CHARLES UNIVERSITY
FACULTY OF MEDICINE IN PLZEŇ

SAFETY OF DIETARY SUPPLEMENT USE
BEZPEČNOST DOPLŇKŮ STRAVY

-habilitation thesis-

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Contributions

The work described in this habilitation thesis is my own original research done unless otherwise stated.

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Contents

Abbreviations

ADI	Acceptable Daily Intake Adverse Drug Reaction
ADR	the Adverse Event Reporting System
CAERS	The CFSAN Adverse Event Reporting System
CAFIA	the Czech Agriculture and Food Inspection Authority
CFSAN	the Center for Food Safety and Applied Nutrition
CNC	Czech Nutrivigilance Centre
CYP	Cytochrom P450
DS	Dietary Supplements
EFSA	European Food Safety Authority
EMA	the European Medicines Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
GRAS	Generally Recognized as Safe
HMPC	The Committee on Herbal Medicinal Products
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NOAEL	No Observed Adverse Effect Level
P-gp	P-glycoprotein
RASFF	the Rapid Alert System for Food and Feed
SIDC	State Institute for Drug Control
WHO	World Health Organization

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Introduction

1 INTRODUCTION

The consumption of dietary supplements (DS) is increasing worldwide. The Global Dietary Supplements Market is estimated to be USD 139.38 billion in 2024, and it's projected to reach USD 173.69 billion by 2029 (1).

In Europe, the market is expected to grow from USD 21.64 billion in 2024 to USD 33.30 billion in 2029 (2).

The market growth is driven by consumers' growing interest in maintaining and improving their overall health. In Europe, an increased demand for DS was especially noted for products supporting the digestive, immune, cardiovascular and skin health. The expansion of the market is further fueled by the digitalization of the retail sector and is expected to also grow due to an increase in popularity of herbal supplements (2).

In Europe, the prevalence rates of dietary supplement usage range from 5% to over 50% (3). When comparing Europe to some other western countries, the USA has the highest dietary supplement consumption rate at 58.5%, followed by Canada (47.3%) and Australia (43.2%) (4-6).

In the Czech Republic, three of four Czechs bought a dietary supplement in the last year and spent an average of 5,700 CZK on DS per year (2023) (7, 8). Czechs were mainly buying DS for the support of their musculoskeletal, gut and skin health. Two fifths of Czechs used a DS to enhance their health while treating an underlying health condition. Multivitamins, single minerals (magnesium, zinc, calcium), single vitamins (vit.C, D, B), probiotics/prebiotics, fish oil, collagen and herbals were the most popular DS used for the maintaince of good health (7).

Approximately one-third of all adults reported using DS concurrently with prescription medications. A doctor-informed medical condition turned out to be a potential risk factor for the concomitant use of DS and prescription medication (9). When individuals use both DS and prescription medications simultaneously, there is a potential for DS-drug interactions (10).

These interactions can affect the effectiveness and safety of prescribed medications, especially for chronic conditions (11, 12). For example, systematic review of Czigle S et al. have identified herb-drug interactions related to commonly used herbs affecting the central nervous which can lead to therapeutic failure and/or side effects of prescribed medication (e.g., concomitant use of *Hyperici herba* and antithrombotic agents can result in an increased risk of bleeding) (13).

Even though DS are generally considered safe and many documented interactions remain of uncertain clinical significance, emphasizing the need for DS-drug interaction awareness is essential in making informed decisions in clinical

practice. For example, a study by Aznar-Lou et al. investigated the prevalence of potentially serious DS-drug interactions among users of selected drugs using a nationally representative data obtained from the National Center for Health Statistics and Centers for Disease Control and Prevention in the United States. The authors reported a prevalence rate of potential DS-drug interaction of 49%. Older age and higher education was strongly associated with the occurrence of a potential interaction (11). In the UK, researchers analyzed older adults registered at UK general practices who frequently use DS to assess the prevalence of the occurrence of DS-drug interactions. Older adults combined DS with prescription drugs in 78% of cases. Almost 33% of them were at risk of potential interactions with DS (12).

Dietary supplements often contain many ingredients which can lead to not only DS-drug interactions but also to other unpredictable and/or undesired effects (14-17), especially in specific population groups such as children, pregnant and lactating women, older people and people with chronic conditions (18).

Some adverse reactions may also be attributable to a lack of standardization, contamination, adulteration, plant misidentification/substitution as well as their inappropriate labeling or improper use (22-30).

In addition, clients frequently fail to discuss the appropriate use of DS with their physicians to ensure their safe use due to their lack of awareness regarding the risks associated with DS use or because health-care providers do not inquire about DS usage during consultations (31, 32).

In clinical practice, time constraints and limited knowledge and/or access to evidence-based information sources of healthcare professionals were mainly reported to hinder the provision of evidence-based information about DS to clients (33-37).

Consumers may also be misled by false or inaccurate information when purchasing DS online, particularly if they fail to consult a healthcare professional, e.g., when marketers of DS make misleading claims about their products treating or preventing diseases (26-30).

In summary, the widespread use of dietary supplements, their potential health benefits, along with possible adverse effects and the need for improved regulation, indeed highlight the importance of conducting more research and implement new findings in these areas. This would be valuable and of interest for health care professionals, consumers and health-care policy makers on local as well as international level.

Therefore, four different aspects of the safety of DS, namely allergy- like immediate reactions in adults and children in connection with herbal use using data from VigiBase®, the risks associated with dietary supplement use in patients in the

pre-operative period, the safety of food additives in top-selling dietary supplements in the Czech Republic, and the quality of information on the internet relating to top-selling dietary supplements in the Czech Republic, were investigated and the results of the studies are further presented in the habiliation thesis.

1.1 Dietary supplements

1.1.1 Definition of dietary supplement vs. medicinal product

Dietary supplement

The European Food Safety Authority (EFSA) defines DS as: "*food supplements… concentrated sources of nutrients (i.e. mineral and vitamins) or other substances with a nutritional or physiological effect that are marketed in "dose" form (e.g. pills, tablets, capsules, liquids in measured doses). A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fibre and various plants and herbal extracts*" (38).

The European Union (EU) defines DS as: "*…food supplements.. means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities"* (39).

The Czech Ministry of Agriculture defines DS as a special category of food. Dietary supplement is defined in Act No. 110/1997 Coll., on foodstuffs and tobacco products and on Amendments to Certain Related Acts, as "*food, the purpose of which is to supplement the normal diet and which is a concentrated source of vitamins and minerals or other substances with a nutritional or physiological effect, contained in food alone or in combination, intended for direct consumption in measured small unit quantities"* (40).

Medicinal products, herbal medicinal products, traditional herbal medicinal products are defined and regulated by Act No. 456/2023 Coll., amending Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Certain Related Acts (the Act on Pharmaceuticals), as amended (41).

Medicinal product

A medicinal product is defined as

"(a) a substance or combination of substances presented as having therapeutic or preventive properties in case of human or animal diseases, or

(b) a substance or combination of substances that can be used in humans or administered to humans, or to use in animals or to administer to animals, either for the purpose of restoration, treatment or influencing physiological functions through pharmacological, immunological or metabolic effect, or for the purpose of determination medical diagnosis" (41).

EU legislation on pharmaceutical products for human use also applies to traditional herbal medicines.

Herbal medicinal product

Herbal medicinal products are defined as: *"any medicinal product, exclusively containing as active ingredients one or more herbal substances, one or more herbal preparations, or a combination of the two. As they are medicinal products, the registration process is the same as for other medicinal products"* (41).

Traditional herbal medicinal product

Traditional herbal medicinal products are herbal medicinal products for human use that meet the following conditions (41):
"(a) are intended to be administered by mouth, externally, or by inhalation;
(b) are intended to be administered exclusively in a certain strength and dosage;
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(c) their indications correspond exclusively to those of traditionally used herbal medicinal products, designed and designed on the basis of their composition and intended use, for use without the supervision of a physician necessary for diagnostic, prescribing or monitoring of treatment
(d) the period of traditional use laid down in paragraph 3(a) has expired; e),
(the period of traditional use for treatment has passed for at least 30 years,
of which at least 15 years in the European Union),
(e) the indications on the traditional use of such a medicinal product are sufficient; In particular, it has been established that the product is not harmful under the conditions of use and that the pharmacological effects or efficacy of the medicinal product are evident from long-term use and experience."

For the approval of traditional herbal medicines, a simplified registration procedure is used where safety data, experience from long-term use in a certain indication based on literature sources, documentation related to the composition, production process, pharmaceutical test results and a list of countries where registration or marketing authorization has been documented need to be

submitted. The Committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency (EMA) focuses on (1) establishing EU monographs covering the therapeutic uses and safe conditions of well-established and/or traditional use for herbal substances and preparations; (2) drafting a EU list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products. A list of herbal substances, preparations, and combinations for use in certain traditional herbal medicinal products has been established by Commission Decision 2008/911/EC. A herbal medicinal product can be introduced to the market after it is registered in compliance with the Herbal Directive 2004/24/EC in one of three main regulatory regimes: a) traditional use registration, b) well-established use marketing authorisation, and c) stand-alone or mixed application (42). Dietary supplements containing herbal ingredients are not included in this category (41).

Borderline preparations

The boundary between DS and some other categories of products is very narrow, and the categorization of a specific preparation must be carried out on a case-by-case basis. Borderline preparations may be subject to the assessment by the State Institute for Drug Control (SIDC) who decides whether the specific product falls into the category of a medicinal product or another category of products (e.g., DS, medical devices ect.) with different regulation. Yet, SIDC have not determined specific rules for product categorization (41).

Unlike DS, medicinal products are regulated by Act No. 456/2023 Coll., amending Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Certain Related Acts (the Act on Pharmaceuticals), as amended, as mentioned earlier (41). Medicinal products are thus used for the prevention and treatment of diseases, dignosis or alleviating health problems. Although DS affect human physiology, they must not be declare any therapeutic effect and are intended only to promote health (43, 44).

While the European Union aims for harmonization in various areas, including food regulations, there are still differences in way how member states interpret and implement these regulations. Food categorization is one such area where discrepancies can occur. Even though products may have identical characteristics, they might end up in different categories due to varying national guidelines (45).

It is important to note that we may find the terms herbal medicine, herbal supplement or dietary supplement containing identical herbals used interchangeably in the literature regardless of the classification status in the respective country and its legislation. Consumers also commonly do not differentiate between the terms dietary supplement, herbal medicine, traditional herbal medicine and quite often

they do believe that all these categories are safe (as they perceive them as natural) and are tested for efficacy and safety (44, 46).

1.1.2 Regulation and labeling of dietary supplements

In the Czech Republic, the Ministry of Agriculture is the competent authority who is responsible for DS (47). In the European Union, the responsibility for DS lays with different organizations in individual EU member states (47).

As mentioned earlier, regulation of DS is important since it is directly related to the quality and safety of DS. Under the current legislation, DS are not subject to the same safety precautions as prescription and over-the-counter medications. Medicinal products are subject to registration before being placed on the market in the Czech Republic. The authorized authority for human medicinal products is the SIDC. The registration procedure requires an extensive documentation in which the applicant proves the safety, efficacy and quality of the product (42).

In the contrary, the manufacturer or distributor of DS does not have to prove the efficacy and safety of DS. Yet, prior to the first introduction of a dietary supplement or fortified food on the market, they shall comply with the notification obligation in accordance with Act No. 110/1997 Coll. on food and tobacco products, by registering via the link on the website of the Ministry of Agriculture and provide information on the composition and other properties of the product and, if necessary, insert the label. By submitting the text of the label, including mandatory information, which will be included on the product's packaging, before the first launch of the DS on the market through the Food Notification System, the legal obligation is fulfilled (40). The Ministry of Agriculture collaborates with National Institute of Public Health. The National Institute of Public Health may assess the product before or during the notification and issue a Health Safety Certificate which is valid for 1 or 3 years. The assessment includes an evaluation of the composition of the product, forms of vitamins and minerals, use of plant parts and their extracts from the point of view of traditional use in the EU, the amount of active ingredients in the recommended daily dose as well as an assessment of the labeling of the product (health claims, recommended warnings for sensitive population groups) from the point of view of health safety and applicable legislation. A laboratory tests are done as well. Efficacy of the product is not tested. If all legislative requirements are met, the dietary supplement can be placed on the market on the same day when notification was sent to the Ministry of Agriculture (48).

The food business operator must also report the dietary supplement to the place of destination, or inform the relevant supervisory authorities (Czech Agriculture

and Food Inspection Authority, CAFIA) about the intake of selected types of food including dietary supplements from another EU Member State or from a third country according to the Decree No. 172/2015 Coll., on the information obligation of the recipient of food at the place of destination, as amended (48).

Dietary supplement composition

Requirements for the composition of DS are regulated in the Czech Republic by Decree No. 58/2018 Coll., on food suplements and composition of foodstufs which refers to substances that can be used for the production of DS and the conditions under which they can be used. Annex No.1 lists the name of the plants, parts of the plants and the maximum permissible amount in the daily dose (44). On the other hand, Annex No. 2 lists substances that cannot be used in the production of food. The Decree No. 58/2018 Coll. also refers to Annexes No. I and II of Directive 2002/46/EC on the approximation of the laws of the Member States relating to DS, as amended by the directly applicable regulations of the European Union, which list vitamins and minerals that can be used for the production of dietary supplements and establishes their recommended daily allowances (49).

Regulation (EC) No. 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and certain other substances to food, also regulates the use of plants in DS by listing substances of herbal origin which are prohibited or restricted in use including requirements for their labeling (e.g., appropriate warnings) (50). A section on plants which the European Commission intends to review for their safety is also included.

If a dietary supplement contains any „new ingredient“ or „a new type of food“ as described in the Regulation (EU) 2283/2015 of the European Parliament and of the Council dated November 25, 2015 on novel foods, amending Regulation (EU) No. 1169/2011 of the European Parliament and Council and repealing Regulation (EC) No. 258/97 of the European Parliament and Council and Commission Regulation (EC) No. 1852/2001, it is subject to an approval process and enough studies on their safe consumption before it is put on the market must be provided (51). For a new ingredient, an evidence of history of consumption in significant quantities before 5/15/1997 in the territory of any EU member state, regardless of the date of accession to the EU, is not documented. A catalogue of substances is published by the European Commission and can be found on the website http://ec.europa. eu/food/safety/novel_food/catalogue/search/public/index.cfm (52). It is a non-binding tool and a non-exhaustive list and serves as orientation on whether a product will need an authorisation under the Novel Food Regulation (53).

Moreover, a national list of some plants, or their parts, for use in the production

of DS in the Czech Republic was created as a consensus by the following parties: Ministry of Agriculture of the Czech Republic, Czech Agriculture and Food Inspection Authority, The National Institute of Public Health, State Institute for Drug Control, Federation of the Food and Drink Industries of the Czech Republic and Czech and Slovak Association of Special Foods. The list applies only to plants created by traditional breeding methods. Conditions of their use are also given for some herbs. It was published in 2021 and is recommendatory in nature only. The list is available at:

https://eagri.cz/public/web/file/721405/Narodni_seznam_nekterych_rostlin_pro_pouziti_pri_vyrobe_doplnku_stravy.pdf (54).

Food additives contained in the final product must comply with other regulations related to the use of food additives or contaminants in foodstuff (55, 56).

Dietary supplement labels

General requirements for food labeling of DS as stated by Act No. 58/2018 Coll. on food supplements and food composition must not attribute properties related to the prevention, treatment or cure of human diseases or refer to these properties (26). Statements stating or implying that a balanced diet cannot provide a sufficient amount of vitamins and/or minerals are not permitted. In addition, it is necessary to state on the packaging of the DS the following: 1. the label "dietary supplement" 2. the name of vitamins, minerals or substances characterizing the product 3. data on the amount of vitamins, minerals or other substances related to the recommended daily dose 4. data on the content of vitamins and minerals also in percentages of the daily recommended dose 5. recommended daily dosage and possibly other conditions of use 6. warning against exceeding the daily recommended dosage 7. warning that the products should be stored out of the reach of children 8. notice that DS is not a substitute for a balanced diet. It is not mandatory for the manufacturers of dietary supplements to provide information on contraindications, DS-drug interactions, and adverse reactions on the label unless otherwise specified for stated cases (26).

Health and nutritional claims

Regulation (EC) No. 1924/2006 harmonizes rules for using nutrition and health claims on food labels and in advertising from the point of view of their nutritional value and impact on health. It aims at increasing consumer protection and unifying conditions for food producers, especially those of DS (57, 58).

Health claim (Regulation (EC) No. 1924/2006) - is any claim that states, suggests, or implies a link between a food category, a food or one of its ingredients and

health. Health claims consist of a) claims about reducing the risk of disease which state, indicate or imply that the consumption of a certain food category, food or any of its components significantly reduces the risk of developing a certain human disease (Article 14 and according to Articles 15, 16, 17 and 19), b) claims regarding the development and health of children (Article 14 and according to Articles 15, 16, 17 and 19), c) claims supported by generally accepted scientific data (functional claims): physiological function, behavioral function and weight loss (according to Article 13.1) and d) claims based on new scientific findings and claims protected by patent (according to No. 18) (57, 58).

Only approved health claims by the European Food Safety Authority (EFSA) after the effectiveness based on scientific findings have been already confirmed can be used on dietary supplement labels and commercial communications (according to Article 13 or 14). On hold claims which EFSA has not yet issued an expert opinion on are valid only temporarily. Both negatively assessed and not-yet-reviewed on-hold health claims can still be used and maybe used while complying with Regulation (EC) No. 1924/2006 and national rules is required until a decision on the on-hold list is taken (57, 58).

Nutrition claims (Regulation (EC) No. 1924/2006, Commission Regulation (EU) No 116/2010 and No 1047/2012 amending Regulation (EC) No 1924/2006 with regard to the list of nutrition claims) - attributes beneficial properties to the food based on energy, nutrients or other substances contained or not contained in food and is thus related to the content.

Medical claim (Regulation (EU) No. 1169/2011) - the term „medical claim“ is not directly defined anywhere in the legislation, on the basis of Article 7, paragraph 3 of Regulation 1169/2011, it can be defined as a claim that ascribes to food a property that enables the prevention, mitigation or cure of a disease. For example, names of diseases (e.g., diarrhoea), names of symptoms (e.g., pain), words otherwise associated with diseases or health problems (e.g., prevention, acute) can be considered medical claims. Nevertheless, it is forbidden to make medical claims on a dietary supplement and give such impression also by means of graphics, as part of a product name or by placing them in categories (57, 59), e.g., in sections in pharmacies. For example, the medicinal product called Condrosulf has the following therapeutic indication based on the Summary of Product Characteristics: „*it is indicated for the treatment of degenerative joint diseases, especially gonarthrosis, coxarthrosis and arthrosis of the finger joints*“ vs. a dietary supplement containing glucosamine sulfate and chondroitin sulfate can only use an approved health claim: „*it can contribute to the normal activity (flexibility, mobility) of the joints*“.

Other claims fall under different legislation (e.g., claims for consumers with lactose intolerance such as „lactose free“, production labels such as „bio“ or „organic“, on aromas) or no legislation (e.g., lifestyle claims such as „active life“, beauty claims such as „for shiny hair“, slogans such as „gives you wings“) (57).

Some aspects of the differences in the provision of DS vs medicines are summarized in Table 1.

Table 1: Differences in the provision of dietary supplements vs medicines (adopted and revised from 60)

	Dietary supplements	**Medicines**
Intended use	A concentrated source of nutrients or other substances, the purpose of which is to supplement the normal diet. Claims about the medicinal, preventive properties of the supplement must not be stated on the packaging of the dietary supplement.	A substance or combination of substances with curative or preventive properties.
Approval process	They are not approved, the manufacturer or importer only has an information obligation to the Ministry of Agriculture of the Czech Republic, to which they must send the text of the Czech label of the dietary supplement before it is put on the market for the first time. Before placing on the market, the manufacturer is not obliged to prove the effectiveness of the dietary supplement.	Medicines must go through an approval procedure (registration) before being put on the market, in this process the effectiveness, quality and safety of the product are evaluated, the manufacturer submits toxicological and pharmacological tests, clinical evaluations, etc.
Method of sale	Dietary supplements are available over the counter and are not subject to a medical prescription.	In justified cases, with regard to the substances contained in the medicine, its use is tied to a medical prescription, i.e. the patient only obtains it on the basis of an examination by a doctor.
Availability	Dietary supplements can be found in pharmacies*, regular grocery stores, drugstores, etc. Dietary supplements are often offered in the form of presentation events or the Internet.	Medicines can only be dispensed in pharmacies**, through their online offers (over-the-counter only) or from sellers of reserved medicines.
Requirements for the seller	The law does not define in any way the professional competence of the staff of dietary supplement stores.	Medicines can only be dispensed by persons specified by law (pharmacists, pharmaceutical assistants, sellers of reserved medicines).
Sales through websites	Dietary supplements are often sold via the Internet, and the Internet seller is also the operator of a food business.	Mail-order sales of medicines can only be carried out by an approved "brick and mortar" pharmacy via mail-order (Internet) sales, only over-the-counter medicines (without a prescription).
Mandatory labeling on the packaging	Each dietary supplement must be marked with the words "dietary supplement". HEM number can still be found on the packaging of some dietary supplements as it was issued prior market circulation by the Ministry of Health of the Czech Republic under the former rules. (formerly Decree No. 225 / 2008 Coll., currently Decree No. 58/2018 Coll.).	Each drug must be marked with the registration number of SÚKL or the European Medicines Agency. (Annex No. 4 and 5 to Decree No. 228 / 2008 Coll.).

*In case of a dietary supplement, the pharmacist must dispense the product based on the approved health claim.
**When dispensing a medicinal product in the pharmacy, the pharmacist must provide the patient with information based on the Summary of product characteristics including the correct and safe use and its storage conditions.

1.1.3 Prevalence and predictors of dietary supplement use

In Europe, the prevalence rates of DS range from 5% to over 50% (3). The systematic review on the prevalence of dietary supplement use in Europe analyzed 53 published studies with varying methodological quality. The review encompassed "any DS use at any time." Finland and Denmark had the highest prevalence of DS use (over 50%) and Italy the lowest (5%) (3). A consumer survey using the same methodology of collecting data on DS use across 14 EU countries from 2022 reported that 9 in 10 respondents had used a DS in the last 12 months in the East European countries (61).

When comparing DS use in Europe and the rest of the world, the USA had the highest DS consumption rate at 58.5%, followed by Canada (47.3%), and Australia (43.2%) (4-6). Limited studies from Africa repored that the majority of the sample used DS (81.3%) (62). In Brazil, the prevalence rate of dietary supplement use ranged from 28.8% to 96.9% across 25 cities (63). On the other hand, only 0.71% of the participants in China reported using DS (64).

The most commonly used DS across investigated countries included multivitamins with minerals, single vitamins (e.g., vitamin D, vitamin C), single minerals (e.g., zinc, magnesium, iron), fish oil, and supplements containing herbal ingredients. Both preventive and curative effects were frequently cited as health-related reasons for using DS (65-67). In Europe, younger adults frequently used multivitamins with minerals. On the contrary, older adults, especially women over 50 years of age, used vitamin D and calcium supplements. Iron and omega-3 fatty acids were commonly used by the middle aged women. Overall health improvement and maintaince was the most frequently cited reason for DS use by the US consumers (66). Similarly to EU, women used calcium supplements for bone health, while men were more likely to take supplements for heart health (66). Consumers who used dietary supplements for treatment purposes tended to be older and reported poorer self-rated health (67).

In the Czech Republic, an online survey on the use of DS in five hundred respondents aged 15 and older who were part of the Czech National Panel was conducted by ResSolution Group and Nielsen (7). Three-quarters of Czechs have used DS in the past year. Every third person took DS regularly. The most commonly used DS were vitamins (vitamin C, D and B), minerals (magnesium, zinc, calcium), multivitamins, probiotics/prebiotics and herbal supplements mainly to support overall health. Fifty percent of respondents used DS to support the musculoskeletal system, while two-fifths aimed to enhance microflora or digestion. Additionally, one-third sought to improve the quality of their hair, skin, and nails (7).

Strongest predictors of dietary supplement use were identified as being a female, younger or older age, higher education and income across most highly developed EU countries, the United States, Canada and Australia (3-6, 61). It also seems that dietary supplement users tend to be those with greater locus of control and active engagement in healthy lifestyle (physical activity, alcohol and tobacco absenthism) (6, 68, 69).

1.2 The safety of dietary supplement use

Dietary supplement side effects and interactions with medication

The type of side effect, frequency and severity to DS vary depending mainly on the characteristics of the products and the consumer. It may range from gastrointestinal complains such as constipation, diarrhea, upset stomach or nausea to hepatotoxicity. Immune or non-immune mediated reactions with dermatological, respiratory, cardiovascular or gastrointestinal complains may occur. The most vulnerable population groups belong to children, older adults, comorbid patients, pregnant and breastfeeding women (14, 15).

Examples of a range of side effects occuring after herbal or vitamin/mineral intake are presented in Tables 2 and in Table 3.

A drug interaction refers to a change how a drug behaves in the body due to recent or concurrent use of another drug, food, beverage, or supplement. These interactions can either increase or decrease the effects of one or both agents leading to either ineffectiveness of the treatment or side effects/even toxicity. A herb-drug interaction can occur at the pharmacodynamic level (altering tissue sensitivity or responsiveness) or the pharmacokinetic level (changing drug absorption, distribution, metabolism, or excretion). Most pharmacokinetic interactions primarily occur due to the modulation of metabolic enzyme activities, especially

the cytochrome P450 (CYP) isozymes (CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2E1 or CYP2D6), and the activities of membrane transporters, notably the efflux transporter P-glycoprotein (P-gp) (13, 70).

Pharmacokinetic interactions have been studied more extensively compared to pharmacodynamic interactions which have received less attention in research. The most well-known examples of herb–drug interactions include *Ginkgo biloba* and *Hypericum perforatum*. Active ginkgolides (*Ginkgo biloba*) act as an inhibitor of P-gp. On the other hand, *Hypericum perforatum* is known for inducing P-gp activity. *Hypericum perforatum* is also an inducer of CYP isoenzymes. Conversely, inhibitors of CYP enzymes include, e.g., *Ginkgo biloba, Valeriana officinalis (70, 71)*. Examples of herbals interacting with CYP450 and their pharmacokinetic herb-drug interactions are shown in Table 4.

Pharmacodynamic interactions occur when one drug changes the presence of the other drug at a site of action and may be synergistic, additive, or antagonistic in nature. Examples of additive effect maybe observed between *Ginkgo biloba* and antithrombotic agents. Ginkgolide B, a potent inhibitor of platelet-activating factor in humans, is just one component of ginkgo extract. Other compounds within ginkgo extract have also been identified as inhibitors of phospholipase A2, which affects both the platelet-activating factor and eicosanoid production. *Hypericum perforatum* seems to inhibit the reuptake of serotonin, norepinephrine, and dopamine and increase the effect of antidepressant drugs (13).

Moreover, herb-drug interactions can be complex as herbal medicines consist of mixtures of multiple active substances, and clinical outcomes may arise from interactions involving both pharmacokinetics and pharmacodynamics.

Conversely, certain interactions can have therapeutic benefits and may contribute to the development of novel therapeutic approaches. Some herbs can enhance drug/herb/vitamin absorption, leading to an increased bioavailability. For example, piperine (*Piper nigrum*) enhances the absorption of curcumin (*Curcuma longa*), thus improving its therapeutic effects (72).

More information on herbal or non-herbal DS side effects and DS-drug interactions including their clinical relevance and available evidence can be found in relevant information sources such as the Natural Medicines Comprehensive Database or Stockley's Herbal Medicines Interactions (73).

1.2.1 Monitoring of safety of dietary supplements

According to Article 14 of Regulation (EC) No. 178/2002 of the European Parliament and of the Council, as amended, the primary legal responsibility for the safety of DS and its labeling lies with the food business operator (which includes manufacturers, importers, and distributors) who places the DS on the market and must meet all legislative requirements (74). Moreover, the National Institute of Public Health may issue a Health Safety Certificate for a given DS

upon the request of the food business operator prior or during the notification process (75).

Supervision of safety of DS after a product enters the market is carried out mainly by the CAFIA and the Czech Trade Inspection Authority. CAFIA checks for the quality, safety, and labeling of foodstuffs in the entire chain from manufacturing companies, importers, transporters and wholesalers to sales in the retail network including online sales (76). CAFIA provides an overview of problematic dietary supplements on the website called www.potravinynapranyri.cz and lists risky websites and products at https://www.potravinynapranyri.cz/ESearch.aspx?lang=cs&design=default&archive=actual&listtype=tiles&page=1 (77, 78). CAFIA also informs the public about dangerous DS through the media in the form of press releases.

The most frequently reported problems with DS identified by CAFIA were: the product did not contain substances that were declared on the packaging, or contained less amount of active substances than indicated on the packaging, did not include information on dosing or declared a "medical" claim attributing therapeutic effects to the product (79).

Anyone can file a complaint about DS quality (e.g., a change in the colour, shape or taste) or any safety issue at CAFIA via a form at www.szpi.gov.cz (80).

Nutrivigilance

The term "pharmacovigilance" defines the activities related to the collection, detection, assessment, monitoring, and prevention of adverse reactions due to pharmaceuticals. It thus involves: *"a) monitoring the use of medicinal products in everyday clinical practice in order to identify previously unrecognised side effects or changes in the nature of adverse reactions, b) evaluation of the risk-benefit balance of medicines to decide what action, if necessary, is necessary to make the use of medicines safer, c) providing information to healthcare professionals and patients to improve the safe and effective use of medicines" (81).*

Recently, the term of "-vigilance" broadened to include safety of herbal products, cosmetics, and nutraceuticals. "Nutrivigilance" is a term used to describe the monitoring of adverse effects related to the use of DS, functional foods, and other nutraceuticals (82).

The Czech National Institute of Public Health defines the term nutrivigilance as "*a system of monitoring foodstuffs of a selected type, the aim of which is to ensure the protection of the health of consumers and thus reduce any negative impact on the health of potential consumers through appropriate measures, based on voluntary reports of adverse health reactions after consumption of these foods*" (83).

It is important to note that the terminology "herbal pharmacovigilance", "phytovigilance" and "nutrivigilance" for herbal containing products maybe used interchangeably in the literature. It is thus a challenge to monitor the safety of herbal products as a herbal product maybe classified as a medicinal product in one country or a dietary supplement in another country (82).

In case of occurence of an adverse reaction to DS, a consumer or a health care provider can report the suspect reaction directly to the food business operator or a Czech Nutravigilance Centre (CNC) established by the National Institute of Public Health (2014) at https://nutrivigilance.szu.cz/online-formular.html (84).

The CNC receives mainly reports of adverse reactions to foodstuff. DS are not reported to a greater extent. Only 37 reports of DS were reported to the CNC between 2015-2020. There were 7, 3 and 8 cases reported each year during the period of 2021-2023, respectively (85).

The State Institute for Drug Control also occasionaly receives reports related to adverse reactions to DS via the reporting system for spontaneous reporting of adverse reactions to drugs since the reporters sometimes do not differentiate between prescription drugs and over-the-counter drugs such as dietary supplements (44).

Based on spontaneous reports from 2015 to 2017, experts at the CNC found that incorrect use of DS by consumers often led to adverse reactions. As a result, the CNC formulated the following recommendations for consumers of DS (86):

- *Purchase products from manufacturers that clearly declare product quality on labels or leaflets. This includes information about composition, raw material origin, and safety analysis results.*
- *Follow recommended dosages and preparation methods.*
- *In specific cases (such as pregnancy, childhood, chronic illness, or medication use), consult with a physician or pharmacist regarding supplement use.*
- *Avoid taking dietary supplements before or during sports performance due to caffeine content.*
- *Refrain from combining multiple supplements with medicinal products.*
- *Supplements for muscle mass development or fat reduction should be avoided by individuals with heart disease, liver or kidney dysfunction, neuropsychiatric disorders, and pregnant or lactating women.*
- *Seek immediate medical advice if unusual heatlh problems occur while consuming supplements.*
- *Basic nutrition knowledge should be acquired during compulsory education, and deeper understanding requires ongoing self-study and consultation with experts educated in the fields of health, nutrition, food, and hygiene.*

Similar recommendations on how to procede when a consumer wants to buy DS was published by the CAFIA on their website (79):

- *Read the label carefully before buying, consult a doctor, pharmacist or nutritionist if you are unsure. The consumer should always be able to familiarize himself with the full composition of a dietary supplement before buying it (even if it is sold on the Internet or through social networks).*
- *Never buy unlabeled dietary supplements or supplements without a Czech label.*
- *Do not believe everything that products promise (weight loss, boosting "masculinity", preventing or treating diseases)*
- *Be cautious when making purchases on the basis of a leaflet or money order sent to home, as part of an unsolicited telephone offer or on suspicious unknown websites (click on List of risky websites and products – article on the CAFIA/PnP website at: https://www.potravinynapranyri.cz/ESearch.aspx?lang=cs&design=default&archive=actual&listtype=tiles&page=1.*

In the EU, legislation does not incorporate a specific provision for establishing a vigilance system focused on DS known as nutrivigilance (87). However, seven EU countries have independently established their own national nutrivigilance systems (Czech Republic, Croatia, Denmark, France, Italy, Portugal and Slovenia). The case-reports are collected online on voluntary basis by consumers, manufacturers and health-care professionals. Underreporting is vast since reporting is not mandatory, the vigilance systems are still not widely known and as health care professionals are unaware that patients are consuming DS and DS are not suspected to cause harm as DS are perceived as natural (88). The numbers of case-reports in a given time period in individual countries were as follows: Czech Republic (The National Institute of Public Health reported 37 cases between 2015 and 2020), Croatia (The Institute of Public Health received 6 reports from the end of 2021 to mid-2022), Denmark (Veterinary and Food Administration received 73 reports between 2014 and 2020), France (French Agency for Food, Environmental and Occupational Health and Safety recorded 4863 reports from 2009 to 2019), Italy (The National Institute of Health documented 1480 reports from 2002 to mid-2020), Portugal (The Ministry of Agriculture documented 136 reports from 2014 to mid-2020) and Slovenia (The National Institute of Public Health registered 107 reports from 2016 to 2019) (88).

In Italy, a Phytovigilance system has been in place since 2002 coordinated by the Italian National Institute of Health to collect spontaneous reports of suspected adverse reactions associated with DS, herbal products, and compounded preparations containing plants. As of October 2020, a total of 2315 reports had been collected,

with 32% of them involving serious reactions such as death, life-threatening events, or hospitalization (89).

In France, an audit of the information reported in newsletters produced from the Nutrivigilance system in France was conducted (August, 2019 – August, 2020). A total of 170 adverse event cases were recorded across a wide age range of adults from 18 to 90 years of age with 10% of reports recorded in children. The most frequently reported complaints were gastrointestinal, allergic, hepatic and cardiovascular in nature (90).

Also, an International Nutrivigilance network was founded by 27 European countries, Brazil and EFSA as an observer in 2014 with the aim to exchange information on nutrivigilance (88).

Vigilance systems if harmonized in EU could better assist decision makers in implementing necessary legal requirements at both the European and country levels to better protect public health. An urgent need to implement dedicated, coordinated, and centralized vigilance systems across Europe was articulated and published previously (21, 87). These systems aim to expand the network for sharing information and facilitate rapid identification of safety issues.

In the USA, the Center for Food Safety and Applied Nutrition (CFSAN) and the Adverse Event Reporting System (CAERS) serves the purpose of collecting adverse events related to food, dietary supplements, and cosmetics received voluntarily by consumers, health professionals, and manufacturers, and the mandatory reports from dietary supplement manufacturers. Overall, a total of 79,071 adverse events related to the use of DS were reported to the centre from 2004 to 2021 (16). Based on the analysis of a total of 15,430 adverse event reports collected during the period of 2004-2013, a reporting rate of DS was estimated at 2%. Serious adverse events were reported as well including death, life-threatening conditions, hospitalizations, congenital anomalies/birth defects, and events requiring interventions to prevent permanent impairments (5.1%) (91).

Based on US data from a nationally representative sample of emergency departments spanning the years 2004 to 2013, DS were linked to an average of 23,000 emergency department visits and 2,000 hospitalizations annually (less than 5% of the reported numbers for pharmaceutical products). Weight-loss, bodybuilding, and sexual-enhancement products were commonly linked to palpitations, chest pain, or tachycardia. Gastrointestinal complains such as nausea, vomiting or abdominal pain were frequently associated with iron or potassium products. Swallowing problems such as dysphagia or globus were the primary cause of emergency department visits related to products containing calcium predominantly among older adults (92).

Another dataset of 41,121 case-reports was evaluated over a 2,5 year period from the databases of marketers of DS in the United States. The most commonly reported DS were marketed for weight loss and glycemic control. The affected system organ classes included cardiovascular, gastrointestinal, and nervous system disorders. Serious adverse events accounted for 0.48% of the total of case-reports (93).

The Rapid Alert System for Food and Feed (RASFF) was created by the EU to facilitate information exchange among member countries' food safety authorities. Its purpose is to swiftly respond to health risks related to food including DS, allowing immediate action to prevent harm (94).

The RASFF detected 2,559 cases of DS with quality problems (1988–2019). Of these, 319 (12.5%) were specifically marketed for weight loss, and 202 (63.3%) contained unapproved synthetic drug components (17).

Similarly to RASFF, the Emerging Risk Exchange Network was established by EFSA in 2010 to facilitating the exchange of information on health risks related to food (95).

1.3 The safety of dietary supplement use in patients during pre-operative period

The prevalence of DS use before surgery ranges from 4.8 to 80% (96-100). Numerous health complaints have been documented after the use of DS in the pre-operative period if DS are not properly discontinued/continued prior surgery, e.g., perioperative bleeding, hypertension, hypotension, tachycardia, angina, water/electrolyte disturbances, hypoglycemia, or prolongation of anesthetic effects. Among preoperative patients, the most frequently used herbals were garlic, ginseng, ginkgo, St. John's wort, and echinacea (101-104).

Apart from herbal supplements, certain vitamins and minerals can also interact with prescribed medication and potentially impact surgery (e.g., interactions between anticoagulants and vitamins K, E, A) (105-109).

Therefore, herbal or non-herbal DS may interfere with pharmacotherapy across all therapeutical classes due to their potential to cause side effects or DS-drug interactions. Thus, safety issues may arise also during perioperative period. For reasons of patient safety, the Society for Perioperative Assessment and Quality Improvement convened a group of experts in the fields of internal medicine and anesthesiology to evaluate available data and provide recommendations regarding DS use prior surgery (110). Also, the FDA (USA) informs potential consumers of DS on the FDA website about the importance of being aware that certain DS can interact adversely with medications before, after, or during surgery. Therefore, the health care professionals may ask consumers to stop taking DS two or three weeks

before the procedure to prevent changes in heart rate, blood pressure, or bleeding risk (111).

A list of most commonly used herbals, their uses and effects including perioperative considerations and discontinuation recommendations is shown in Table 5.

1.4 Safety of food additives in dietary supplements

According to the Food and Agriculture Organization of the United Nations (FAO/WHO) Codex Alimentarius, a food additive is defined as *"any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result, (directly or indirectly) in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods"* (113).

Additives, as the name implies, are added to food and DS during production, packaging, transportation or storage. Food additives are categorized into several functional classes depending on how they are used in food, e.g., preservatives, nutritional additives, colouring agents, flavouring agents, texturizing agents, etc. (114). Food additives are also used as pharmaceutical excipients and play an important role in the production and preparation of medicines as well as DS. Pharmaceutical excipients enable and facilitate the processing of the substance into an application form and effect its stability and bioavailability. They can have the function of a solvent, preservative, stabilizer or taste-correcting component. In the case of solid pharmaceutical forms, they act as a filler or a binder. Additives or their intermediate products become part of them, in contrast to auxiliary substances, which are present during the technological processing of the product, but are contained in the final product in a maximum of trace amounts (115). This maximum permissible value is established on the basis of toxicological studies. The No Observed Adverse Effect Level (NOAEL) values are determined during the tests (the dose at which a harmful effect on the organism has not yet been observed). The Acceptable Daily Intake (ADI) value is obtained by reducing the NOAEL value by a hundredfold, in the case of a toxic substance with serious effects up to a thousandfold, and indicates the amount of the substance in mg per kg of body weight that can be consumed in food and dietary supplements without any health risk daily and throughout life (116).

At European Union level, food additives are assessed by the EFSA and an international body the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (116). Before being used in a product, each additive must be evaluated for safety, and the justification and necessity of using the additive in the product is also demonstrated. Food additives are regulated on the level of the European Union by Regulation (EC) No. 1333/2008 of the European Parliament and Council on food additives which lists approved additives and conditions for their use and labeling.

The specifications for food additives listed in Annexes II and III of Regulation No. 1333/2008 are determined by Commission Regulation (EU) No. 231/2012 (117, 118). Food additives are also covered by another Regulation (EC) No. 1331/2008 of the European Parliament and of the Council, which lays down a unified authorization procedure for food additives, food enzymes and food flavoring substances (119). Food additives for individual food categories can be found in the database of additives on the website of the European Commission (https://webgate.ec.europa.eu/foods_system/main/?sector=FAD&auth=SANCAS) (120) or in the online database of FAO/WHO within the Codex Alimentarius (http://www.fao.org/gsfaonline/index.html;jsessionid=961CB02B3E61115A41C4D06 8B4EE8954) (121). Moreover, the safety of food additives is reinforced by the The State Agricultural and Food Inspection (CAFIA) and the State Veterinary Administration who oversee the compliance with the EU regulations in the Czech setting. In the European Union, all food additives are labeled with an abbreviated „E" and a number, and can be found on the packaging of the product where both the function of the additive and the specific food additive is listed and identified by the abbreviation „E" + number identifier (e.g. E 171) or its full name (122).

Even though the food additives are well regulated and the prevalence of adverse reactions to food additives in adults is estimated to be less than 1% (123, 124), unwanted health problems from dietary supplements cannot be ruled out as the safety of food additives is subjected to constant re-evaluation process in line with the latest scientific knowledge (123, 124).

For example, the EFSA updated its safety assessment of the food additive titanium dioxide (E 171) from 2016 following a request by the European Commission in March 2020. The revised evaluation, considering new scientific studies and data, concluded that *„titanium dioxide can no longer be considered safe as a food additive due to potential genotoxicity concerns. With a new regulation, the European Commission is withdrawing titanium dioxide from the list of authorised food additives (foods containing it can be produced until August 7, 2022 and then sold while stocks last)"* (125).

Another example of a new scientific finding which revealed new association between approved food additive intake and its impact on health were recently published by the National Research Institute for Agriculture, Food, and Environment in France. The study was conducted investigating the association between food emulsifier intake and the risk of developing type 2 diabetes. Data from 104,139 French adults enrolled in the NutriNet-Santé prospective cohort study between 2009 and 2023 was analyzed. Even though emulsifiers had been previously evaluated as safe food additives, the data suggest that emulsifiers may disrupt the gut microbiota and increase the risk of inflammation and metabolic disruption and increase the risk of

developing type 2 diabetes in association with emulsifier exposure widely used in processed food (126).

Other unwanted health problems from dietary supplements cannot be ruled out in vulnerable population groups such as small children, elderly or specifically ill persons. For example, the prevalence rate of adverse events to food additives in children was estimated at 1.2% with higher prevalence rates in atopic children with comorbidities such as asthma or urticaria (7%) (127-129).

The reasons are mainly immature pharmacokinetic processes, e.g., absorption, distribution, metabolism and excretion as well as the health status and other relevant factors. Recently, the American Academy of Pediatrics has given rise to doubts regarding the safety of food additives generally recognized as safe (GRAS) for adults which can be risky for children. GRAS is a list of about 1000 substances that are considered safe by experts and are exempted from the usual tolerance requirements. Among potentially harmful excipients for children were included, e.g., aspartame, sorbitol, benzylalcolhol, polysorbate 80, benzalkonium, parabens and benzoates (130).

Below, examples of food additives and their types of adverse reactions are given, along with considerations from the EFSA's Scientific Panel:

• tartrazine (dye) – it is capable of provoking IgE and non-IgE dependent reactions and cause asthma, urticaria, periorbital oedema, and facial flushing

• cochineal/carmine (dye) – it is capable of causing anaphylactic reactions and asthma (the EFSA's Scientific Panel considered that „*since no threshold dose can be established for allergic reactions, it is advisable that exposure to the eliciting allergens, such as proteinaceous compounds, is avoided by introducing appropriate purification steps in the manufacturing process*") (131)

• guar gum, tragacanth, xanthan, carrageenan – it may induce allergic reaction, may cause undesirable effects of abdominal discomfort, such as flatulence, regurgitation, abdominal pain (cramps), bowel obstruction, constipation or on the contrary soft stools and diarrhoea (in March of 2024, the EFSA's Scientific Panel considered that „*the allergenic potential of guar gum used as a food additive should be reduced as much as possible, e.g., by decreasing the presence of proteins in the guar gum used as a food additive, which can be achieved by clarification of the gum*") (132)

• aspartame (sweetener) – data suggests that a small subset of the population maybe susceptible to aspartame-induced headaches (because of the limitations of the studies the panel concluded „*it is not possible to conclude on a relationship between aspartame consumption and headaches*"); allergic dermatologic reactions, such as rashes, sore throat/mouth, swelling and itching (the EFSA's Scientific Panel „*cannot exclude the possibility that in rare instances individuals could be susceptible to allergic reactions following aspartame ingestion*") (133)

• glycerol – it most often causes headache, nausea or vomiting, diarrhea, dizziness, dry mouth or increased thirst (The EFSA's Scientific Panel concluded that *„glycerol has low acute toxicity and that local irritating effects of glycerol in the gastrointestinal tract reported in some studies was likely due to hygroscopic and osmotic effects of glycerol and that the acute bolus exposure to glycerol by its use as a food additive should stay below doses at which pharmacological or side effects could occur. The Panel considered that a conservative estimate of the lowest oral bolus dose of glycerol required for therapeutic effect was 125 mg/kg bw per hour. The Panel considered this dose would also be responsible for the side effects (nausea, headache and/or vomiting) observed in some patients.*") (134)

Information regarding the health impact of cumulative intake of food additives from foods, drinks, medication and DS in humans as well as the potential of the 'cocktail' effects/interactions to cause harm have not been fully investigated (135) considering the fact that the average consumption of food additives is estimated to be at least 3–4.5 kg per year per person (given the fact that Western diet consists of 75 % of processed foods) (136). Nevertheless, the first research efforts had been made, e.g., a distribution and co-occurrence of food additives were analyzed in 126,000 food products on the French market. Six clusters of additives that frequently co-occur in food products were identified in order to investigate their association with chronic disease risk, including potential "cocktail effects" (137).

No study has yet been carried out in the Czech Republic nor abroad evaluating the safety of DS with regards to the presence of food additives despite their growing popularity.

1.5 Quality of information on the internet related to dietary supplements

Based on the International Health Report 2021 survey, 42% of consumers in the Czech Republic bought DS online (138).

This represented twice the European average. When Europeans including Czech Republic were asked about their preferred place to purchase over-the-counter medication, a significant portion of respondents mentioned community pharmacies as their top choice (43%). Other options included drugstores (21%), supermarkets (15%), and online pharmacies (12%) (139).

The internet also serves as a valuable resource for health-related information. Approximately 55% of Europeans and 74.4% of the U.S. population used the internet to seek health-related information on injury, disease, nutrition, and strategies for improving overall health (140, 141).

The quality of health and DS-related information published on websites

is therefore crucial due to our reliance on online health-related information. Nevertheless, evaluations of online health information consistently reveal that its quality is frequently inconsistent and of poor quality (142-144).

Several studies have found that marketers of DS did not meet the regulations when selling their products online. In 2022, the U.S. Food and Drug Administration (FDA) issued Warning Letters to seven companies. These companies were illegally selling DS that claimed to cure, treat, mitigate, or prevent cardiovascular disease or related conditions, such as atherosclerosis, stroke, or heart failure (145).

Similarly, FDA reviewed DS frequently sold on websites and social media platforms that claimed to prevent, treat, or cure Alzheimer's disease. They found out that 17 companies were violating the FDA regulation. The FDA advises consumers to stay vigilant when shopping online as such products are ineffective, unsafe, and could discourage individuals from seeking proper diagnosis and treatment (146).

In 2017, the European Commission initiated the first EU-coordinated control program for online food products, including DS. The program targeted supplements with medicinal claims, which are prohibited. Authorities examined approximately 1100 websites of which a high percentage of websites were not compliant with EU regulations. The mission of the program was to encourage greater engagement from EU countries in regulating the e-commerce food market. It was concluded that authorities should consider a more ambitious coordinated plan to increase the oversight of online sales (147).

Also, over 90% of retail websites also did not offer information about potential adverse effects, DS-drug interactions, and other safety considerations related to DS (28, 148). Additionally, only 10.5% of these sites recommended consulting with a healthcare professional (28, 148).

A review by Denniss et al. on online DS-related information concluded that such information is often inaccurate and of low quality. Therefore, more action is needed to improve the public's and media health literacy and the reliability of online DS-related information (149).

Scarce data exits on this topic in the Czech Republic and therefore, a study focusing on the quality of information on the internet relating to DS could be of interest to health care providers, consumers and policy-makers.

2

Scope and outline of the thesis

2 SCOPE AND OUTLINE OF THE THESIS

The aim of these studies was to assess four selected safety aspects of dietary suplement use:

1) allergy-like immediate reactions in adults and children in connection with herbal use using data from VigiBase® with regards to: (a) general information (country of origin, type of reporter), (b) patient-related information (age, sex, and comorbidity), (c) adverse reaction-related information (time of onset, dechallenge, rechallenge, outcome and causality assessment), and (d) substance-related information (type of suspect herbal and dose, concomitant medication, duration of intake),
2) the risks associated with dietary supplement use in patients in the pre-operative period,
3) the safety of food additives in top-selling dietary supplements in the Czech Republic,
4) and the quality of information on the internet relating to top-selling dietary supplements in the Czech Republic.

Data sources used in this habilitation thesis

For the conduct of vigilance studies, we used data from the World Health Organisation (WHO) database - Vigibase. The Uppsala Monitoring Centre (UMC) maintains Vigibase since 1978, in collaboration with 81 national centres around the world. The reports contain information related to the patient, the substance and the adverse event. The case reports are anonymous and heterogeneous and vary as regards source, documentation and relationship likelihood. Reporters are physicians, pharmacists and other health care professionals. In a few countries, in particular the USA, reports directly from patients are also accepted.

3

References

3 REFERENCES

1. Mordor Intelligence. Dietary Supplements Market Size & Share Analysis - Growth Trends & Forecasts (2024 - 2029). [online]. 30. 04. 2024 [cit. 14. 06. 2024]. Available from: https://www.mordorintelligence.com/industry-reports/dietary-supplement-market

2. Mordor Intelligence. Europe Dietary Supplements Market Size. [online]. 30. 04. 2024 [cit. 14. 06. 2024]. Available from: https://www.mordorintelligence.com/industry-reports/europe-dietary-supplement-market

3. Papatesta EM, Kanellou A, Peppa E, Trichopoulou A. Is Dietary (Food) Supplement Intake Reported in European National Nutrition Surveys? *Nutrients.* 2023;15(24):5090. doi: 10.3390/nu15245090.

4. CDC - Centers for Disease Control and Prevention. National Health Statistics Reports. [online]. 18. 4. 2023 [cit. 14. 06. 2024]. Available from: https://www.cdc.gov/nchs/data/nhsr/nhsr183.pdf

5. Statistics Canada. Use of Nutritional Supplements. [online]. 2015 [cit. 14. 06. 2024]. Available from: https://www150.statcan.gc.ca/n1/pub/82-625-x/2017001/article/14831-eng.htm

6. O'Brien SK, Malacova E, Sherriff JL, Black LJ. The Prevalence and Predictors of Dietary Supplement Use in the Australian Population. *Nutrients.* 2017;21;9(10):1154. doi: 10.3390/nu9101154.

7. Pharmaprofit. Každý třetí Čech pravidelně užívá doplňky stravy. [online]. 30. 04. 2024 [cit. 14. 06. 2024]. Available from: https://www.pharmaprofit.cz/2024/04/30/kazdy-treti-cech-pravidelne-uziva-doplnky-stravy/

8. NADA. Češi utratí za vitamínové doplňky stravy v průměru 5 700 Kč za rok, uvádějí NÁRODNÍ DATA. [online]. 2. 11. 2023 [cit. 14. 06. 2024]. Available from: https://www.nada.cz/blog/5-700-kc-rocne-utrati-v-prumeru-cesi-za-vitaminove-doplnky-stravy-uvadeji-narodni-data

9. Farina EK, Austin KG, Lieberman HR. Concomitant dietary supplement and prescription medication use is prevalent among US adults with doctor-

informed medical conditions. *J Acad Nutr Diet.* 2014;114(11):1784-90. doi: 10.1016/j.jand.2014. 01. 016.

10. Ronis MJJ, Pedersen KB, Watt J. Adverse Effects of Nutraceuticals and Dietary Supplements. *Annu Rev Pharmacol Toxicol*. 2018;6;58:583-601. doi: 10.1146/annurev-pharmtox-010617-052844.

11. Aznar-Lou I, Carbonell-Duacastella C, Rodriguez A, Mera I, Rubio-Valera M. Prevalence of Medication-Dietary Supplement Combined Use and Associated *Factors. Nutrients.* 2019;11(10):2466. doi: 10.3390/nu11102466.

12. Agbabiaka TB, Spencer NH, Khanom S, Goodman C. Prevalence of drug-herb and drug-supplement interactions in older adults: a cross-sectional survey. *Br J Gen Pract.* 2018;68(675):e711-e717. doi: 10.3399/bjgp18X699101.

13. Czigle S, Nagy M, Mladěnka P, Tóth J; OEMONOM. Pharmacokinetic and pharmacodynamic herb-drug interactions-part I. Herbal medicines of the central nervous system. *PeerJ.* 2023;11:e16149. doi: 10.7717/peerj.16149.

14. Hassen G, Belete G, Carrera KG, Iriowen RO, Araya H, Alemu T, Solomon N, Bam DS, Nicola SM, Araya ME, Debele T, Zouetr M, Jain N. Clinical Implications of Herbal Supplements in Conventional Medical Practice: A US Perspective. *Cureus.* 2022;14(7):e26893. doi: 10.7759/cureus.26893.

15. Anselmo F, Driscoll MS. Deleterious side effects of nutritional supplements. *Clin Dermatol*. 2021;39(5):745-756. doi: 10.1016/j.clindermatol.2021. 05. 002.

16. Li W, Wertheimer A. Narrative Review: The FDA's Perfunctory Approach of Dietary Supplement Regulations Giving Rise to Copious Reports of Adverse Events. *Innov Pharm*. 2023;14(1):10.24926/iip.v14i1.4989. doi: 10.24926/iip.v14i1.4989.

17. Koncz D, Tóth B, Roza O, Csupor D. A Systematic Review of the European Rapid Alert System for Food and Feed: Tendencies in Illegal Food Supplements for Weight Loss. *Front Pharmacol*. 2021;11:611361. doi: 10.3389/fphar.2020.611361.

18. Cross LV, Thomas JR. Safety and Efficacy of Dietary Supplements for Diabetes. *Diabetes Spectr.* 2021;34(1):67-72. doi: 10.2337/ds19-0068.

19. Bailey RL. Current regulatory guidelines and resources to support research of dietary supplements in the United States. *Crit Rev Food Sci Nutr*. 2020;60(2):298-309. doi: 10.1080/10408398.2018.1524364.

20. Sirois J, Reddy S, Nguyen T, Walker H, Rendall J, Bergen G, Reimers M, Cermak E, Tiwary A, Helmes E, Palmer J, Teo S, Mackle T, Park M, Wang C. Safety considerations for dietary supplement manufacturers in the United States. *Regul Toxicol Pharmacol.* 2024;147:105544. doi: 10.1016/j.yrtph.2023.105544.

21. Menniti-Ippolito, F., Aiello, E., Arzenton, E. et al. Erice Manifesto 2022: On the Surveillance of Potential Harms Caused by Food Supplements in Europe. *Drug Saf*. 2023;46:435–437. doi:10.1007/s40264-023-01284-6.

22. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. *JAMA Netw Open*. 2018;1(6):e183337. doi: 10.1001/jamanetworkopen.2018.3337. Erratum in: JAMA Netw Open. 2018;1(7):e185765. doi: 10.1001/jamanetworkopen.2018.5765.

23. White CM. Dietary Supplements Pose Real Dangers to Patients. *Ann Pharmacother.* 2020;54(8):815-819. doi: 10.1177/1060028019900504.

24. White CM. Continued Risk of Dietary Supplements Adulterated With Approved and Unapproved Drugs: Assessment of the US Food and Drug Administration's Tainted Supplements Database 2007 Through 2021. *J Clin Pharmacol.* 2022;62(8):928-934. doi: 10.1002/jcph.2046.

25. Amidžić M, Banović Fuentes J, Banović J, Torović L. Notifications and Health Consequences of Unauthorized Pharmaceuticals in Food Supplements. *Pharmacy* (Basel). 2023;11(5):154. doi: 10.3390/pharmacy11050154.

26. Rosenberg K. Dietary Supplement Labels May Be Inaccurate and Misleading. *Am J Nurs.* 2022;122(12):56. doi: 10.1097/01.NAJ.0000904100.46205.b5.

27. Crawford C, Avula B, Lindsey AT, Walter A, Katragunta K, Khan IA, Deuster PA. Analysis of Select Dietary Supplement Products Marketed to Support or Boost the Immune System. *JAMA Netw Open*. 2022;5(8):e2226040. doi: 10.1001/jamanetworkopen.2022.26040.

28. Crawford C, Boyd C, Avula B, Wang YH, Khan IA, Deuster PA. A Public Health Issue: Dietary Supplements Promoted for Brain Health and Cognitive Performance. *J Altern Complement Med.* 2020;26(4):265-272. doi: 10.1089/acm.2019.0447.

29. You H, Abraham EJ, Mulligan J, Zhou Y, Montoya M, Willig J, Chen BK, Wang CK, Wang LS, Dong A, Shamtsyan M, Nguyen H, Wong A, Wallace TC. Label compliance for ingredient verification: regulations, approaches, and trends for testing botanical products marketed for "immune health" in the United States. *Crit Rev Food Sci Nutr*. 2024;64(9):2441-2460. doi: 10.1080/10408398.2022.2124230.

30. European commission. 2022 Annual Report Alert and Cooperation Network. [online]. 30. 04. 2024 [cit. 14. 06. 2024]. Available from: https://food.ec.europa.eu/system/files/2023-10/acn_annual-report_2022.pdf

31. Foley H, Steel A, Cramer H, Wardle J, Adams J. Disclosure of complementary medicine use to medical providers: a systematic review and meta-analysis. *Sci Rep.* 2019;9(1):1573. doi: 10.1038/s41598-018-38279-8.

32. Foley H, Steel A, McIntyre E, Harnett J, Sibbritt D, Adams J. Disclosure of conventional and complementary medicine use to medical doctors and complementary medicine practitioners: A survey of rates and reasons amongst those with chronic conditions. *PLoS One.* 2021;16(11):e0258901. doi: 10.1371/journal.pone.0258901.

33. Risvoll H, Risør T, Halvorsen KH, Waaseth M, Stub T, Giverhaug T, Musial F. General practitioners' role in safeguarding patients with dementia in their use of dietary supplements. A qualitative study. *Scand J Prim Health Care*. 2024;42(1):16-28. doi: 10.1080/02813432.2023.2283182.

34. Stanojević-Ristić Z, Mrkić I, Ćorac A, Dejanović M, Mitić R, Vitković L, Rašić J, Valjarević D, Valjarević A. Healthcare Professionals' Knowledge and Behaviors Regarding Drug-Dietary Supplement and Drug-Herbal Product Interactions. *Int J Environ Res Public Health.* 2022;19(7):4290. doi: 10.3390/ijerph19074290.

35. Risvoll H, Musial F, Halvorsen KH, Giverhaug T, Waaseth M. Pharmacy employees' involvement in safeguarding persons with dementia who use dietary supplements: Results from a survey of Norwegian pharmacies. *BMC Complement*

Altern Med. 2019;19(1):179. doi: 10.1186/s12906-019-2587-4.

36. Brunelli L, Arnoldo L, Mazzilis G, d'Angelo M, Colautti L, Cojutti PG, Parpinel M. The knowledge and attitudes of pharmacists related to the use of dietary supplements: An observational study in northeastern Italy. *Prev Med Rep*. 2022;30:101986. doi: 10.1016/j.pmedr.2022.101986.

37. Waddington F, Naunton M, Kyle G, Thomas J, Cooper G, Waddington A. A systematic review of community pharmacist therapeutic knowledge of dietary supplements. Int J Clin Pharm. 2015;37(3):439-46. doi: 10.1007/s11096-015-0092-5. Epub 2015 Mar 13. Erratum in: *Int J Clin Pharm*. 2017;39(2):492-493. doi: 10.1007/s11096-016-0422-2.

38. EFSA - European Food Safety Authority. Food Supplements. [online]. [cit. 17.11.2023]. Available from: https://www.efsa.europa.eu/en/topics/topic/food-supplements#:~:text=Food%20supplements%20are%20intended%20to, to%20support%20 specific%20physiological%20functions.

39. DIRECTIVE 2002/46/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

40. Zákon č. 110/1997 Sb., o potravinách a tabákových výrobcích a o změně a doplnění některých souvisejících zákonů. (Zákon č. 174/2021 Sb., kterým se mění zákon č. 110/1997 Sb., o potravinách a tabákových výrobcích a o změně a doplnění některých souvisejících zákonů, ve znění pozdějších předpisů, a další související zákony)

41. ČESKO. Zákon č. 378/2007 Sb. Parlamentu České republiky o léčivech a o změnách některých souvisejících zákonů. (Zákon č. 456/2023 Sb., kterým se mění zákon č. 378/2007 Sb., o léčivech a o změnách některých souvisejících zákonů, ve znění pozdějších předpisů)

42. European Medicines Agency. EMA. Human regulatory: Herbal medicinal products. [online]. [cit. 17. 11. 2023]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products

43. Vyhláška č. 58/2018 Sb., o doplňcích stravy a složení potravin.

44. SUKL. Hraniční přípravky: Jaký je rozdíl mezi doplňky stravy a volně prodejnými léčivými přípravky? [online]. [cit. 17. 11. 2023]. Available from: https://www.sukl.cz/leciva/jaky-je-rozdil-mezi-doplnky-stravy-a-volne-prodejnymi

45. Dwyer JT, Coates PM, Smith MJ. Dietary Supplements: Regulatory Challenges and Research Resources. *Nutrients.* 2018;10(1):41. doi: 10.3390/nu10010041.

46. Dodge T. Consumers' perceptions of the dietary supplement health and education act: implications and recommendations. *Drug Test Anal.* 2016;8(3-4):407-9. doi: 10.1002/dta.1857.

47. EUROPEAN COMISSION, Health & Food Safety Directorate-General. List of competent authorities of the Member States within the meaning of Article 4(6) of Directive 2002/46 on food supplements [online]. European Comission, 2019. [cit. 20. 5. 2024]. Available from: https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndacompetentauthorities.pdf

48. Informační centrum bezpečnosti potravin. Bezpečnost potravin: Doplňky stravy. [online]. [cit. 17. 11. 2023]. Available from: https://bezpecnostpotravin.cz/kategorie/doplnky-stravy/

49. Směrnice Evropského parlamentu a Rady 2002/46/ES ze dne 10. června 2002, o sbližování právních předpisů členských států týkajících se doplňků stravy.

50. 1925/2006 Nařízení Komise (ES) č. 1170/2009, kterým se mění směrnice Evropského parlamentu a Rady 2002/46/ES a nařízení Evropského parlamentu a Rady (ES) č. 1925/2006, pokud jde o seznamy vitaminů a minerálních látek a jejich forem, které lze přidávat do potravin, včetně doplňků stravy.

51. Nařízení Evropského parlamentu a Rady (EU) č. 2283/2015 ze dne 25. listopadu 2015, o nových potravinách, o změně nařízení Evropského parlamentu a Rady (EU) č. 1169/2011 a o zrušení nařízení Evropského parlamentu a Rady (ES) č. 258/97 a nařízení Komise (ES) č. 1852/2001.

52. EUROPEAN COMISSION. EU Novel Food status Catalogue (New) [online]. European Comission, 2020. [cit. 20. 5. 2024]. Available from: https://food.ec.europa.eu/safety/novel-food/novel-food-status-catalogue_en

53. Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods.

54. eAGRI. Doplňky stravy [online]. Ministerstvo zemědělství, 2009. [cit. 20. 5. 2024]. Available from: https://eagri.cz/public/web/file/721405/Narodni_seznam_nekterych_rostlin_pro_pouziti_pri_vyrobe_doplnku_stravy.pdf

55. Nařízení Komise (EU) č. 1130/2011, kterým se mění příloha III nařízení Evropského parlamentu a Rady (ES) č. 1333/2008 o potravinářských přídatných látkách zavedením seznamu potravinářských přídatných látek Unie schválených pro použití v potravinářských přídatných látkách, potravinářských enzymech, potravinářských aromatech a živinách.

56. Nařízení Komise (ES) č. 1881/2006, kterým se stanoví maximální limity některých kontaminujících látek v potravinách, v platném znění.

57. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Vodítka k problematice zdravotních a výživových tvrzení [online]. SZPI, 2018. [cit. 20. 08. 2024]. Available from: https://www.szpi.gov.cz/clanek/voditka-k-problematice-zdravotnich-a-vyzivovych-tvrzeni.aspx

58. Nařízení Evropského parlamentu a Rady (ES) č. 1924/2006 ze dne 20. prosince 2006, o výživových a zdravotních tvrzeních při označování potravin.

59. Nařízení Evropského parlamentu a Rady (EU) č. 1169/2011 ze dne 25. října 2011, o poskytování informací o potravinách spotřebitelům, o změně nařízení Evropského parlamentu a Rady (ES) č. 1924/2006 a (ES) č. 1925/2006 a o zrušení směrnice Komise 87/250/EHS, směrnice Rady 90/496/EHS, směrnice Komise 1999/10/ES, směrnice Evropského parlamentu a Rady 2000/13/ES, směrnic Komise 2002/67/ES a 2008/5/ES a nařízení Komise (ES) č. 608/2004.

60. SÚKL. Infolisty – Informační listy Státního ústavu pro kontrolu léčiv určené široké laické veřejnosti. Léky vs. doplňky stravy [online]. SÚKL, 2014. [cit. 20. 3. 2020]. Available from: https://www.olecich.cz/uploads/infoLISTY/03191_SUKL_Infolisty_2014_07_01.pdf

61. Food Supplement Europe. Consumer survey on food supplements in the EU. [online]. [cit. 26. 06. 2024]. Available from: https://foodsupplementseurope.org/wp-content/uploads/2022/07/FSE-Consumer_Survey-Ipsos-2022.pdf

62. Braun, M., & Venter, I. Use of dietary supplements, and awareness and knowledge of the recommended fruit and vegetable intakes and consumption of health food store customers in the Cape Town city bowl. *South Afr. J Clin. Nutr.* 2008;21(4), 323–330. doi:10.1080/16070658.2008.11734174.

63. Mendes, Alessandra & Invernizzi, Noela. (2017). Nutritional Supplements in Brazil: Use, Regulation and Health Risks. *Food Science & Nutrition Technology*. 2017;2:1-12. doi: 10.23880/FSNT-16000113.

64. Gong W, Liu A, Yao Y, Ma Y, Ding C, Song C, Yuan F, Zhang Y, Feng G, Chen Z, Ding G. Nutrient Supplement Use among the Chinese Population: A Cross-Sectional Study of the 2010–2012 China Nutrition and Health Surveillance. *Nutrients.* 2018;10(11):1733. doi: 10.3390/nu10111733.

65. Dickinson A., MacKay D. Health habits and other characteristics of dietary supplement users: A review. *Nutr. J.* 2014;13:14. doi: 10.1186/1475-2891-13-14.

66. Bailey R.L., Gahche J.J., Miller P.E., Thomas P.R., Dwyer J.T. Why US adults use dietary supplements. *JAMA Intern. Med.* 2013;173:355–361. doi: 10.1001/jamainternmed.2013.2299.

67. Frey A., Hoffmann I., Heuer T. Characterisation of vitamin and mineral supplement users differentiated according to their motives for using supplements: Results of the German National Nutrition Monitoring (NEMONIT) *Public Health Nutr*. 2017;20:2173–2182. doi: 10.1017/S1368980017001021.

68. Iłowiecka K, Maślej M, Czajka M, Pawłowski A, Więckowski P, Styk T, Gołkiewicz M, Kuzdraliński A, Koch W. Lifestyle, Eating Habits, and Health Behaviors Among Dietary Supplement Users in Three European Countries. *Front Public Health.* 2022;10:892233. doi: 10.3389/fpubh.2022.892233.

69. Denham BE. Psychosocial Correlates of Dietary Supplement Use: Results from the National Survey of Midlife Development in the United States. *Ecol Food Nutr*. 2017;56(2):171-186. doi: 10.1080/03670244.2016.1277711.

70. Prieto, J.M., Mazzari, A.L.D.A. (2022). Herb-Drug Interactions: Fundamental Mechanisms, Prevalence and Challenges in Their Identification. In: Barnes, J. (eds) Pharmacovigilance for Herbal and Traditional Medicines. Adis, Cham. doi:10.1007/978-3-031-07275-8_5.

71. Hakkola J, Hukkanen J, Turpeinen M, Pelkonen O. Inhibition and induction of CYP enzymes in humans: an update. *Arch Toxicol*. 2020;94(11):3671-3722. doi: 10.1007/s00204-020-02936-7.

72. Jain, Sourabh. A Systematic Review of Piperine as a Bioavailability Enhancer. *J. drug deliv.ther.* 2023;13:133-136. doi:10.22270/jddt.v13i4.5781.

73. Zhang Y, Man Ip C, Lai YS, Zuo Z. Overview of Current Herb-Drug Interaction Databases. *Drug Metab Dispos.* 2022;50(1):86-94. doi: 10.1124/dmd.121.000420.

74. Nařízení Evropského parlamentu a Rady (ES) č. 178/2002 ze dne 28. ledna 2002, kterým se stanoví obecné zásady a požadavky potravinového práva, zřizuje se Evropský úřad pro bezpečnost potravin a stanoví postupy týkající se bezpečnosti potravin.

75. SZU. Uvádění doplňků stravy do oběhu. [online]. [cit. 20. 5. 2024]. Available from: https://szu.cz/temata-zdravi-a-bezpecnosti/zdravi-vyziva-a-bezpecnost-potravin-a-predmetu-bezneho-uzivani/doplnky-stravy-zdravotni-tvrzeni/uvadeni-doplnku-stravy-do-obehu/

76. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Kontrolní činnosti SZPI [online]. SZPI, 2024. [cit. 23. 06. 2024]. Available from: https://www.szpi.gov.cz/clanek/kontrolni-cinnost-szpi.aspx

77. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Potraviny na pranýři [online]. SZPI, 2024. [cit. 23. 06. 2024]. Available from: https://www.potravinynapranyri.cz/

78. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Potraviny na pranýři. Rizikové webové stránky [online]. SZPI, 2024. [cit. 23. 06. 2024]. Available from: https://www.potravinynapranyri.cz/ESearch.aspx?lang=cs & design=default & archive=actual & listtype=tiles & page=1

79. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Doplňky stravy [online]. 28. 06. 2022 [cit. 20. 8. 2023]. Available from: https://www.szpi.gov.cz/clanek/doplnky-stravy.aspx

80. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Kontrolní činnosti SZPI [online]. SZPI, 2024. [cit. 23. 06. 2024]. Available from: https://www.szpi.gov.cz/clanek/jak-podat-podnet-ke-kontrole.aspx

81. SÚKL. Státní ústav pro kontrolu léčiv. Co je farmakovigilance. [online]. SUKL, 2010. [cit. 20. 8. 2023]. Available from: https://www.sukl.cz/leciva/co-je-farmakovigilance

82. Luthra VR, Toklu HZ. Nutrivigilance: the road less traveled. *Front Pharmacol*. 2023;14:1274810. doi: 10.3389/fphar.2023.1274810.

83. STÁTNÍ ZDRAVOTNÍ ÚSTAV. Nutrivigilance – Zdravotní bdělost nad potravinami [online]. SZÚ, 2014. [cit. 20. 8. 2023]. Available from: https://nutrivigilance.szu.cz/nutrivigilance.html

84. STÁTNÍ ZDRAVOTNÍ ÚSTAV. Nutrivigilance – Zdraví, výživa, potraviny [online]. SZÚ, 2014. [cit. 20. 8. 2023]. Available from: https://nutrivigilance.szu.cz/online-formular.html

85. STÁTNÍ ZDRAVOTNÍ ÚSTAV. Nutrivigilance – Zdraví, výživa, potraviny. Hodnocení a závěry [online]. SZÚ, 2014. [cit. 20. 8. 2023]. Available from: https://nutrivigilance.szu.cz/hodnoceni-zavery.html

86. STÁTNÍ ZDRAVOTNÍ ÚSTAV. Nutrivigilance – Zdraví, výživa, potraviny [online]. SZÚ, 2014. [cit. 20. 8. 2023]. Available from: at https://nutrivigilance.szu.cz/uzivatel/aktuality/02.2017%20Spotrebitele.pdf

87. Vo Van Regnault G, Costa MC, Adanić Pajić A, Bico AP, Bischofova S, Blaznik U, Menniti-Ippolito F, Pilegaard K, Rodrigues C, Margaritis I. The need for European harmonization of Nutrivigilance in a public health perspective: a comprehensive review. *Crit Rev Food Sci Nutr.* 2022;62(29):8230-8246. doi: 10.1080/10408398.2021.1926904.

88. BfR. German federal institute for risk assessment [online]. 1. 07. 2022 [cit. 20. 6. 2024]. Available from: https://www.bfr.bund.de/cm/349/nutrivigilance-of-food-supplements-in-europe.pdf

89. Menniti-Ippolito, F., Firenzuoli, F. (2022). The Italian Phytovigilance Spontaneous Reporting Scheme. In: Barnes, J. (eds) Pharmacovigilance for Herbal and Traditional Medicines. Adis, Cham. doi:10.1007/978-3-031-07275-8_17.

90. Pourshahidi LK, Mullan R, Collins N, et al. Reporting adverse events linked to the consumption of food supplements and other food products: an audit of Nutrivigilance newsletters. *Proc. Nutr. Soc.* 2021;80(OCE3):E133. doi:10.1017/S0029665121002561.

91. Timbo BB, Chirtel SJ, Ihrie J, Oladipo T, Velez-Suarez L, Brewer V, Mozersky R. Dietary Supplement Adverse Event Report Data From the FDA Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), 2004-2013. *Ann Pharmacother*. 2018;52(5):431-438. doi: 10.1177/1060028017744316.

92. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, Mozersky RP, Budnitz DS. Emergency Department Visits for Adverse Events Related to Dietary Supplements. *N Engl J Med*. 2015;373(16):1531-40. doi: 10.1056/NEJMsa1504267.

93. Schmitz SM MD, MPH, Lopez HL MD, MS, Mackay D ND, Nguyen H BS, Miller PE BS. Serious Adverse Events Reported with Dietary Supplement Use in the United States: A 2.5 Year Experience. *J Diet Suppl.* 2020;17(2):227-248. doi: 10.1080/19390211.2018.1513109.

94. EUROPEAN COMISSION. Rapid Alert System for Food and Feed (RASFF) [online]. European Comission, 2020. [cit. 23. 6. 2024]. Available from: https://food.ec.europa.eu/safety/rasff_en

95. EFSA – EUROPEAN FOOD SAFETY AUTHORITY. EMERGING RISKS IDENTIFICATION IN FOOD SUPPLEMENTS (UPDATE) [online]. EFSA, 8. 06. 2023 [cit. 20. 8. 2023]. Available from: https://www.efsa.europa.eu/sites/default/files/2023-07/j.-8.3-emerging-risks-identification-in-food-supplements-update.pdf

96. Ruiz SF, Maldonado PG. Dietary supplements and the anaesthesiologist:

research results and state of the art. *Rev Colomb Anestesiol.* 2014;42:90–9. doi: 10.1016/j.rca.2013. 09. 002.

97. Leung JM, Dzankic S, Manku K, Yuan S. The prevalence and predictors of the use of alternative medicine in pre-surgical patients in five California hospitals. *Anesth Analg.* 2001;93:1062–8. doi: 10.1097/00000539-200110000-00041.

98. Lucefonte E, Gallo E, Pugi A, Giommoni F, Paoletti A, Vietri M, et al. Complementary and alternative drug use among preoperative patients: a cross-sectional study in Italy. *J Evid Based Complementary Altern Med.* 2012;2012:1–6. doi: 10.1155/2012/749842.

99. Onyeka TC, Ezike HA, Nwoke OM, Onyia EA, Onuorah E, Anya SU, et al. Herbal medicine: a survey of use in Nigerian presurgical patients booked for ambulatory anaesthesia. *BMC Complement Altern Med.* 2012;12:130. doi: 10.1186/1472-6882-12-130.

100. Lee A, Chui PT, Aun CST, Lau ASC, Gin T. Incidence and risk of adverse perioperative events among surgical patients taking traditional Chinese herbal medicines. *Anesthesiology.* 2006;105:454–61. doi: 10.1097/00000542-200609000-00008.

101. Levy I, Attias S, Ben-Arye E, Goldstein L, Matter I, Somri M, Schiff E. Perioperative Risks of Dietary and Herbal Supplements. *World J Surg.* 2017;41(4):927-934. doi: 10.1007/s00268-016-3825-2.

102. Levy I, Attias S, Ben-Arye E, Goldstein L, Schiff E. Potential drug interactions with dietary and herbal supplements during hospitalization. *Intern Emerg Med.* 2017;12(3):301-310. doi: 10.1007/s11739-016-1548-x.

103. Rasheed H, Ahmed S, Sharma A. Changing Trends Towards Herbal Supplements: An Insight into Safety and Herb-drug Interaction. *Curr Pharm Biotechnol.* 2024;25(3):285-300. doi: 10.2174/1389201024666230718114606.

104. Hatfield J, Saad S, Housewright C. Dietary supplements and bleeding. *Proc (Bayl Univ Med Cent).* 2022;35(6):802-807. doi: 10.1080/08998280.2022.2121575.

105. Werner SM. Patient safety and the widespread use of herbs and supplements. *Front Pharmacol.* 2014;5:142. doi: 10.3389/fphar.2014.00142.

106. Levy I, Attias S, Ben-Arye E, Goldstein L, Schiff E. Interactions between dietary supplements in hospitalised patients. *Intern Emerg Med.* 2016;11:917–27. doi: 10.1007/s11739-016-1444-0.

107. Wong A, Townley SA. Herbal medicines and anaesthesia. *BJA CEPD*. 2011;11:14–7. doi: 10.1093/bjacepd/11. 1. 14.

108. Row DJ, Baker AC. Perioperative risks and benefits of herbal supplements in aesthetic surgery. *Aesthet Surg J*. 2009;29:150–7. doi: 10.1016/j.asj.2009. 01. 002.

109. Shakeel M, Newton JR, Ah-See KW. Complementary and alternative medicine use among patients undergoing otolaryngologic surgery. *J Otolaryngol Head Neck Surg.* 2009;38:355–61. doi: 10.2310/7070.2009.0001.

110. Kenneth C. Cummings et al. Preoperative Management of Surgical Patients Using Dietary Supplements. Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement. Thematic review on perioperative medicine. *Mayo Clin Proc.* 2021;96(5):1342-1355. doi: 10.1016/j.mayocp.2020. 08. 016.

111. U. S. Food and Drug Administration. Mixing Medications and Dietary Supplements Can Endanger Your Health. [online]. [cit. 20. 06. 2024]. Available from: https://www.fda.gov/consumers/consumer-updates/mixing-medications-and-dietary-supplements-can-endanger-your-health

112. Elvir Lazo OL, White PF, Lee C, Cruz Eng H, Matin JM, Lin C, Del Cid F, Yumul R. Use of herbal medication in the perioperative period: Potential adverse drug interactions. *J Clin Anesth.* 2024;95:111473. doi: 10.1016/j.jclinane.2024.111473.

113. FAO/WHO. The Codex Alimentarius. Glossary of terms. [online]. [cit. 23. 06. 2024]. Available from: https://www.fao.org/fao-who-codexalimentarius/GSFA-online/Glossary

114. Chemistry of Food Additives. Functionality of Food Additives. [online]. 04. 04. 2024 [cit. 23. 06. 2024]. Available from: https://www.intechopen.com/online-first/89381

115. Vyhláška č. 4/2008 Sb., kterou se stanoví druhy a podmínky použití

přídatných látek a extrakčních rozpouštědel při výrobě potravin. Sbírka zákonů. 3. ledna 2008.

116. World Health Organisation. Principles for Risk Assessment of Chemicals in Food [online]. [cit. 23. 06. 2024]. Available from: https://www.who.int/docs/default-source/food-safety/publications/chapter5-dose-response.pdf?sfvrsn=32edc2c6_5

117. Nařízení Evropského parlamentu a Rady (ES) č. 1333/2008 ze dne 16. prosince 2008, o potravinářských přídatných látkách.

118. Nařízení Komise (EU) č. 231/2012 ze dne 9. března 2012, kterým se stanoví specifikace pro potravinářské přídatné látky uvedené v přílohách II a III nařízení Evropského parlamentu a Rady (ES) č. 1333/2008.

119. Nařízení Evropského parlamentu a Rady (ES) č. 1331/2008 ze dne 16. prosince 2008, kterým se stanoví jednotné povolovací řízení pro potravinářské přídatné látky, potravinářské enzymy a látky určené k aromatizaci potravin.

120. EVROPSKÁ KOMISE. Food Additives [online]. Evropská komise, 2020. [cit. 20. 5. 2024]. Available from: https://webgate.ec.europa.eu/foods_system/main/?sector=FAD & auth=SANCAS.

121. CODEX ALIMENTARIUS. Codex General Standard for Food Additives (GSFA) Online Database [online]. FAO/WHO, 2020. [cit. 20. 5. 2024]. Available from: http://www.fao.org/gsfaonline/index.html;jsessionid=961CB02B3E61115A41C4D068B4EE8954.

122. STÁTNÍ ZEMĚDĚLSKÁ A POTRAVINÁŘSKÁ INSPEKCE. Přídatné látky - aditiva [online]. SZPI, 2023. [cit. 23. 06. 2024]. Available from: https://www.szpi.gov.cz/clanek/-ecka-a-dalsi-latky-v-potravinach-pridatne-latky-aditiva.aspx

123. Andreozzi L, Giannetti A, Cipriani F, Caffarelli C, Mastrorilli C, Ricci G. Hypersensitivity reactions to food and drug additives: problem or myth? *Acta Biomed.* 2019;90(3-S):80-90. doi: 10.23750/abm.v90i3-S.8168.

124. Randhawa S, Bahna SL. Hypersensitivity reactions to food additives. *Curr Opin Allergy Clin Immunol.* 2009;9(3):278-83. doi: 10.1097/ACI.0b013e32832b2632.

125. EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Frutos Fernandez MJ, Fürst P, Gundert Remy U, Gürtler R, Husøy T, Manco M, Mennes W, Moldeus P, Passamonti S, Shah R, Waalkens-Berendsen I, Wölfle D, Corsini E, Cubadda F, De Groot D, FitzGerald R, Gunnare S, Gutleb AC, Mast J, Mortensen A, Oomen A, Piersma A, Plichta V, Ulbrich B, Van Loveren H, Benford D, Bignami M, Bolognesi C, Crebelli R, Dusinska M, Marcon F, Nielsen E, Schlatter J, Vleminckx C, Barmaz S, Carfí M, Civitella C, Giarola A, Rincon AM, Serafimova R, Smeraldi C, Tarazona J, Tard A and Wright M, 2021. Scientific Opinion on the safety assessment of titanium dioxide (E171) as a food additive. *EFSA Journal* 2021;19(5):6585, 130 pp. https://doi.org/10.2903/j.efsa.2021.6585.

126. Salame C, Javaux G, Sellem L, Viennois E, de Edelenyi FS, Agaësse C, De Sa A, Huybrechts I, Pierre F, Coumoul X, Julia C, Kesse-Guyot E, Allès B, Fezeu LK, Hercberg S, Deschasaux-Tanguy M, Cosson E, Tatulashvili S, Chassaing B, Srour B, Touvier M. Food additive emulsifiers and the risk of type 2 diabetes: analysis of data from the NutriNet-Santé prospective cohort study. *Lancet Diabetes Endocrinol.* 2024;12(5):339-349. doi: 10.1016/S2213-8587(24)00086-X.

127. Sadighara P, Safta M, Limam I, Ghanati K, Nazari Z, Karami M, Abedini A. Association between food additives and prevalence of allergic reactions in children: a systematic review. *Rev Environ Health.* 2022;38(1):181-186. doi: 10.1515/reveh-2021-0158.

128. Randhawa S, Bahna SL. Hypersensitivity reactions to food additives. *Curr Opin Allergy Clin Immunol.* 2009;9(3):278-83. doi: 10.1097/ACI.0b013e32832b2632.

129. Higher in atopy children Fuglsang G, Madsen G, Halken S, Jørgensen M, Østergaard PA, Østerballe O. Adverse reactions to food additives in children with atopic symptoms. *Allergy.* 1994;49:31–7. doi: 10.1111/j.1398-9995.1994.tb00770.x.

130. Trasande L, Shaffer RM, Sathyanarayana S; COUNCIL ON ENVIRONMENTAL HEALTH. Food Additives and Child Health. *Pediatrics.* 2018;142(2):e20181410. doi: 10.1542/peds.2018-1410.

131. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the re-evaluation Tartrazine (E 102) on request from the European Commission. *EFSA Journal* 2009; 7(11):1331. [52 pp.]. doi:10.2903/j.

efsa.2009.1331.

EFSA Panel on Food Additives and Nutrient Sources Added to Food, 2015. Scientific Opinion on the re-evaluation of cochineal, carminic acid, carmines (E 120) as a food additive. *EFSA Journal* 2015; 13(11):4288, 65 pp. doi:10.2903/j.efsa.2015.4288.

132. EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes, M., Aquilina, G., Castle, L., Degen, G., Engel, K.-H., Fowler, P., Frutos Fernandez, M.J., Fürst, P., Gürtler, R., Husøy, T., Manco, M., Mennes, W., Moldeus, P., Passamonti, S., Shah, R., Waalkens-Berendsen, I., Wright, M., Dusemund, B… Gundert-Remy, U. (2024). Re-evaluation of guar gum (E 412) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as food additive for uses in foods for all population groups. *EFSA Journal*, 22(5), e8748. https://doi.org/10.2903/j.efsa.2024.8748.

133. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2013. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. *EFSA Journal* 2013; 11(12):3496, 263 pp. doi:10.2903/j.efsa.2013.3496.

134. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Dusemund B, Frutos MJ, Galtier P, Gott D, Gundert-Remy U, Leblanc JC, Lindtner O, Moldeus P, Mosesso P, Parent-Massin D, Oskarsson A, Stankovic I, Waalkens-Berendsen I, Woutersen RA, Wright M, Younes M, Boon P, Chrysafidis D, Gürtler R, Tobback P, Rincon AM, Tard A and Lambré C, 2017. Scientific opinion on the re-evaluation of glycerol (E 422) as a food additive. *EFSA Journal* 2017; 15(3):4720, 64 pp. doi:10.2903/j.efsa.2017.4720.

135. Zengin N, Yüzbaşioğlu D, Ünal F, Yilmaz S, Aksoy H. The evaluation of the genotoxicity of two food preservatives: sodium benzoate and potassium benzoate. *Food Chem. Toxicol.* 2011;49:763-769. doi: 10.1016/j.fct.2010. 11. 040.

136. Chazelas E, Druesne-Pecollo N, Esseddik Y, de Edelenyi FS, Agaesse C, De Sa A, Lutchia R, Rebouillat P, Srour B, Debras C, Wendeu-Foyet G, Huybrechts I, Pierre F, Coumoul X, Julia C, Kesse-Guyot E, Allès B, Galan P, Hercberg S, Deschasaux-Tanguy M, Touvier M. Exposure to food additive mixtures in 106,000 French adults from the NutriNet-Santé cohort. *Sci Rep.* 2021;11(1):19680. doi:10.1038/s41598-021-98496-6.

137. Chazelas, E., Deschasaux, M., Srour, B., Kesse-Guyot, E., Julia, C., Alles, B., Druesne-Pecollo, N., Galan, P., Hercberg, S., Latino-Martel, P., Esseddik, Y., Szabo, F., Slamich, P., Gigandet, S., & Touvier, M. Food additives: distribution and co-occurrence in 126,000 food products of the French market. *Scientific Reports 2020;*10,3980. doi: 10.1038/s41598-020-60948-w.

138. Pharmaprofit. Češi hojně nakupují doplňky stravy on-line. [online]. 23. 06. 2021 [cit. 14. 06. 2024]. Available from:
https://www.pharmaprofit.cz/2021/06/23/cesi-hojne-nakupuji-doplnky-stravy-on-line/

139. STADA. Stada health report 2021. [online]. 2021 [cit. 14. 06. 2024]. Available from: https://www.stada.com/media/health-reports/stada-health-report-2021

140. Eurostat. One in Two EU Citizens Look for Health Information Online. [online]. 6. 4. 2021 [cit. 14. 06. 2024]. Available from:
https://ec.europa.eu/eurostat/web/products-eurostat-news/-/edn-20210406-1

141. Finney Rutten L.J., Blake K.D., Greenberg-Worisek A.J., Allen S.V., Moser R.P., Hesse B.W. Online health information seeking among US adults: Measuring progress toward a healthy people 2020 objective. *Public Health Rep.* 2019;134:617–625. doi: 10.1177/0033354919874074.

142. Sun Y., Zhang Y., Gwizdka J., Trace C.B. Consumer evaluation of the quality of online health information: systematic literature review of relevant criteria and indicators. *J Med Internet Res.* 2019;21(5) doi: 10.2196/12522.

143. Ng J.Y., Ahmed S., Zhang C.J. Dietary and herbal supplements for weight loss: assessing the quality of patient information online. *Nutr J.* 2021;20(1) doi: 10.1186/s12937-021-00729-x.

144. Ng JY, Popal S, Selvanayagam S. Dietary and herbal supplement consumer health information for pain: A cross-sectional survey and quality assessment of online content. *Integr Med Res.* 2023;12(4):100996. doi: 10.1016/j.imr.2023.100996.

145. US Food and Drug Administration. FDA Issues Warning Letters to Companies Selling Dietary Supplements that Claim to Treat Cardiovascular Disease. [online]. 17. 11. 2022 [cit. 14. 06. 2024]. Available from:

https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-warning-letters-companies-selling-dietary-supplements-claim-treat-cardiovascular-disease

146. US Food and Drug Administration. FDA takes action against 17 companies for illegally selling products claiming to treat Alzheimer's disease. [online]. 11. 2. 2019 [cit. 14. 06. 2024]. Available from:
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm631064.htm

147. European Commission. Online offered food. [online]. 2017 [cit. 14. 06. 2024]. Available from: https://food.ec.europa.eu/safety/eu-agri-food-fraud-network/eu-coordinated-actions/online-offered-food-2017_en

148. Owens C, Baergen R, Puckett D. Online sources of herbal product information. *Am J Med.* 2014;127(2):109-15. doi: 10.1016/j.amjmed.2013. 09. 016.

149. Denniss E, Lindberg R, McNaughton SA. Quality and accuracy of online nutrition- related information: a systematic review of content analysis studies. *Public Health Nutr.* 2023;26(7):1345-1357. doi: 10.1017/S1368980023000873.

4

Studies on the safety of dietary supplements

4.1

Allergy-Like Immediate Reactions with Herbal Medicines: A Retrospective Study Using Data from VigiBase®.

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ABSTRACT

Introduction: Herbal medicines are used worldwide and with an increasing popularity in Western countries. Although often perceived as ‚naturally safe', herbals may cause severe adverse drug reactions (ADRs), with immediate allergic reactions being particularly life threatening.

Objectives: The aim of this study was to analyse immediate allergy-like ADRs to herbals documented in VigiBase®, the WHO international pharmacovigilance database.

Methods: The documentation of all suspected ADRs in association with herbal exposure reported to VigiBase® from 1969 to August 2014 was retrieved. Among all reports in which WHO-ART reaction terms were indicative of acute allergic reactions, those classified as ‚suspect' with a documented causality assessment and latency time of ≤1 day were selected. For the most frequent specific herbal-ADR combinations, the information component (IC) as a measure of disproportionality based on Bayesian statistics was calculated.

Results: We identified 757 reports out of 1039 ADRs. Products with mixed herbals (36.0%) as well as those administered orally (63.2%) were predominant. The most frequent reactions were urticaria and rash (49.2%). Anaphylactic reactions accounted for 9.5%. Disproportionally frequent reporting of mouth edema (IC = 1.81) and anaphylactic reactions (IC = 1.24) to *Phleum pretense* were noted.

Conclusion: Our findings indicate that herbal medicines for oral use carry a risk of causing immediate allergy-like ADRs. Studies using the Vigibase® database can identify specific combinations of particular herbs and adverse reactions. Healthcare professionals and patients should be aware of these risks and report any serious experiences.

Commentary:

While herbal products for oral use are generally regarded as safe, international data indicate that many such products carry a risk for acute allergy-like adverse reactions. The recognition of the occurrence of such reactions with specific products is needed for their timely diagnosis as well as for prevention.

The aim of the study was to investigate the possible connection between herbal use and the development of allergy allergy-like immediate reactions obtained from VigiBase maintained by the Uppsala Monitoring Centre of the World Health Organization.

All reports containing allergy-like adverse event terms in suspected connection with herbals were retrieved from Vigibase and evaluated (August, 2014). A total of 757 unique reports containing 1039 ADRs (i.e., more than one reaction term could be reported per case) were received between 1969 and August 2014, of allergy-like adverse event terms occurring in patients using herbal product. More than 50 % of all the included reports came from only three countries: Germany, Australia and Thailand. The most frequent primary reporters were physicians, followed by hospitals and pharmacists.

Of the data regarding herbals a substantial proportion concerned allergy-like events: Asthma-like reactions accounted for only 4.8% of all ADR. The most commonly reported allergy-like immediate adverse reactions associated with herbals were "rash", "urticaria" and "rash erythematous". Anaphylactic and anaphylactoid reactions accounted altogether for 9.5% of reported ADR (anaphylactic reaction 4.5%, anaphylactic shock 2.8%, anaphylactoid reaction 2.2%), and other serious ADR such as bronchospasm or larynx oedema.

Preparations that contained a mixture of several herbals were the suspected cause in 36% of all ADR and therefore by far the most frequently reported herbal products in association with ADR, followed by *Andrographis paniculata* (several common names including kalmegh), *Echinacea purpurea* and *Ginkgo biloba*. Oral administrations accounted for almost two thirds of ADRs.

Allergic-like events during herbal use were reported in various age groups, probably reflecting the general user population. In the light of the large scale world-wide use of herbals the numbers or case reports were small and the frequency of such reactions is probably low. On the other hand underreporting is vast but unknown and the frequency remains uncertain and likely underestimated.

Any pharmacologically active product including herbal has the potential to cause harm.

We found that herbal products for oral use carry a risk for allergy-like immediate ADR and that studies using the Vigibase can identify specific associations between particular herbals and adverse reactions. As the prevalence of herbal use is increasing, healthcare professionals as well as patients need to become better informed about the possible risks associated with these substances. When healthcare professionals record drug histories, they should also actively solicit information from their patients about all self-dministered herbal products. In addition, further studies are needed to establish associations and risk factors that are related to herbal use and allergic reactions.

4.2

Allergy-like immediate reactions with herbal medicines in children: A retrospective study using data from VigiBase®.

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ABSTRACT

Background: The use of herbal medicines in children and the general population is continually on the rise with an overall herbal lifetime and current use ranging between 0.8%- 85.5% and 2.2%-8.9%, respectively. Although acute hypersensitivity reactions are generally considered to be rare, little knowledge exists on the frequency and type of these reactions especially in specific populations like children.

Objectives: To assess the patterns of acute hypersensitivity reactions to herbal medicines reported to the WHO global individual case safety report (ICSR) database VigiBase® in children.

Study design: From the original VigiBase® extract for the time between 1968 and 2014, we included all reports with adverse drug reactions (ADR) associated with herbal medicines in children where WHO-ART reaction terms were indicative of acute hypersensitivity reactions.

Results: VigiBase® contained 2646 ICSRs with 14860 distinct adverse reactions reported in association with herbal medicine in children. Among those, 79 cases with 107 allergy- like reactions met our inclusion criteria. The most commonly reported WHO-ART terms were urticaria or rash/rash erythematous (59.8%), and allergic reaction (8.4%). The most frequently reported suspected herbal medicines were mixed herbal products (51.4%), *Hedera helix* (15.0%), and *Echinacea purpurea* (5.6%). Most frequent routes of administration were oral (75.9%), topical (8.9%), and rectal (3.8%). Over 30% of cases were reported in the age group from 7 to 12 years. The majority of reports were received from Germany (29.1%), Thailand (21.5%), and Australia (11.4%).

Conclusion: VigiBase® contains a considerable number of acute hypersensitivity reactions in children associated with herbal medicines, including life-threatening reactions such as anaphylactic shock.

Commentary:

Little data regarding the safety profile of herbal products in the pediatric population exist. Data regarding hypersensitivity reactions associated with herbals use in children is particularly rare in the literature and case reports are the main source of information. Most research regarding drug safety in children has been conducted for prescription and non-prescription drugs, in particular vaccines, antidepressants, antipsychotics, other central nervous system drugs, corticosteroids, antibiotics, antivirals and general anaesthetics. A study using data from spontaneous reporting systems that analyse worldwide adverse event data for hypersensitivity reactions in paediatric patients related to herbals was thus conducted.

The objective of this study was to analyze worldwide ADR reports of hypersensitivity reactions in children under the age of 18 related to herbals between 1968 and August 2014 and identify frequently reported herbals associated with hypersensitivity reactions as reported in VigiBase®. The WHO's global individual case safety report database VigiBase® reporting system counted over 10 million reports as of April 2015. Data extract provided by the Upsalla Monitoring Center in Sweden for the period of 1968 and August 2014 was used. The UMC manages the WHO's global individual case safety report database VigiBase®. Analysis of the data aimed to provide information about herbals most commonly related to allergic and asthma-like symptoms, as well as factors such as gender, reporting frequency by country and year, reaction outcomes and reporter qualification. WHO-ART reaction terms were indicative of acute hypersensitivity reactions were used.

The results of our study highlighted the potential of herbal products to cause serious allergic reactions in children. The cohort in our study consisted of 107 case-reports indicative of an allergic reaction following the use of one or more herbals in children under 18 years of age representing 0.05% of ADRs of the original VigiBase® extract. The majority of case-reports came from Germany, followed by Sweden and Thailand, representing over half of all cases included in the analysis. The most commonly reported suspect herbals were mixed herbals, *Hedera helix*, and *Echinacea purpurea*. Urticaria was the most commonly used WHO-ART preferred term, followed by rash and anaphylactoid reaction.

While herbal products for oral use in children and adolescents are generally regarded as safe, data indicate that many such products carry a risk of causing acute allergy-like adverse reactions. The recognition of the possibility of such reactions—with the use of, for example, *Hedera helix*, *Pelargonium* roots, and *Echinacea purpurea*—is needed for a timely diagnosis as well as for the prevention of potentially severe ADRs.

The global increase in herbal product use calls for improved, standardized, and more consistent reporting of ADRs associated with herbals to ultimately provide safer treatment options for children and adolescents. Due to the lack of clinical studies in pediatrics for both conventional and herbal products, it is also important to realize the potential of vigilance data as a tool in signal detection for pediatric patients, and improvements at all levels of the vigilance process need to be made. The reporting rate and awareness of the public and medical staff of the importance of vigilance needs to be raised.

4.3

Use of Dietary Supplements by Patients in the Pre-operative Period in the Czech Republic.

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ABSTRACT

Background: The prevalence of dietary supplement use in the pre-operative period ranges from 4.8 to 80%. According to the Food and Drug Administration, some dietary supplements may show side effects before, during and after surgery.

Objective: The main aim of the study was to determine the prevalence of dietary supplement use in patients before surgery at University Hospital Hradec Kralove and the predictors of use. The secondary aim was to determine patient awareness regarding the correct use of and possible risks associated with dietary supplements. Setting University Hospital Hradec Kralove.

Methods: Between March 2017 and June 2018, a cross-sectional study focused on patients in the pre-operative period in different departments at University Hospital Hradec Kralove was conducted. The questionnaires were anonymous and entirely voluntary. The obtained data were evaluated using descriptive statistics and a regression model in Microsoft Excel 2016 and IBM SPSS version 24. Main outcome measure - The prevalence and predictors of dietary supplement use in patients before surgery.

Results: 256 questionnaires were returned (a response rate of 77.41%). 111 dietary supplements were used by a total of 42% of the respondents in the 30-day period prior to surgery. Patients with a higher probability of dietary supplement use included patients with urogenital (OR 3.8, 95% CI 1.2, 12.1), otorhinolaryngological (OR 3.9, 95% CI 1.1, 13.8) and musculoskeletal health problems (OR 3.9, 95% CI 1.1, 13.8). The proportion of dietary supplement users increased with the number of drugs taken concomitantly, with the probability of use being more than three times higher compared with non-dietary supplement users (OR 3.4, 95% CI 1.2, 9.4). A total of 45.8% of the respondents thought there was no risk associated with their current use of dietary supplements and drugs.

Conclusions: There is a high prevalence of dietary supplement use in hospitalized patients, with independent predictors being comorbidity and polypharmacy. No official recommendations or guidelines exist for physicians and anaesthesiologists in the Czech Republic which focus on patients that use dietary supplements in the pre-operative period. National guidelines focusing on dietary supplement use in the pre-operative period would be appropriate.

Commentary:

The widespread and increasing use of DS by the general population has been published by many studies. The prevalence of dietary supplement use prior surgery has been also reported to be high and ranges from 4.8% to 80%. No such data yet exist in the Czech Republic. Since DS lack the same regulation as conventional pharmaceuticals, safety issues may arise. This became a challenge to clinicians in the perioperative period since it may increase perioperative risk and complications may occur when using DS prior surgery (e.g., myocardial infarction, stroke, bleeding, inadequate post-surgery anticoagulation, prolonged anaesthetic effects, transplant rejection, and possible drug–drug interaction).

Therefore, the main aim of this study was to determine the prevalence of dietary supplement use in patients before surgery at University Hospital Hradec Kralove as well as predictors of use. Data were collected from 9 departments at the hospital from March 2017 to July 2018 using a questionnaire consisting of sixteen open and close-ended questions on DS use during the 30-day period prior to surgery.

Out of the 332 questionnaires, 256 valid questionnaires (77%) were returned. Altogether, 42% of respondents (107) had used at least one dietary supplement within 30 days prior surgery. On average, they took 1.3 DS per patient. The majority were women (57%) and the most prevalent chronic conditions were musculosceletal and urogenital disorders.

The most commonly used DS were omega-3 fatty acids, *Ginkgo biloba*, *Echinacea purpurea*, and Ginger. Ten percent of respodents were concomitanly using prescription medication. The most frequently used drugs were for the treatment of cardiovascular, gastrointestinal and immune system.

Responents with university education and higher number of prescribed medication were more likely to use a DS prior surgery.

A total of seventy five respondents who used at least 1 DS were at risk of developing complications in the peri-operative period. Based on the type of DS taken, the complications which were likely to occur as a result of the type of DS consumed prior sugery were bleeding, hepatotoxicity, or changes in heart rate and blood pressure.

The majority of respondents were not knowledgeable about DS/herb-drug interactions or adverse reactions of DS and also believed that DS are tested for efficacy in clinical trials. Only 14% of the respondents were aware that combination of DS and prescription drugs may result in serious health problems.

On avarage, 80% of respondents did not inform their physician during hospitalizatoin prior surgery about DS use and neither were asked about DS use by

their physician.

In summary, the study's results on the use of DS by patients in the pre- operative period in the Czech Republic showed a relatively high prevalence of DS use in patients prior to surgery, while it pointed to the low level of patient awareness with regard to the possible risks associated with DS. Physicians were generally not informed about the use of DS. At the same time, the physicians did not actively ask their patients about their DS use. This can lead to an increased risk of the occurrence of a DS adverse effect or DS-drug interaction, especially when there is a low level of patient awareness of the risks of DS use.

There currently are no official recommendations or guidelines for physicians and anaesthesiologists in the Czech Republic that focus on patients that use DS in the pre- operative period. For this reason, national guidelines focusing on DS use in the pre-operative period, which could be based on already available global data, would be appropriate.

4.4

Safety assessment of food additives in top-selling dietary supplements in the Czech Republic

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ABSTRACT

Background: Food additives find use not only in the food industry but also in the pharmaceutical sector. Food additives should be safe if the acceptable daily intake is complied with; however, some individuals can experience immediate effects such as headache or impaired mental concentration, behavior, and immune response. Long-term effects may increase cancer or cardiovascular disease risk in some individuals.

Objective: The aim of this study is to evaluate the frequency of potentially harmful excipients in the top-selling dietary supplements in the Czech Republic and to consider their adverse effects.

Methods: From the list of the best-selling dietary supplements (DS) in the Czech Republic in 2014, their active ingredients and excipients were identified using the database of the information system Decisions of the Chief Public Health Officer (IS RoHy). The IS RoHy collects data on any DS registered in the Czech Republic. Adverse effects of the excipients were retrieved from the PubMed and Medline databases and from the websites of the European Safety Authorities, Joint FAO/WHO Expert Committee on Food Additives, and Codex Alimentarius.

Results: In total, 418 DS were identified, including 54.5% DS for children under 12 years of age. Of these, 66.7% contained at least one additive known to have a negative health effect. On average, there were five additives per DS. The most frequently reported additives were glycerol (28.7%), titanium dioxide (26.3%), sorbitol (12.9%), lecithin (10.5%) and beeswax (6.0%). The most commonly found potential adverse effects caused by additives as reported in the literature were gastrointestinal symptoms (51.0%), hypersensitivity reactions (31.3%), or attention-deficit/hyperactivity disorder (6.5%).

Conclusions: An EU list of approved and therefore safe additives has been established. Nevertheless, half of the most commonly used DS contained additives known to have adverse health effects. Such effects may potentially occur in predisposed patients and vulnerable groups of the population such as children or chronically ill patients, especially in the case of intake of multiple products containing the same additive. Further studies are needed to assess the clinical impact of adverse effects in DS users.

Commentary:

Food additives are used for a variety of reasons, such as preservation, colouring, and sweetening not only in food and drinks but also in pharmaceutical products and DS. Food additives must be checked by The Joint FAO/WHO Expert Committee on Food Additives for potential harmful effects on human health before they can be used by consumers. Before a food additive can be used without having harmful effects on human health, first the ADI must be established (an estimate of the amount of an additive in food or drinking water that can be safely consumed daily over a lifetime without adverse health effects). Nevertheless, adverse reactions cannot be ruled out in predisposed individuals, or high risk groups or when consumers use more products with the same food additive at the same time. Moreover, the impact of food additive-food additive interactions on human health were not properly investigated in studies and thus many of them remain unknown.

The aim of the study was to identify the most commonly used additives in the 100 top- selling DS in 2014 on the market and describe their short- and long-term side effects.

The list of food additives were retreived from the database „Information System of Decisions" of the Chief Public Health Officer. Synonymous names for additives were retrieved from the database PubChem Compound. Adverse effects of the listed additives were retrieved from the databases PubMed and Medline, websites of the EDSA, JECFA, Codex Alimentarius, and articles available in the Wiley Online Library. The keywords used for retrieval were food additives, food additives safety, food additives adverse effects, and pharmaceutical excipients. Altogether, 418 dietary supplements were used for the analysis containing about 2064 food additives (an average of five food additives per DS). Slightly more then fifty percent of the products were intended for use in children under the age of 12 years.

Nearly 50% of the DS were of herbal origin and more then one third of non-herbal origin. Vitamins and minerals made up about one fifth of the DSs. The most common additive classes were humidifiers and lubricants, binders, colorants, fillers, and emulsifiers and stabilizers. Tablets and capsules were the most common dosage forms.

Food additives with potential negative impact on human health were identified in almost two thirds of the top-selling DS in the Czech Republic. The most common short-term adverse effects were gastrointestinal symptoms and hypersensitivity reactions. Possible accumulation of food additives in body organs or negative effects on metabolic processes or human behavior belonged to the most common long-term adverse effects.

Although food additives should be safe, if consumed in higher doses, eg., simultineous consumption of the same food additive in foods, drinks, DS or medications, adverse reaction cannot be ruled out, especially in predisposed individuals suffering from food hypersensitivities or food intolerances and high risk groups such as children who may be more susceptable to adverse reactions of food additives. Still, the incidence of adverse effects caused by food additives as well as their clinical relevance need further study.

4.5

The quality of information on the internet relating to top-selling dietary supplements in the Czech Republic.

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ABSTRACT

Background: The purchase of dietary supplements (DS) via the Internet is increasing worldwide as well as in the Czech Republic. Objective The aim of the study is to evaluate the quality of information on DS available on the Internet. Setting Czech websites relate to dietary supplements.

Methods: A cross-sectional study was carried out involving the analysis of information placed on the websites related to the 100 top-selling DS in the Czech Republic in 2014, according to IMS Health data. Main outcome measure The following criteria were evaluated: contact for the manufacturer, recommended dosage, information on active substances as well as overall composition, permitted health claims, % of the daily reference intake value (DRIV) for vitamins and minerals, link for online counseling, pregnancy/breastfeeding, allergy information, contraindications, adverse reactions, and supplement-drug interactions (some criteria were evaluated from both points of view).

Results: A total of 199 web domains and 850 websites were evaluated. From the regulatory point of view, all the criteria were fulfilled by 11.3% of websites. Almost 9% of the websites reported information referring to the treatment, cure, or prevention of a disease. From the clinical point of view, all the criteria were only met by one website.

Conclusions: The quality of information related to DS available on the Internet in the Czech Republic is quite low. The consumers should consult a specialist when using DS purchased online.

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Commentary:

The aim of the study was to evaluate the quality of information of the 100 best-selling DS marketed on the internet in 2014. The accuracy and completeness of information as well as compliance with legal requirements was assessed using numerous clinical and regulatory criteria. Each criterium was awarded one point. The sum of selected criteria resulted in an overall score which was computed for each website (quality score for regulatory (=6 points) and clinical (=10 points) criteria). The best-selling DS in the Czech Republic in 2014 were selected according to Intercontinental Marketing Statistics Health data. The products labelled as "medicinal products" and "protein bars, soups, or snacks" were excluded from the study. Internet searches were performed using the most commonly search engines in the Czech Republic from July-Novermber 2015.

A total of 199 web domains and 850 websites were evaluated. Vitamins/minerals were the most frequently represented DS, followed by herbals and non-herbals. From the regulatory point of view, 11.3% of websites fulfilled all the criteria. The average score per page was 3.85 points of a total score of 6 (range 1–6; SD = 1.35). The websites least often stated the daily reference intake value percentage for vitamins and minerals, authorised health claims, and information on the overall composition. Almost 10% of websites referred to the treatment, prevention, or cure of a disease.

From the clinical point of view, the average number of points per page was 4.24 of a total score of 10. Almost 44% of websites gained more than five points. More then two thirds of websites did not disclose information on food allergens, adverse reactions, DS-drug interactions, contraindications, or use during pregnancy and breastfeeding.

Our study on the quality of information on the internet relating to top-selling DS in the Czech Republic showed that in most cases, websites presenting DS need quality control in order to comply with the EU regulations (e.g., unproven health claims or health claims from the on hold list or pending approval have been stated in some cases on the websites). More guidance or more supervision by the appropriate regulatory bodies (e.g., Ministry of Agriculture of the Czech Republic and State Agriculture and Food Inspection) should be given to website providers to disclose the information required by law. The quality of information on websites could also be improved by implementing a system for reporting trustworthy as well as noncompliant websites.

Although not required by law, clinically relevant and important information on DS-drug interactions, contraindications, and adverse reactions as well as use during pregnancy or while breastfeeding was in many cases missing. In order to ensure

a safe use of DS by consumers, it should become mandatory for the manufacturers to include this information in the product characteristics in the future.

The consumers should be aware of the risks associated with purchasing DS online and should be encouraged to check out trustworthy websites (e.g., of the well-known internet pharmacies) as well as to get expert advice (e.g., from a local pharmacist) before taking DS.

5

List of publications

5 LIST OF PUBLICATIONS

1. Pokladnikova J, Meyboom RH, Meincke R, Niedrig D, Russmann S. Allergy-Like Immediate Reactions with HerbalMedicines: A Retrospective Study Using Data from VigiBase®. *Drug Saf.* 2016 May;39(5):455-64. IF2016: 3,435 (Q1Q1Q1); AIS2016: 1,001 (Q1Q1Q2)

2. Meincke R, Pokladnikova J, Straznicka J, Meyboom RHB, Niedrig D, Russmann S, Jahodar L. Allergy-like immediate reactions with herbal medicines in children: A retrospective study using data from VigiBase®. *Pediatr Allergy Immunol.* 2017 Nov;28(7):668-674. IF2017: 4,137 (Q1Q2Q2); AIS2017: 1,022 (Q1Q2Q2)

3. Zubrova J, Pokladnikova J, Draessler J. The use of dietary supplements by patients in the pre-operative period in the Czech Republic. *Int J Clin Pharm.* 2020 Oct;42(5):1304-1310. IF2020: 2,054 (Q4); AIS2020: 0,574 (Q3)

4. Strážnická J, Pokladnikova J, Jahodar L. Safety assessment of food additives in top-selling dietary supplements in the Czech Republic. *Acta Poloniae Pharmaceutica.* 2017, 74 (6), 1929-1935. ISSN 0001-6837. IF2017: 0,531 (Q4); AIS2017: 0,166 (Q4)

5. Baudischova L, Straznicka J, Pokladnikova J, Jahodar L. The quality of information on the internet relating to top-selling dietary supplements in the Czech Republic. *Int J Clin Pharm.* 2018 Feb;40(1):183-189. IF2018: 1,692 (Q4); AIS2018: 0,526 (Q3)

6

Summary

6 SUMMARY

There is an increased prevalence of use of DS among the adult population in many western countries. The public often considers DS as safe since they are natural and is unaware that DS are not tested by regulatory agencies for their safety and efficacy. Also, the majority of professional community perceives them as safe and with minimal occurrence of systemic side effects. Most consumers usually combine DS with medical treatment which may result in potential harm to the patient in form of drug-DS interactions or adverse reactions, especially when the vast majority of the consumers use DS as part of their self-treatment without informing or consulting its use with their health care provider or pharmacist.

The sole or adujvant use of DS should result in a safe and cost-effective use of DS by consumers, especially those suffering from chronic conditions. Four main aspects of safety of DS were addressed in the habilitation thesis:

- allergy-like immediate reactions in adults and children in connection with herbal use using data from VigiBase®
- the risks associated with dietary supplement use in patients in the pre-operative period,
- the safety of food additives in top-selling dietary supplements in the Czech Republic,
- and the quality of information on the internet relating to top-selling dietary supplements in the Czech Republic.

Herbals were shown not to be "safe" as perceived by many consumers worldwide. Our safety studies indicate that there are systemic adverse effects such as allergy-like reactions that may develop during the herbal use in adults. Potential of herbals to cause serious systemic allergic reactions was highlighted also in pediatric population. Herb-related safety issues need to be communicated to the professional community, health care providers as well as parents and patients. Further studies are needed to confirm herb-adverse event associations and determine the risk factors that predispose individuals to such reactions.

Another study pointed out the low awarness of patients in the pre-operative period as well as the health care staffs about the risks associated with DS use prior to surgery and a lack of information on DS use by patients before surgery. Patients and hospital personnel should be thus more informed about the risks associated with dietary supplement use prior to surgery and disclose the information of DS use prior to hospitalization given the fact that many of the DS/herb-drug interactions or

DS-related adverse reactions during surgery are well-established and international guidelines regarding DS use prior surgery exist. Raisining awarness about this topic among health care providers as well as patients is essential to help increase the safety of patients during perioperative period and support positive health outcomes after surgery.

Adverse reactions to DS may be caused not only by the active ingredient in the DS formula but may stem from the listed food additive as well. Unwanted health effects from food additives cannot be ruled out as it was demonstrated in our study when analysing the potential health effects of food additives in the best-selling DS on the market. Unwanted health effects from food additives maybe often overlooked or underestimated as they do not receive the same attention as active ingredients and are often viewed as only a chemical possessing technical benefits. Thus all listed ingredients in the DS formula should be considered when it comes to DS safety evaluation.

Last but not least, the quality of health or product-related information presented on the websites are cruical as many DS are sold online nowadays. Our study showed that the information presented on the website is often inaccurate and incomplete and it does not always meet the regulatory requirements stated by the law. High quality of DS-related information on the websites is of high importance in assuring consumers safety as for example unproven health claims can result in ineffective treatment, diagnosis delay, or in some severe cases, can even damage the patient's health. The need arises to promote the awareness of both health professionals and consumers/ patients about the possible direct and indirect risks associated with DS use in order to meet the growth of the consumer'/patients' demands on DS.

Overall, the trends which are driving the integration of DS in contemporary healthcare are diverse and may stem from the growing interest in maintaining and improving overall health as well as the fact that non-communicable or chronic diseases continue to rise globally and are not adequately prevented or treated by modern medicine which is often accompanied by high rates of adverse side effects. Also, as the population is ageing, polymorbidity and polypharmacy represents a great clinical and socioeconomical burden to the society.

The preventive value of individual DS is constantly evolving and is determined by the latest available knowledge there is on efficacy, risks, and economic aspects of therapeutic options for a given condition across different populations.

The current research on the safety of dietary supplement use in the Czech Republic should inspire further research in this area and support healthcare professionals to monitor the safety of DS and make informed decisions in order to select the most optimal cost-effective preventive and therapeutic choice for the greatest patient's benefit.

FINAL CONCLUSIONS AND RECOMMENDATIONS:

- Increase awarness about DS-drug interactions and adverse effects of DS in patients, consumers and health care professionals

- Incentives for providing information about DS use by consumers and patients to their health care providers

- Incentives for actively asking about the use of DS by health care professionals

- Monitoring of safety of DS with regards to concurrent use of other DS, medications and over-ther-counter drugs by health care professionals

- Increase awarness of DS safety prior surgery in patients as well as health care professionals and their active involvement in DS use disclosure prior surgery

- Development and implemention of guidelines on the safe use of DS in preoperative care (e.g., collaborating partners – academic and professional organisations, Spojené akreditační komise, o.p. s., Ministry of Health ect.)

- Keep in mind that unwanted health effects from food additives cannot be ruled out especially when

    - a food additive is consumed in higher doses as a result of concurrent use of other DS, medication, foods and drinks containing the same food additive

    - a food additive is consumed by predisposed individuals (e.g., food hypersensitivities)

    - a food additive is consumed by high risk groups (e.g., children)

- Potential risk exists when purchasing DS online without a professional advice as a result of inaccurate and incomplete information

- Incentives for quality checks of websites by regulatory health authorities on accuracy, completness and comprehensiveness in DS-related information and other disclosures

- Enforcement efforts against inaccurate and misleading claims

- Research into how consumers use DS

- Incentives for state and privately funded research into testing efficacy and safety of DS