action - Maximum dose/day (mg or g/day), according to EU Decision/Regulation	Adverse reactions/ Warnings	Consumption mode (eg: mono-ingredient)
RYR * - monocholine K * (36)	EFSA Journal 2018; 16 (8): 5368 (36)	Maintaining the normal concentration of LDL-cholesterol in the blood: • 10 mg monocholine K from RYR/day (36).	- multicellular-skeletal distortion; - fatigue; - pain and gastrointestinal symptoms; - hepatic side effects (37).	Mono and multi-ingredients (37)
Florotanins from *Ecklonia cava* * (38)	EU Regulation no. 460/2018 (38)	Food supplements, as defined in Directive 2002/46/EC, intended for the general population, except for children under 12 years of age: • 163 mg/day for adolescents between 12 and 14 years old; • 230 mg/day for adolescents over 14 years of age; • 263 mg/day for adults (38).	EFSA Warning *: the intake of iodine from food supplements containing fluorotanins from *Ecklonia cava* may be of concern to people at risk of thyroid disease and for those who are not at risk for thyroid disease but consuming food supplements containing fluorotanins from *Ecklonia cava* in addition to other dietary supplements containing iodine, since their total iodine intake may exceed the upper limit established for iodine (38).	Mono and multi-ingredients (38)

L-ergotionein (39)	Reg. (EU) no. 462/2018 (39)	Food supplements, as defined in Directive 2002/46/EC: • 30 mg/day for the general population (except pregnant and lactating women); • 20 mg / day for children older than 3 years (39).	No possible side effects have been reported (39).	Mono and multi-ingredients (39)
Extract from the roots of three plants (*Cynanchum wilfordii Hemsley*, *Phlomis umbrosa Turcz.* and *Angelica gigas Nakai*) (40)	Reg. (EU) no. 469/2018 (40)	Food supplements, as defined in Directive 2002/46/EC, intended for the adult population: • 175 mg / day (40)	Possible allergic side effects (40).	Mono and multi-ingredients (39)
Yeast for ultraviolet-treated bakery (*Saccharomyces cerevisiae*) (41)	Reg. (EU) no. 1018/2018 (41)	Food supplements, as defined in Directive 2002/46/EC: • CN (41).	No possible side effects have been reported (41).	Multi-ingredients (41)
Quinoa pyrroloquinoline disodium salt * (42)	Reg. (EU) no. 1122/2018 (42)	Food supplements, as defined in Directive 2002/46/EC, intended for the adult population, with the exception of pregnant women and lactating women: • 20 mg/day (42).	- no side effects have been reported (42); - no comprehensive assessment of renal function has been performed (43); - pro-oxidant activity (43); - no information on allergenicity has been provided (43).	Multi-ingredients (43)
Dry aerial parts of Hoodia parviflora (43)	Reg. (EU) no. 1113/2018 (43)	Food supplements, as defined in Directive 2002/46/EC, intended for the adult population: • 9.4 mg/day (43).	Insufficient characterization of novel food, limited allergenicity assessment, insufficient data to exclude risk to children over 12 years of age, insufficient information on specifications, stability, consumption assessment and toxicological data (43).	Multi-ingredients (43)
Cranberry extract in powder form (44)	Reg. (EU) no. 1631/2018 (44)	Food supplements, as defined in Directive 2002/46/EC, intended for the adult population: • 350 mg/day (44).	Possible nutritional risks associated with excessive consumption of polyphenols in children aged one to three years, resulting from the intake of polyphenols in novel foods and other sources of polyphenols in children's diets (44). Insufficient data to exclude the risk for young children aged one to three	Mono-/multingredient (44)

			years, the incomplete nature of the novel food specification and the lack of information on the protein content needed to exclude the risk of allergy (44). Possible side effects: Gastroesophageal reflux, nausea, digestive disorders (45).	
Whey Protein Isolate from Cow's Milk (46)	Reg. (EU) no. 1632/2018 (46)	Starting formulas, as defined in Regulation (EU) No. 609/2013: • 30 mg/100 g (powder); • 3.9 mg/100 ml (reconstituted). Follow-up formulas as defined in Regulation (EU) no. 609/2013: • 30 mg/100 g (powder); • 4.2 mg/100 ml (reconstituted). Substitutes for a total diet for weight control as defined in Regulation (EU) no 182/2011. 609/2013: • 300 mg/day. Foods intended for special medical purposes, as defined in Regulation (EU) no 182/2011. 609/2013: • 58 mg/day for young children; • 380 mg/day for children and adolescents aged 3 to 18 years; • 610 mg/day for adults (46).	Clinical studies with basic whey protein isolate from bovine milk have not been provided. The most clinical studies were related to the main components of the whey protein basic protein isolate: bLF * and bLP * (47). Allergies (47).	Mono-ingredient (47)
Refined shrimp peptide concentrate* (48)	Reg. (EU) no. 1633/2018 (48)	Food supplements, as defined in Directive 2002/46/EC, for the adult population: • 1,200 mg/day (48).	No possible RAs have been reported regarding the blood pressure and interaction of the concentrate with the drugs used in treatment of blood pressure disorders (48, 49). Allergen (49).	Mono-ingredient (48, 49)
Egg Membrane Hydrolyzate (50)	Reg. (EU) no. 1647/2018 (50)	Food supplements, as defined in Directive 2002/46/EC, for the general adult population: • 450 mg/day (50).	Adverse reactions reported in subjects included in the clinical trial: - hypertension; - allergies (51).	Mono-ingredient (51)

Xylo-oligosaccharide (52)	Reg. (EU) no. 1648/2018 (52)	Breakfast cereals: • 14 g/kg. Chocolate confectionery: • 30 g/kg (52).	Reported side effects: - transient gastrointestinal disorders: diarrhea (53). RA possible: - allergy (low probability) (53).	Mono-/Multi-ingredient (53)

Ultraviolet-treated mushrooms (Agaricus bisporus) *- with high levels of vitamin D2 (35);* ***Ecklonia cava*** *- edible seaweed (38);* ***EFSA*** *– Authority European Food Safety Authority;* ***quinine pyrroloquinoline disodium salt*** *- produced from the bacterium Hyphomicrobium denitrificans;* ***bLF*** *- bovine lactoferrin;* ***bLP*** *- lactoperoxidase, the refined peptic concentrate of shrimp - by enzymatic hydrolysis of the shells and heads of northern shrimp (Pandalus borealis).*

Table 3. Adverse reactions caused by new food ingredients authorized by EFSA in the European Union, in the period 2019-2021.

Ingredient/ substance approved as a novel food ingredient in EU	EU Decision/ Regulation	Category of products for which it has been authorized or action - Maximum dose/day (mg or g/day), according to EU Decision/Regulation	Adverse reactions/ Warnings	Consumption mode (eg mono-ingredient)
Schizochytrium sp. Oil (54)	Reg. (EU) no. 109/2019 (54)	Food supplements, as defined in Directive 2002/46/EC: • 250 mg DHA/day for the general population; • 450 mg DHA/day for pregnant and lactating women. Replacements of a total diet for weight control, as defined in Regulation (EU) no. 609/2013 and substitutes for a weight control table: • 250 mg/portion. Milk-based beverages and similar products for young children: • 200 mg/100 g (54).	No side effects/possible side effects reported (55).	Mono-ingredient (55)
Allanblackia seed oil (56)	Reg. (EU) no. 110/2019 (56)	Yellow spreadable fats and cream products: • 30 g/100 g. Mixtures of vegetable oils (*) and milk (falling into the food category: Dairy products, including beverage bleaching preparations): • 30 g/100 g (56).	No side effects/possible side effects reported (57).	Mono-ingredient (57)
Yarrowia lipolytica yeast biomass (58)	Reg. (EU) no. 760/2019	Food supplements, as defined in Directive 2002/46/EC, with the exception of food supple-	No clinical studies have been presented on the safety of Yarrowia lipolytica	Multi-ingredient (58, 59)

	(58)	ments for infants and young children: • 6 g/day for children over 10 years of age, adolescents and the general adult population; • 3 g/day for children aged 3 to 9 years (58).	yeast biomass in humans. Possible side effects: - allergies (59).	
The mixture of 2'-fucosyl-lactose/ difucosyl-lactose * (60)	Reg. (EU) no. 1979/2019 (60)	Replacements of a total diet for weight control, as defined in Regulation (EU) no. 609/2013: • 4.0 g/l (drinks); • 40 g/kg (products other than beverages). Foods intended for special medical purposes, as defined in Regulation (EU) No 182/2011. 609/2013: • in accordance with the specific nutritional needs of the persons for whom the products are intended. Food supplements, as defined in Directive 2002/46/EC, intended for the general population, except infants: • 4.0 g/day (60).	No clinical trials have been reported to verify the safety of the mixture 2'-fucosyl-lactose/difucosyl-lactose. Studies performed with 2'-fucosyl-lactose alone, in amount of 20 g/day, over 2 weeks were provided. Gastrointestinal RAs have been reported: - nausea; - ballooning; - diarrhea (61).	Mono-ingredient (61)
Partially defatted chia seed powder (*Salvia hispanica*) (62)	Reg. (EU) no. 500/2020 (62)	Food supplements within the meaning of Directive 2002/46/EC, with the exception of food supplements for infants and young children: • 7.5 g/day (62).	There are no clinical studies to verify the safety of Chia seeds in humans. The studies followed the benefits and few parameters for safety (eg blood pressure, histological parameters). Allergies may occur. No side effects have been reported (63).	Mono-ingredient (63)
Mushroom powder with vitamin D2 (64)	Reg. (EU) no. 1163/2020 (64)	Maximum vitamin D2 levels. Meal substitutes in the form of bars and drinks: • 2.25 µg of vitamin D2/100 g/l; • 125 µg of vitamin D2/100 ml (drinks). Foods intended for special medical purposes, as defined in Regulation (EU) no. 609/2013, except for those for infants: • 15 µg/day.	No specific studies have been provided on the safety of vitamin D2 fungus in humans. The studies made available to the Authority * by the applicant were performed with similar products. These studies show a little evidence in assessing the potential health effects of vitamin D2 mushroom powder. Regarding allergenicity, the applicant	-

		Food supplements, as defined in Directive 2002/46/EC, intended for the general population, except infants: • 15 µg/day (64).	referred to EFSA's conclusion on ultraviolet-treated mushrooms* (*Agaricus bisporus* (35)) (65).	
Sugars derived from cocoa pulp (*Theobroma cacao L.*) (66)	Reg. (EU) no. 1634/2020 (66)	Used as an ingredient for the population as a whole (66).	The Commission considers that, in the case of the current application, it is not necessary for EFSA to do so (66).	-
Alga *Euglena gracilis* * (67)	Reg. (EU) no. 1820/2020 (67)	Food supplements, as defined in Directive 2002/46/EC, with the exception of infant food supplements: • 100 mg/day for young children; • 150 mg/day for children aged 3 to 9 years; • 225 mg/day for children aged 10 years and adolescents (up to 17 years); • 375 mg/day for adults (67).	Based on the results, EFSA considers that the highest dose that has been tested and at which an adverse effect may occur is 3300 mg of seaweed Euglena gracilis desicatga/kg body weight/day (68).	-
Extract of *Panax notoginseng* and *Astragalus membranaceus* (AstraGin™) (69)	Reg. (EU) no. 1821/2020 (69)	Food supplements, as defined in Directive 2002/46/EC, for the general adult population, excluding food supplements for pregnant women: • 35 mg/day (69).	The applicant did not provide clinical trials and there were no extensive human studies published in the literature on the safety of Panax notoginseng and Astragalus membranaceus in humans. Possible side effects: allergies (70).	-
Yeast Biomass (*Yarrowia lipolytica*) with chromium content (71)	Reg. (EU) no. 1822/2020 (71)	Food supplements as defined in Directive 2002/46/EC, with the exception of food supplements for infants and young children: • 2 g/day for children aged 3 to 9 years, which means 46 µg of chromium per day; • 4 g/day for children over 10 years of age, adolescents and adults, which means 92 µg of chromium per day (71).	Possible side effects: - allergies (low risk) (72).	Mono-ingredient (72)
Selenium-containing yeast biomass (*Yarrowia lipolytica*) (73)	Reg. (EU) no. 1993/2020 (73)	Food supplements, as defined in Directive 2002/46/EC, with the exception of food supplements for infants and children under 4 years of age: • 50 mg/day for children aged 4 to 6 years, which means 10 µg of selenium per day; • 100 mg/day for children aged 7 to 10 years, which means 20 µg of selenium per day; • 500 mg/day for adolescents aged 11 to 17 years, which means 100 µg of selenium per day;	Possible side effects: - Allergies (low risk) (72,74).	Mono-ingredient (72, 74)

		• 800 mg/day for adults, which means 160 µg of selenium per day (73).		
Partially defatted rapeseed powder of *Brassica rapa L.* and *Brassica napus L.* * (75)	Reg. (EU) no. 120/2021 (75)	Grain mix sticks: • 20 g/100 g. Bread and buns with special ingredients added (such as seeds, raisins, herbs): • 7 g/100 g (75).	Possible side effects: - Allergies, in the case of people allergic to mustard (76).	-

Schizochytrium sp oil - oil extracted from *Schizochytrium sp microalgae;* **2'-fucosyl-lactose/difucosyl-lactose mixture** - obtained by fermentation microbial with a genetically modified strain of *Escherichia coli* K12 DH1; **Authority** - EFSA, Commission - European Commission, alga *Euglena gracilis* - whole cells dried by *Euglena gracili*

In addition to the product categories mentioned in Table 1, the oil extracted from the microalga *Schizochytrium sp*. (ATCC PTA-9695) may be added to dairy products, other than milk-based beverages, for cheeses, dairy products, excluding beverages or, for cheese-like products, spreadable fat and salad dressings, bakery products (bread and buns), sweet biscuits, cereal bars, cooking fats, non-alcoholic beverages (including similar dairy products and milk-based drinks), preparations for infants and preparations for young children – used in accordance with Directive 2006/141/EC, cereal-based preparations and baby foods for infants and young children, including those used in accordance with Directive 2006/125 (8).

Regarding food supplements, special medical foods and foods for use in low-calorie diets listed in Table 1, refined Buglossoides arvensis seed oil is approved as a novel food ingredient in dairy products and the like, beverages, cheese and cheeses, butter and other fat and oil emulsions, including spreads (not for cooking or frying), breakfast cereals (14).

The European Commission has approved lacto-N-neotetraose (tab. 1) (16) as a novel food ingredient in pasteurized and sterilized milk products (including UHT), non-flavored, non-flavored fermented milk products, beverages and other products than beverages, flavored fermented milk products, including heat-treated products in beverages and non-beverages, cereal bars, tabletop sweeteners, infant formulas, as defined in Directive 2006/141/EC.

In vitro and in vivo studies suggest that trans-resveratrol sulphate may inhibit CYP enzymes in humans and may interact with drugs that are primarily metabolised by CYP2C9 (22).

Other authorized uses for yeast beta glycans (Saccaromyces cerevisiae) are the following: beverages based on fruit juice and/or vegetable juice including concentrated and dehydrated juice, fruit flavored beverages, powdered form for cocoa-based beverages, breakfast cereals, breakfast cereals, whole grain breakfast cereals (instant hot cooking), cookies, crackers, milk drinks, dairy products fermented milk, similar dairy products, dehydrated milk/milk powder, soups and mixes for soups, chocolate and sweets, protein bars and protein powder, jam, marmalade and other fruit spreads (25).

The extended conditions under which taxifolin-rich extract may be used are the plain yogurt/fruit yoghurt (when used in dairy products, taxifolin-rich extract may not replace, in whole or in part, any constituent of milk), kefir, sour milk, powdered milk, cream, fermented cream, cheese, butter, chocolate confectionery, soft drinks (28).

Commercially grown Agaricus bisporus mushrooms are subjected to ultraviolet treatment after harvest, which results in a vitamin D_2 content of ≤ 10 µg/100 g fresh weight. UVB radiation: a process of radiation in ultraviolet light with a wavelength in the range 290-320 nm. Vitamin D2 in the finished product: 5-10 µg/100 g fresh weight at the end of the shelf life (35).

The Scientific Opinion issued by EFSA on monacolin K in RYR (36), it has the same structure as lovastatin, the active ingredient in several medicines authorized to treat hypercholesterolemia in the EU. With the help of the Mintel Global New Products (MintelGNPD) database, which lists the contents of all product labels containing monacolin K from RYR, 40 products containing monacolin K from RYR were identified and included in the category "Vitamins and dietary supplements". Approximately 25% of the total products identified provided the daily intake of 10 mg monacolin K recommended by EFSA, and only 8 products were identified as mono-ingredients, containing only RYR preparation (36). Although studies underlying this scientific opinion have shown that monacolin K and lovastatin rapidly convert from the lactone form to an identical form of hydroxy acid (HA), the latter being responsible for the inhibition of 3-hydroxy-3. Methylglutaryl-coenzyme A (HMG-CoA) enzyme reductase involved in cholesterol biosynthesis, and the acid form occurs naturally in RYR. The bioavailability of lovastatin increases by 30-50% when taken as a standard dose. Due to the involvement of the CYP3A4 isoform in its metabolism, there have been found interactions with drugs or food ingredients with inhibitors of this enzyme, leading to increased plasma statin levels and a possible increased risk of toxic effects (36).

The WHO, FDA, EMA, and ANSES have published common side effects for RYR and lovastatin: damage to musculoskeletal and connective tissue, liver, nervous system, gastrointestinal tract, skin, and subcutaneous tissue (4, 36).

The case reports used to carry out the aforementioned scientific opinion, specified the daily intake of monacolin K in which SE (rhabdomyolysis, hepatitis and skin disorders) occurred was 3 mg/day for a period between 2 weeks and 1 year (36).

L-ergothioneine is also accepted as a novel food ingredient in the following food categories: non-alcoholic beverages, milk-based beverages, fresh dairy products – maximum 0.040 g/kg (when used in dairy products, L-ergothioneine cannot replace, in whole or in part, any milk constituent), cereal bars. The name of the novel food mentioned on the label of foods containing it is "L-ergothioneine" (39).

In addition to food supplements, the European Commission and EFSA have approved yeast for ultraviolet-baked bread (Saccharomyces cerevisiae) and for the addition of yeast-leavened bread and buns, yeast-leavened bakery products, fresh or dried pre-packaged yeast for home baking (41).

In accordance with Article (5) of Regulation (EU) no. 1133/2018 (43), in its opinion, the Authority did not confirm the safety of dry aerial parts of Hoodia parviflora in food for the uses and use levels proposed by the applicant, as consumption would exceed the level considered safe (0.134 mg/kg body weight). However, the Authority concluded that the dry aerial parts of Hoodia parviflora are safe for adults when added to food supplements in a maximum daily dose of 9.4 mg, which corresponds to the safe level of consumption of an adult with a body weight of 70 kg.

In the case of refined shrimp peptic concentrate - by enzymatic hydrolysis of shells and heads of northern shrimp (Pandalus borealis) (48), according to point (13) of Regulation (EU) no. 1633 of 2018, data from the 90-days oral toxicity study served as a basis for assessing the toxicity profile of refined shrimp peptide concentrate and for establishing the level at which no adverse effects are observed. Data from the study evaluating the antihypertensive effects and safety of the refined peptide concentrate in shrimp in healthy subjects with mild to moderate hypertension, as well as data from the parallel double-blind, placebo-controlled study on the evaluation of the antihypertensive effect and safety dietary supplement with refined shrimp peptide concentrate in the case of healthy individuals with mild or moderate hypertension, served as a basis for establishing the safety of the novel food for this category of consumers.

Therefore, it is considered that, in the absence of data from the unpublished reports of those studies, it would not have been possible to reach these conclusions on the safety of the refined shrimp peptide concentrate. In carrying out this study, the applicant replied that some Member States had objected to the safety of refined shrimp peptide concentrate in the case of hypo-, normo- and hypertensive consumers given its alleged antihypertensive effects, its potential side effects related to its presumed ability to inhibition of angiotensin converting enzyme (ACE) and its potential cardiac effects, and on potential drug interactions used in the treatment of blood pressure disorders (48).

Powder with a high content of partially defatted chia seed protein (*Salvia hispanica*) (62), in addition to food supplements (tab. 1) may also be added in unflavored fermented dairy products, including unflavored natural sour milk (excluding sterilized sour milk), untreated after fermentation, non-flavored fermented milk products, heat-treated after fermentation, flavored fermented milk products, including heat-treated products, confectionery, fruit juices within the meaning of Directive 2001/112/EC and vegetable juices, fruit nectars within the meaning of Directive 2001/112/EC and vegetable nectars and similar products, flavored beverages. Powder with a high content of partially defatted chia seed fibers (*Salvia hispanica*) is accepted by EFSA for addition to confectionery, fruit juices within the meaning of Directive 2001/112/EC and vegetable juices, fruit nectars within the meaning of Directive 2001/112/EC and vegetable nectars and similar products, flavored beverages (62).

Given the clinical trials conducted by various teams of specialists, EFSA considers that in the case of yeast biomass (*Yarrowia lipolytica*) (72) containing selenium, it should be re-evaluated (74).

Probiotics that can cause human sepsis, generally in elderly patients and those suffering from chronic diseases, are Lactobacilli (strains of *L. rhamnosis*, due to its high translocation potential) (77), *Lactobacillus sp*. bacteremia which is sometimes fatal (77), infectious endocarditis

(77) caused *by L. rhamnosus*, *L. casei, L. acidophilus, L. jensenii, L. plantarum and L. paracasei* (77). They can cause anaphylactic response in patients who have *undergone* cardiovascular surgery (77) or localized infection in diabetes associated with old age and liver transplantation (77).

Thus, for terbinafine (78) which is metabolised by the enzyme CYP3A4 and the clearance (or intracellular concentration) of this drug may be influenced by dietary supplements/other products containing *Agaricus blazei Murrill*, *Aloe vera*, *Artemisia annua*, *Andrographis paniculata*, *Matricaria recutita*, *Chrysanthemum morifolium*, *Vitex agnus castus*, *Taraxacum officinale*, *Echinacea purpurea*, *Tanacetum parthenium*, *Zingiber officinale*, *Allium sativum*, *Hydrastis Canadensis*, *Centella asiatica*, *Commiphora mukul*, *Crataegus monogyna*, *Cymbopogon citratus* , *Artemisia annua*, *Urtica dioica, Mentha piperita L*, 3,3', 4', 5,7-pentapentahydroxyflavone (quercetin), *Monascus purpureus (Red Yeast Rice)*, *Trifolium pratense*, 3,5, 4'-trihydroxystilbene (resveratrol), *Rhodiola rosea, Serenoa repens, Glycine max* (Soy), *Turmeric longa* (79).

The CYP2C9 enzyme metabolizes dermatological drugs such as voriconazole (80) and can be inhibited by dietary supplements/other products containing *Andrographis paniculata*, Sulphydryl proteolytic enzyme, cysteine proteinase, *Matricaria recutita*, *Harpagophytum procumbens*, *Tanacetum parthenium*, *Allium sativum*, *Centella asiatica*, *Cymbopogon citratus* (Lemongrass), *Magnolia officinalis*, *Urtica dioica*, *Mentha piperita L.* (Peppermint), *Trifolium pratense*, 3,5,4'-trihydroxystilbene (resveratrol), *Serenoa repens*, *Eleutherococcus senticosus* (79).

As regarding "Nutrivigilance that is a new activity referring to dietary supplements" (2), the authors Morgan C, Ghibu S, Juncan AN et al presented the current use of SE and the interaction with drugs of certain substances or herbs, such as Aloe Vera, *Aristolochic acids/Aristolochia sp, Chelidonium majus, Citrus sp, Cytisus sp, Echinacea purpurea, Ginkgo biloba, Green tea extract, Camellia sinensis, Hypericin St. John's wort/Hypericum perforatum, Lamiaceae sp*. With high contents in *Rosmarinic acid, Valeriana officinalis*, etc.

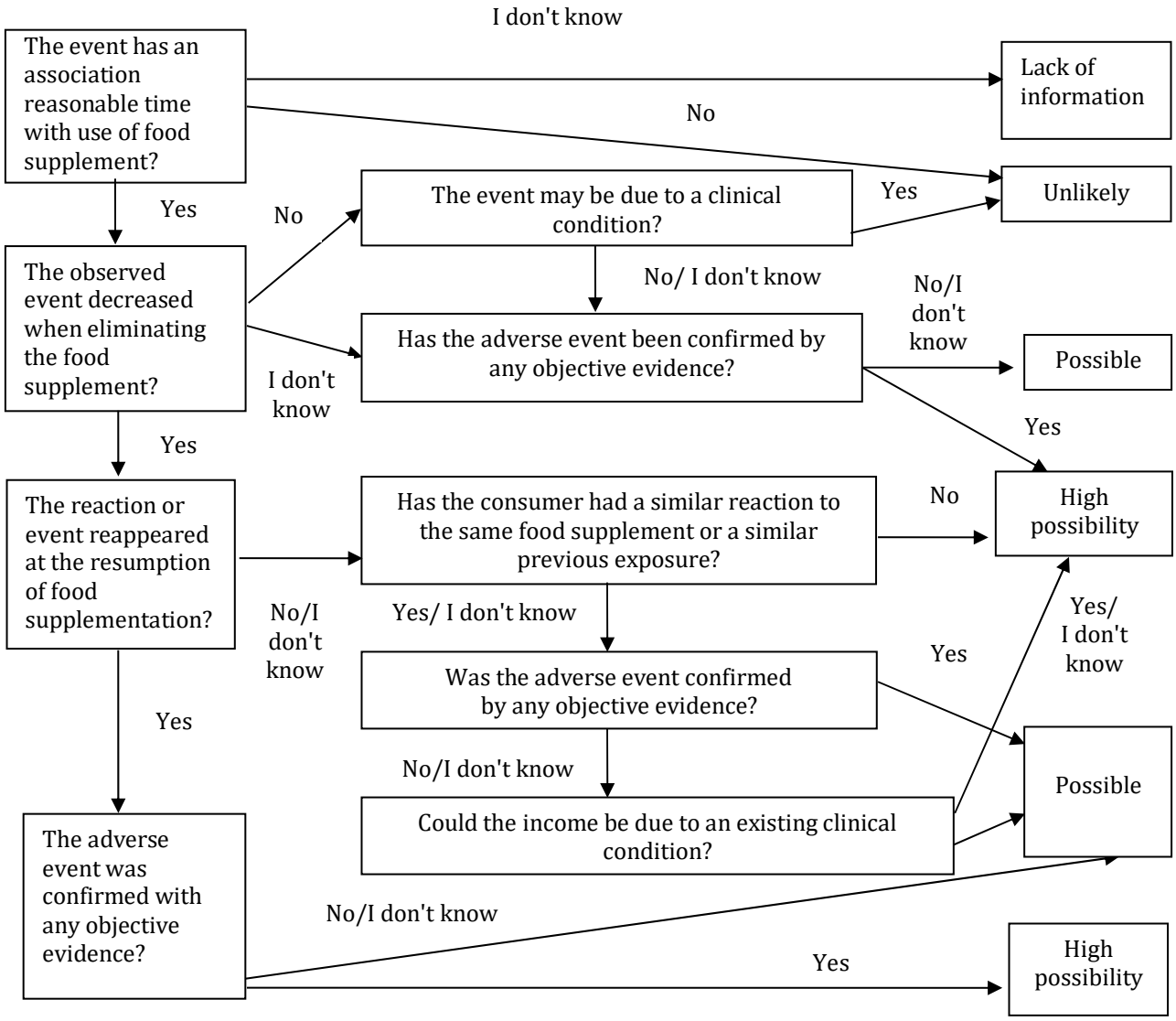
To establish the severity-causality relationship in the case of SA, authors such as Kazuki I, Hiroshi Y, Mamoru K et al. (79) propose the use of algorithms used in pharmacovigilance, for drug-induced RA: Naranjo scale, FDA, Kramer scale, Liverpol scale, WHO scale.

Table 4 and Figure 1 show the Naranjo and FDA algorithms.

Table 4. Naranjo algorithm (81).

Nr. No	The question	Yes*	Not*	I do not know *
1	Is there a notification about the reaction, on the label or in the package leaflet food supplement?			
2	Did the side effect occur after taking the food supplement?			
3	Did the adverse reaction improve when the suspected food supplement was discontinued?			
4	Did the adverse event recur when the food supplement was given?			
5	Are there any causes other than the dietary supplement that could have caused side effects?			
6	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?			
7	Did the consumer have a similar adverse reaction to the similar food supplement in the previous exposure?			
8	Has the adverse event been confirmed by any objective evidence?			

** Scores applied: ≥ 9 most likely, 5 - 8 likely, 3 - 4 very likely, 1 - 2 possible, ≤ 0 unlikely.*



DISCUSSIONS

Given that new food ingredients can be added to food supplements and a wide range of foods, in which new food ingredients, the lifestyle of many people can be added, there is a risk of reaching and/or exceeding the maximum allowable dose and challenging AR identified or unidentified up to date. A major risk is the large amount of commercial information on the benefits of various plant resources, without a possible and scientifically proven/clinically proven AR and their interaction with food or medicine.

Nutrivigilence is also important from the perspective of CYP's transformation of certain plant components into toxic or mutagenic

substances and reactive, carcinogenic metabolites by 1'-hydroxylation to allylic side chains and the bioactivation of alkylbenzenes, such as CYP1A1, CYP1A2, and CYP1A2, and by their high catalytic capacity they contributed to the metabolic activation of elemicin, by the formation of 1'-hydroxyelemicine (82). Thus, excessive intake of foods and spices containing elemicin can lead to cellular toxicity. This is an argument why nutrivigilence is important in both the food and food supplements, dietetics and nutrition and pharmaceutical industries.

We propose the application of the algorithm model for drug-induced RA to food supplements. One method of collecting information on possible ARs caused by FS is by telephone survey, including the following criteria: the substance involved, the age of the patient (adult/paediatric), the type of ingestion (accidental or intentional), the food consumed and their approximate amount, where he bought FS (hypermarket, health food store, community pharmacy, online pharmacy or vari-

ous websites), the symptoms recorded, evaluated according to severity and causality.

Another method of collecting information about AR caused by FS are online questionnaires distributed through social networks, or through companies organizing medical events or otherwise.

We joined the signal sent by colleagues Morgan C, Ghibu S, Juncan AN et al (2) and supported the urgent need to legislate the reporting of adverse reactions caused by dietary supplements, including their interaction with food or medicine. The veracity of the practical applicability of the legislation and the existence of an educational program of the population, proved that this intervention is not to be null and void.

We consider that the formation of multidisciplinary teams of regional specialists, as well as their cooperation on a regular basis, might have a constructive brainstorming for data collection (adverse reactions, age, etc.), the database formation and the identification of severity-causality, which could be a good start for implementing nutrivigilance in Romania.

Given the mandatory pharmacovigilance process in pharmaceutical companies, a similar system of nutrivigilance is needed in food and food supplement factories in Romania. The implementation of the nutrition surveillance system may be one of the methods of re-evaluation of food additives and ingredients approved by the European Food Safety Authority (EFSA) and European Commission.

Due to the complexity of nutrivigilence, this article has the following weaknesses: the methodology of approaching the problem and the existing scientific basis.

CONCLUSIONS

1. The formation of territorial teams of specialists and their involvement in risk assessment, monitoring and management of unauthorized exposure to food supplements, especially among vulnerable population groups, can have a constructive impact on the collection of medical and pharmaceutical data (adverse reactions, age, etc.).
2. The formation of a pharmacovigilence database and the identification of the causality of the reported side effects could be a good start in implementing nutrivigilence in Romania.
3. We recommend conducting a pilot study in Romania and possibly in collaboration with colleagues from the Republic of Moldova, to test the two algorithms and adapt to the conditions in this area.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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Irina Mihaela MATRAN, ORCID ID: 0000-0001-5491-0796, Web of Science Researcher ID: O-3431-2019, SCOPUS Author ID: 55941866400
Daniela Lucia MUNTEAN, ORCID ID: 0000-0002-6263-0708
Cristina NICULAS, ORCID ID: 0000-0003-2879-5813
Roxana Maria MARTIN-HADMAS, ORCID ID: 0000-0003-1499-5398, SCOPUS Author ID: 23670523500
Monica TARCEA, ORCID ID: 0000-0001-7299-118x, Web of Science Researcher ID: AAB-8622-2019, SCOPUS: Author ID 24401852300