Journal of Functional Foods 72 (2020) 103990

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Adverse effects to food supplements containing botanical ingredients

Francesca Colombo[a], Chiara Di Lorenzo[a,*], Simone Biella[a], Sarah Vecchio[b], Gianfranco Frigerio[c], Patrizia Restani[a]

[a] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Italy
[b] Servizio per le Dipendenze, ASL Biella, Italy
[c] Department of Clinical Sciences and Community Health, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Italy

ARTICLE INFO

Keywords:
Botanicals
Plant Food Supplements
Adverse effects
Poison Centres
Prebiotic fibres

ABSTRACT

The use of Plant Food Supplements (PFS) has increased significantly in the last decades. The wide diffusion of these products has raised concerns about their safety and to solve at least some critical points the EU Project PlantLIBRA was financed. The project included among its goals the collection of adverse effects due to PFS; using different sources: 1) the scientific literature; 2) European Poison Centers; 3) the PlantLIBRA consumer survey. New data from the Pavia Poison Centre, ANSES and FDA were elaborated after the end of EU Project. Adverse effects were analysed according to the WHO causal relationship criteria. *Valeriana officinalis* and *Camellia sinensis* were the plants most frequently involved in adverse effects in European countries. Although mild/moderate symptomatology were generally described, some severe outcomes occurred, including fatal cases. Nervous and gastrointestinal systems were the main targets; the intestinal disorders were associated with fibres and polyphenols present in some plants.

1. Introduction

In recent years, products containing botanical ingredients have gained great popularity among consumers, representing an increasing portion of the food market. According to the European Safety Authority (EFSA), the term "botanical" means "medicinal, cosmetic and aromatic plants", that can be used as such or processed to be included as "ingredients of foods, food supplements, cosmetic, drugs, medical devices, animal feed, household products, pesticides, biocidal products" and are regulated by different legislation (EFSA Scientific Committee, 2009). Fig. 1 illustrates the classification of products containing botanicals.

The European legislation is not totally harmonized when products containing botanicals are considered. Most EU countries considers botanicals as ingredient of food supplements, regulated by food law; other prefer the inclusion in products of traditional medicine, regulated by drug law. According to the Directive 2002/46/EC, food supplements are defined as "foodstuffs that are meant 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, where nutrients could be vitamins, minerals, herbal extracts and other ingredients" (European Commission, 2002). In this paper, food supplements containing botanicals are named Plant Food Supplements (PFS).

The great diffusion of these products on the market has been associated with different factors; among the most important there are: 1) the increasing request by consumers, due to a growing mistrust in conventional medicine: 2) the perception that "natural" means "not chemical" and then "safe"; 3) the availability on the market without medical prescription required (Egan, Hodgkins, Shepherd, Timotijevic, & Raats, 2011; Vargas-Murga et al., 2011).

In parallel, there is a growing interest in this area from industries (both food and pharmaceutical companies), since PFS are characterized by a relatively cheap cost of production (depends on quality control) and reduced legislative requirements.

Considering the high number of companies producing botanicals (including raw material) and food supplements/PFS present on market, quality, efficacy and safety aspects have become question of concern.

Abbreviations: EFSA, European Safety Authority; OTC, Over The Counter; TC, Third Countries; PFS, Plant Food Supplements; PlantLIBRA, PLANT food supplements: Levels of Intake, Benefit and Risk Assessment; ANSES, French Agency for Food, Environmental and Occupational Health & Safety; FDA, Food and Drug Administration; GAP, Good Agricultural Practices; RASFF, Rapid Alert System for Food and Feed; POA, Pentacyclic Oxindole Alkaloids; TOA, Tetracyclic Oxindole Alkaloids; TMC, Traditional Chinese Medicine; CAERS, Adverse Event Reporting System; EGCG, epigallocatechin-3-gallate; EMA, European Medicines Agency.

* Corresponding author at: Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, via Balzaretti 9, Milan, Italy.
E-mail address: chiara.dilorenzo@unimi.it (C. Di Lorenzo).

https://doi.org/10.1016/j.jff.2020.103990
Received 28 February 2020; Received in revised form 23 April 2020; Accepted 27 April 2020
Available online 24 June 2020

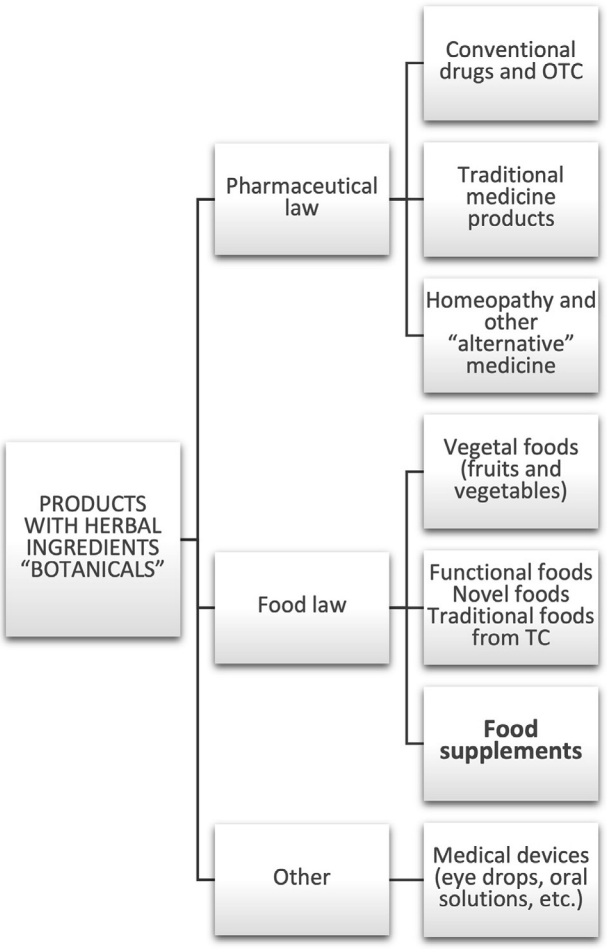

Fig. 1. Classification of products containing botanicals according to the European legislation (OTC: Over The Counter; TC: Third Countries; adapted from: Restani, 2019).

To face some of the most critical aspects, the EU funded the Project PlantLIBRA (PLANT food supplements: Levels of Intake, Benefit and Risk Assessment) in the 7th framework program. The main goals of this project were: 1) the promotion of the safe use of botanicals and PFS; 2) the dissemination of concepts of quality and health benefits of PFS among operators and consumers, 3) the collection of data to perform assess a risk/benefit assessment, and 4) the production of new data to allow a better science based decision-making by regulators and food chain operators.

This review focuses primarily on the collection of PFS-related adverse events from various sources: 1) critical review of the adverse effects reported in the scientific literature (case reports and human clinical studies); 2) retrospective study involving several European and a Brazilian Poison Centers; 3) assessment of adverse effects self-reported by people participating to the PlantLIBRA consumers' survey; 4) collection of adverse effects made available by the Pavia Poison Centers, ANSES and FDA. The first three sources come from the European PlantLIBRA project.

2. Factors contributing to adverse effects to plant food supplements

Several factors are involved in the adverse effects to botanicals. Table 1 lists the factors related to product quality, that can significantly contribute to consumers' safety problems.

The quality of raw material (botanical) is always important for consumers' safety. PFS are classified as food and therefore must comply with food legislation requirements, in terms of production and control. However, it is necessary to emphasize that PFS are not common foods, since they contain ingredients from which something more than a nutritional intake is expected. The consumer buys them to improve his health, and, in some cases, erroneously expecting a therapeutic activity. As a consequence, the quality of the botanical ingredient requires greater attention as its composition can vary significantly with possible consequences on the safety of the commercialized PFS.

The raw material control is the first step in the food supply chain and a crucial role in defining the quality of the final product. For this reason, the plants that will be included in PFS must be strictly controlled for biological (bacteria, viruses, moulds and related toxins) and chemical (pesticides, heavy metals) contaminants. To reduce the risks for consumers, farmers should follow the rules of good agricultural practice (GAP) for the use of pesticides or fertilizers or comply with the regulations for organic agriculture, depending on the agronomic strategy used (Schilter et al., 2003; WHO, 2004).

To demonstrate how critical the quality control of PFS is, the reports published by RASFF (Rapid Alert System for Food and Feed) in 2018 can be cited. RASFF reported 3662 notifications of food and feed irregularities; 255 of them were referred to dietetic products and food supplements, in terms of composition: 134 were due to the presence of pharmaceutical ingredients, illicit additions, molecules regulated by national and international directives; 10 reported the presence of pollutants, 12 of heavy metals, 10 of un declared allergens, 3 pesticides and 6 pathogens (RASFF, 2018).

Illicit additions were frequently found both in EU and extra-European Countries. From 2007 to 2016, FDA identified 776 adulterated dietary supplements, mainly containing illicit drugs, such as sexual enhancers (45.5%), weight loss promoters (40.9%), or muscle builders (11.9%) (Tucker, Fischer, Upjohn, Mazzera, & Kumar, 2018). Adulteration is frequently found in products imported from Eastern Countries, including those belonging to Traditional Chinese Medicine (TMC) (Dunnick & Nyska, 2013). Another aspect to keep under control is the presence in PFS of known active molecules, which are allowed but the quantity of which is regulated by national or international directives. For example, in PFS containing bitter orange (*Citrus aurantium* L.), the synephrine daily intake should not be higher than 30 mg (corresponding to 800 mg of *C. aurantium* extract titrated at 4% synephrine), and octopamine (as marker for all active amines) must be lower than 1/8 of synephrine (Ministero della Salute, 2018). These limits have been established to protect the consumer from the possible cardiovascular adverse effects reported in the literature (Bouchard, Howland, Greller, Hoffman, & Nelson, 2005). As far as heavy metals are concerned, it should be underlined that, alongside the possible contamination of environmental origin, there is the possibility that these elements are intentionally added in Ayurvedic products and are often present in high concentrations in TCM preparations, with important clinical consequences both in children (Ernst & Thompson Coon, 2001) and adults. In Ayurvedic medicine, the inclusion of heavy metals (lead, arsenic, aluminium, cadmium, etc.) can represent a part of the therapy, while in TCM several cases of contamination are described, mainly due to a lack of application of international standardization guidelines for processing, manufacturing and marketing.

Other factors related to raw materials and potentially contributing to adverse effects are the misidentification of botanicals used in PFS; the main problem is the use of common names instead of the binomial Latin names, as suggested by the Good Production Practices. In fact, a single common name can be used for different species, as in the case of "Echinacea" that refers to a genus including nine species: among them, *Echinacea angustifolia, Echinacea purpurea* and *Echinacea pallida* are the commonly used. The common name can be extremely dangerous if it includes also toxic species. As an example, the common name "fang ji", refers both to *Stefania tetranda* and *Aristolochia fangchi*, the latter involved in several cases of kidney cancer in Europe (Tankeu, Vermaak, Chen, Sandasi, & Viljoen, 2016).

Table 1
Factors related to the quality of PFS involved in the incidence of adverse effects.

Quality of ingredients	Presence of Contaminants	Counterfeits	Illicit additions
Unsatisfactory quality of raw material	Pesticides	Intentional use of low-quality botanicals	Conventional drugs such as antibiotics, amphetamines, etc.
Misidentification	Heavy metals	Use of botanicals different from those declared in the label (lower cost)	Stimulating molecules (ephedrine, active amines, sildenafil, etc.)
Wrong part of botanical (leaves instead of root, etc.)	Mycotoxins		Doping (e.g. hormones)
Presence of different plant chemotypes	Pollutants		
Low quality of extracts/derivatives			

Adverse effects can occur when the wrong part of the plant is used, or when two plants are so similar to be confused by people without specific expertise in botanical sciences. As an example, *Digitalis lanata*, with heart stimulant components can be confused with *Plantago major*. Accidental contaminations can also be responsible for serious adverse effects. Among them, plants producing pyrrolizidine alkaloids must be mentioned for their harmful effects on human health. More than 600 alkaloids belonging to this class have been identified; taking into consideration the high number and diffusion of plants – more than 6000 - containing pyrrolizidine alkaloids with hepatotoxic and carcinogenic effects, the risk of accidental contamination of other plants used for animal feed and human nutrition is concrete, as documented by several studies (Li, Xia, Ruan, Fu, & Lin, 2012; Schulz et al., 2015).

Finally, another factor that should be considered regarding the quality of botanical preparations is the presence of different plant chemotypes, defined as the same species/subspecies/varieties of a plant or organism containing different secondary metabolites or the same secondary metabolites in different amounts (Polatoglu, 2013). The presence of chemotypes can raise several concerns since a plant extract could be a mixture of chemotypes, not distinguishable from each other, that could be responsible of different biological effects, both positive and negative. For example, the plant giant fennel (*Ferula communis* L.) from Sardinia (Italy) is present in two chemotypes with different biological activities. One chemotype is poisonous, responsible for ferulosis in sheep, goats, cattle, and horses, due to the presence of prenylcoumarins; the other chemotype is safe and contains daucane esters, responsible for some beneficial effects (Poli et al., 2005; Rubiolo et al., 2006). Another example is represented by the two chemotypes of *Uncaria tomentosa* (cat's claw), which can contain oxindole alkaloids as pentacyclic (POA) or tetracyclic (TOA) derivatives characterized by antagonistic effects (lymphocyte antiproliferative and proliferative effects, respectively) (Kaiser et al., 2016).

3. Factors associated with consumers

As previously reported, the market of food supplements is rapidly growing across the world. In 2016, the US sales of dietary supplements and PFS reached 27.6 and 6.4 billion dollars, respectively (Smith, Lynch, Johnson, Kawa, Bauman, & Blumenthal, 2015) and the trend of the European market is also rising, as indicated by the increasing of sales (+9.6% form 2014 to 2015 and a further +6.3% is expected by the end of 2020). Although the global data on PFS consumption are limited for the cited regulatory differences, it is estimated that about 20% of European consumers regularly use PFS, hoping to get benefits (Garcia-Alvarez et al., 2014). Similar rates (17.7%) were found in USA (Barnes, Bloom, & Nahin, 2009).

Generally speaking, according to different studies, the use of food supplements is mainly associated with being female, high education level, high household income, older age and use of over the counter drugs (Bailey, Saldanha, Gahche, & Dwyer, 2014; Timbo, Ross, Mccarthy, & Lin, 2006). Similar characteristics were observed among European consumers, where a healthy lifestyle and a good health status were also reported (Garcia-Alvarez et al., 2014). Despite the consumers are now generally aware and careful about their health status, the growing use of botanicals has been associated with a possible risk of adverse effects, taking also into consideration the thousands of PFS present of the market. Although the incidence of mild-severe adverse effects is generally low (about 4% according to European and US data from surveys among consumers) and some plants have been traditionally used from thousands of years, many of them have not been tested in scientific studies and their efficacy and safety not established enough (Di Lorenzo et al., 2015; Lüde et al., 2016; Restani et al., 2016; Timbo et al., 2006).

At present, social aspects have a special role in modulating the incidence of adverse effects to PFS, as reported in Table 2.

The large consensus received by botanical preparations has been attributed also to individual and social factors which include: 1) preference of consumers for herbal supplements for solving transient complaints preventing chronic diseases and improving/maintaining the health status; 2) erroneous belief that herbal products are superior in efficacy and safer than chemical products; 3) to counteract adverse effects of drugs; 4) dissatisfaction with pharmaceutical therapies and the belief that botanicals can be effective in solving transient upsets when conventional therapies resulted ineffective; 5) the consumers

Table 2
Social co-factors contributing to the onset of adverse events.

Consumers' factors	Information	Interactions	Irregular products
Consumer perception that "natural is always safe"	Consumers are not informed on PFS. Advise from friends	Consumers are not always informed on interactions between PFS and nutrients	Consumers do not take due account of the risks of illicit additions
Consumer perception that natural products have always high quality	PFS do not require a prescription and are mainly self-administered	Consumers are not always informed on interactions between conventional drugs and PFS	The unusual effectiveness of a natural extract does not cause alarm although this is often due to the presence of undeclared pharmacologically active molecules
Distrust of conventional medicine in favor of alternative medicine	Nutritional claims are strictly regulated in EU and labels are only rarely informative		Poor public disclosure of PFS withdrawn due to irregularities unlike common foods
Belief that natural products can effectively replace drugs (distorted news from internet)	"Alternative markets" are very active and dangerous (gym, internet, etc.)		

perception that PFS can improve the control on their health, including the management of chronic diseases; 6) great availability of PFS on the market without medical prescription requirements; 7) increasing attitude of consumers to not consulting the physician if is chronically treated with conventional drugs. For example, several reports describe the interactions between licorice and anti-hypertensive, or valerian and benzodiazepines (Di Lorenzo et al., 2015); 8) increasing influence of mass media on consumers choices. Marketing strategies by various manufacturers, advertisements in the mass media including social media, television and radio programs have significantly stimulated consumers' interest, also providing sometimes misleading information. This point is particularly critical considering the number of consumers using internet to retrieve information about health-related issues and the potential inadequate labelling of PFS sold on the internet, including the amplified positive effects and very low warnings about the safety (Zickuhr, 2010). A study by Owens, Baergen, and Puckett (2014), revealed that out of more than 1170 websites selling herbal products, < 8% provided information or warnings about possible adverse effects, < 3% cited scientific studies and only 10% recommended to consult the physician about the use of the botanical.

Particular attention should be paid to subjects with higher risk of adverse events. Pregnant or lactating women should avoid use of PFS or strictly follow the physician's indications; children must use only products specifically formulated and under the pediatrician control. A recent Italian retrospective analysis (2002–2018) of suspected adverse effects to complementary and alternative medicine among children (0–18 y), performed by the Phytovigilance system, collected 206 reports, 57% of which related to dietary supplements, and 39% to products containing 2–5 ingredients. More than sixty adverse effects occurred in infants (2–3 months) and about one hundred in children (2–12 y) (Lombardi et al., 2019). Finally, particular attention should also be given to consumers with diseases associated with food, such as celiac and allergic subjects (Restani, 2019).

Considering the different aspects involved in adverse effects occurrence, it is essential to increase the awareness of consumers by providing different tools and increasing the availability of source of reliable scientific information on botanicals and PFS, such as websites managed by regulatory bodies. Furthermore, continuous updating of medical practitioners could be a tool for better monitoring the use of these products and recognizing the occurrence of adverse effects.

4. Adverse effects to botanicals: comprehensive analysis from different sources

As discussed above, it is clear that several aspects can contribute in increasing the risk of adverse events among PFS consumers. The EU Project PlantLIBRA collected and analyzed data on adverse effects from different sources, which included: the scientific literature, (Di Lorenzo et al., 2015); a multicenter retrospective study performed by the European Poison Centers, that collected cases of adverse effects due to PFS or foods from 2006 to 2010 (Lüde et al., 2016); adverse effects self-reported by participants of the PlantLIBRA Consumers' Survey (Restani et al., 2016). After the end of PlantLIBRA project, new cases were further collected from the Italian Pavia Poison Centre and National Toxicology Information Centre, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) kindly supplied by Dr. Aymeric Dopter, and the Adverse Event Reporting System (CAERS) by FDA (https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers) (Di Lorenzo et al., 2018). Criteria of inclusion of cases used by the different sources are illustrated in Table 3.

The period considered for the analysis of adverse effects covered a total of 10 years (2006–2016). Even though the number of ingredients was quite high (from 66 to 192), only few botanicals were frequently involved in adverse effects. This conclusion was partially due to the application of strict criteria of causal relationship, which allowed the

Table 3
Criteria used by different sources to collect adverse effects.

	Review from the scientific literature (PlantLIBRA)	Poison Centers retrospective study (PlantLIBRA)	Self-reported adverse effects (PlantLIBRA)	Pavia Poison Centre retrospective study	Reports from ANSES	Reports from CAERS (FDA)
Period	From databases inception to 2014	2006–2010	2011–2012	2011–2015	2009–2016	2010–2016
Age	Adults and children	Adults (≥17 y) and children (< 16 y)	Adults (≥18 y)	Adults (≥15 y)	Adults (> 17 y) and children (≤15 y)	Adults and children
N. PFS	66 botanicals most frequently used in PFS	71 plants most frequently use in PFS and selected in PlantLIBRA project	72 botanical ingredients, representing the botanicals involved in the 87 adverse effects reported	229 plants	192 plants	2450 commercial products
Causality criteria for selection of cases	Selection of cases with the highest classes of causality (certain, probable/possible) according to the WHO criteria	Cases were classified according to the WHO criteria	Symptomatology was evaluated on the basis of WHO and Poison Centers criteria	WHO criteria	ANSES criteria (Very likely, likely, possible, doubtful unlikely)	Not provided
N. Plants selected /N. cases	14 cases were for plants as such and 11 for interactions (at least ≥ 10 papers with high causal relationship) Total cases = 492	15 plants selected (at least ≥ 3 cases) Total cases = 57	14 plants were cited in 68 cases Total cases = 87	21 plants (at least ≥ 3 cases) Total cases = 229	28 plants (at least ≥ 10 cases) Total cases = 92	42 plants in mono-ingredient products involved in 414 cases

selection of those cases where the cause-effect was demonstrated by the information reported, including clinical outcome. The only exception was the collection of reports from CAERS, which refers not only to cases reported by health care professionals, but also to those obtained by consumers, without any scientific revision.

The number of verified cases on the overall consumption of PFS was about 23% (982 possible/probable cases on 4284 total cases collected from the different studies). Apart from the PlantLIBRA survey among consumers, where adverse effects were due only to botanicals as ingredients of food supplements, in the retrospective Poison Centers studies as well as in the literature review it was not always possible to separate the cases due to botanicals used as food/food supplements or traditional medicines. As well-known, there is a lack of international harmonization in their classification, also in EU. The legal status of an herbal preparation depends on the law of the specific country, meaning that a preparation can be classified as a supplement in one country and traditional medicine in another. In addition, the wide range of different terminology used for PFS, which can be referred to in the literature as 'plant foods', 'plant extracts', 'botanicals', 'herbals', and/or 'herbs' adds further complexity to data interpretation. Similar observations can be done regards the pharmaceutical forms (traditional medicine, Chinese medicine, etc.). In this review, we tried to select as much as possible the adverse effects due to PFS. In the literature it is reported that the cause of adverse effects due to botanicals in Italy (from 2002 to 2007) were distributed as follows: natural products (n = 233), 68% herbal products (of these, 4% related to Ayurvedic remedies and 3% to products from Traditional Chinese Medicine), 21% to dietary supplements and 11% to homeopathic preparations (Menniti-Ippolito et al., 2008). In addition, as previously reported, a recent analysis of adverse effects due to complementary alternative medicines collected by the Italian Phytovigilance system among children (2002–2018), showed that of the 206 reports, 57% were due to PFS and 23% to homeopathic remedies. The increase of the number of adverse effects due to PFS can be also explained by the increase popularity and diffusion of these preparation among consumers (Lombardi et al., 2019).

The studies included in the present review involved both adults and children in four out of six studies. The PlantLIBRA consumers' survey included only participants aged > 18 years, so that self-reported events are related only to adults (Garcia-Alvarez et al., 2014). In Pavia Poison Centre retrospective study, the selection subjects > 15 years was due to the very low percentage of adverse effects involving children and to avoid the selection of adverse effects caused by accidental ingestion.

Fig. 2 shows the plants most frequently involved in adverse effects from different studies (only mono-ingredients PFS were considered).

Comparing the frequency of adverse effects, *Valeriana officinalis* and *Camellia sinensis* L. were among the most cited botanicals in five out of the six data sources included: PlantLIBRA Poison Centers retrospective study, Pavia Poison Centre retrospective study, and PlantLIBRA consumers' survey. Data from the literature and ANSES showed that *Camellia sinensis* was the third plant most cited being 8.7% and 5.4%, respectively. In the literature, *Camellia sinensis* (green tea) has been associated with hepatotoxic effects mainly due to the intake of high amounts of epigallocatechin-3-gallate (EGCG). This effect is also mediated by the type of extraction used: hydroalcoholic extract were more involved in adverse effects (Di Lorenzo et al., 2015; Federico, Tiso, & Loguercio, 2007). *Camellia sinensis* was also cited in interactions with drugs, such as statins (rhabdomyolysis was the principal clinical symptoms) and warfarin (the reduced anticoagulant effect of the drug was mediated by the antagonism of vitamin K in green tea) (Mazzanti et al., 2009).

On the other hand, consumers participating to the PlantLIBRA survey reported gastrointestinal symptoms (nausea, gastric problems, diarrhea) associated with the intake of PFS containing *Camellia sinensis*, probably due to caffeine content, as also reported by the European Medicines Agency (EMA) (EMA, 2013). Cardiovascular symptoms due to caffeine were recorded in ANSES database, mainly associated with black or oolong teas.

Adverse effects of *Valeriana officinalis,* cited in four out of six data sources, were mainly associated with somnolence, as expected. Other symptoms described by consumers, with a possible causality, were constipation, flatulence and migraine, as also reported in EMA documents (EMA, 2016).

Panax ginseng was responsible for adverse effects on central nervous system (nervousness and maniac episodes due to drug interactions with antidepressants) and cardiovascular symptoms (tachycardia) in association with *Paullinia cupana*, probably due to synergistic effects (EMA, 2012). Other eight botanicals, cited in three out of the six data sources, were *Glycine* max (allergic reactions), *Melissa officinalis* (dizziness and insomnia), *Glycyrrhiza glabra* (hypokalemia and hypertension, also due to drug interactions), *Ginkgo biloba* (interaction with anticoagulant drugs and insomnia), *Citrus aurantium* (tachycardia and hypertension), *Cynara scolymus* (gastrointestinal effects), *Paullinia cupana* (tachycardia

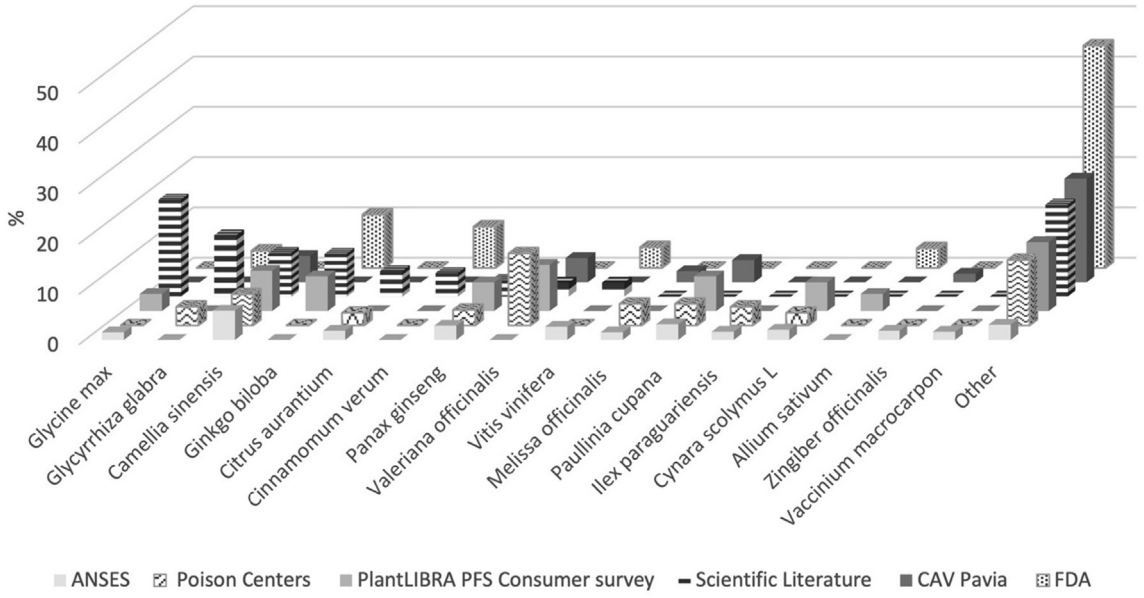

Fig. 2. Plants most frequently involved in adverse effects as reported from the different data sources.

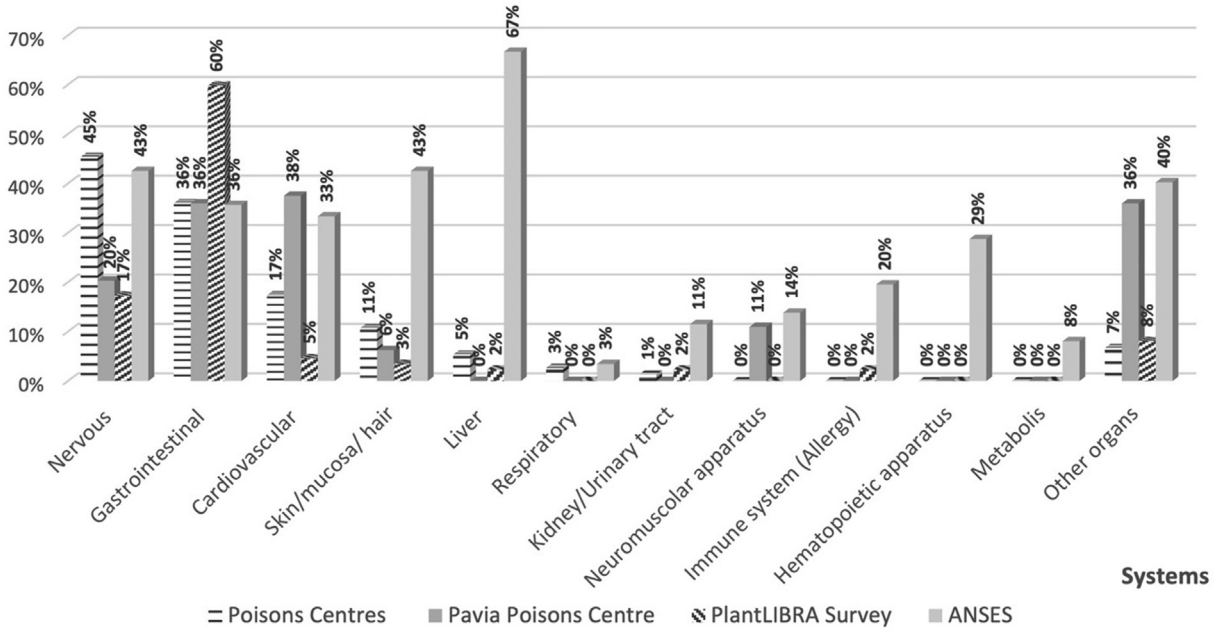

Fig. 3. Organ/system target of adverse effects as reported by the different data sources.

and dizziness).

The daily intake of botanicals and active molecules is an important aspect associated with the occurrence of adverse effects. However, only in relatively few papers these details are indicated for the following reasons: 1) the adverse effects are generally described in case reports where the specific composition of the products is often missing. 2) In some cases, the plant extracts responsible for the adverse effects are included in tea or infusion where the concentration of active molecules is not reported. 3) Cases collected by Poison Centers, only rarely are correlated with analytical data on the PFS responsible of the adverse effect. As far as *Camellia sinensis* is concerned, the most serious adverse effects described in the literature are referred to supplements containing an 80% ethanolic dry extract of green tea standardized at 25% catechins, expressed as EGCG. This kind of extraction can increase the extraction of some molecules, including catechins. Other case reports described a consumption of green tea as extract in doses up to 1800 mg/day or as infusion (> three cups/day) (Federico et al., 2007; Sharma, Wong, Tsai, & Wong , 2010). The period of intake was extremely variable: from few days to two years of daily consumption. The hepatotoxic effects described these reports raised several concerns that have been faced by the European Commission, who asked EFSA an opinion about the safety aspect of green tea catechins. On the basis of the data available, EFSA concluded that doses equal or above 800 mg EGCG/day from food supplements can increase the risk for liver injury, while catechins from green tea infusion can be considered safe taking into consideration the intakes in the European Countries (EFSA Ans Panel, 2018).

Caffeine is another active components of *Camellia sinensis* responsible for some adverse effects. According to EMA, the caffeine content in green tea extract ranges between 2.5 and 4% dry weight (EMA, 2013). The intake of caffeine by tea derivatives in some consumers from the PlantLIBRA survey, reporting insomnia and nausea, was lower than the acceptable intake of 300 mg/day; however, the individual susceptibility and other dietetic sources of caffeine (including botanicals such as *Paullinia cupana*) could be involved in these unexpected negative effects.

Valeriana officinalis, one of the plants most frequently involved in adverse effects, was consumed both as infusion and extract in food supplements. When consumed as food supplement, the mean dose of valerian root extract was 300 mg/day for a period between 2 days and 12 months. However, the content of valerian active components in PFS was not reported.

Adverse effects due to *Citrus aurantium* were mainly due to synephrine content. However, the composition of PFS and the specific amount consumed before the adverse effect appearance, were rarely reported. As reported above, synephrine and other Citrus active amines content is under national regulation. Some reports describe the intake of multi-ingredient supplements (up to 2 capsules/day for more than 1 months), where the content of *Citrus aurantium* extract (standardized at 5% synephrine) was < 20% of capsule weight (600 mg) (Vitalone et al., 2011).

Finally, *Ginkgo biloba* was responsible for different kind adverse effects: hemorrhagic complications (chronic use at the average dose of 240 mg/day) and effects on central nervous system (insomnia, dizziness): in the latter case the dose was not specified but the duration of intake was > 6 months (Miller & Freeman, 2002; Pedroso et al., 2011).

In adverse effects due to interactions, the influence of plant extracts on metabolic enzymes or on pharmacodynamic mechanisms was less dependent on the doses assumed.

5. Severity of clinical symptoms and organs/systems involved

Generally speaking, the severity of clinical signs associated with adverse events to PFS have minor or moderate entity. The PlantLIBRA Poison Centre study observed an increase of severity with multi-ingredient PFS; they caused moderate and severe symptoms in 33.3% of cases, while mono-ingredients only in 10%. Only few severe cases were observed (< 10% of total adverse effects), with some fatal outcome. A total of seventeen cases of death were reported from the different data sources; however, only two of them were associated with the intake of a PFS or botanicals with probable/possible causality. *Ginkgo biloba* was identified as responsible of a fatal breakthrough seizure occurred in a patient suffering from epilepsy who was in therapy with anticonvulsant drugs phenytoin and valproic acid; ginkgolides probably induced CYP2C19 causing a reduction of drug plasmatic concentrations (Kupiec & Raj, 2005). Another fatal case, reported by ANSES, occurred in a 72 years old man, who developed encephalopathy and fulminant hepatitis after taking a supplement containing *Desmodium adscendens* and some concomitant drugs (aspirin, anti-hypertensive drugs, sulpiride). The other 15 cases of death were published in the CAERS of FDA, but

Table 4
Adverse effects associated to the plants mostly involved in adverse effects from the different sources.

	Review from the literature	Poison Centers	PlantLIBRA PFS Consumer Survey	ANSES	FDA
• *Allium sativum*	• NR	• C	• Allergic reactions • Gastric problems	• NR	• C
• *Camellia sinensis*	• Hepatotoxicity • Drug interactions	• Hepatotoxicity • Myocardial infarction	• Gastric problems (nausea) • Insomnia • Diarrhoea	• Hepatotoxicity • Cardiovascular effects	• C
• *Cimicifuga racemosa*	• Hepatotoxicity • Myopathy • Reversible complete heart block with bradycardia • Cutaneous vasculitis • Cutaneous pseudolymphoa	• NR	• NR	• NR	• C
• *Cinnamomum verum*	• Stomatitis • Hyperkeratotic plaques • Allergic reactions • Squamous cell carcinoma of the tongue • Contact dermatitis	• NR	• NR	• Vomit • Tachycardia • Dizziness	• Cardiovascular adverse effects
• *Citrus aurantium* L.	• Hypertension • Tachycardia • Ventricular extrasystoles • Ischaemic colitis • Allergic bronchospasm • Hepatitis	• Myocardial infarction	• Gastric problems	• Insomnia • Anxiety	• NR
• *Cynara scolymus* L.	• C	• Anaphylaxis	• Increased diuresis • Diarrhoea • Gastric problems (nausea)	• Rhabdomyolysis • Myalgia • Kidney failure	• NR
• *Dioscorea villosa* L.	• NR	• Hepatotoxicity	• NR	• C	• NR
• *Echinacea purpurea*	• Allergic reactions • Hepatotoxicity • Erythema nodosum • Diarrhoea • Vomiting • Headache • Drowsiness	• NR	• Gastric problems • Tachycardia	• C	• NR
• *Echinacea spp*	• NR	• C	• Gastric problems	• NR	• NR
• *Equisetum arvense*	• NR	• NR	• Gastric problems • Hair loss/fragile nail • Constipation	• Thrombocytopenic purpura	• NR
• *Foeniculum vulgare*	• C	• NR	• Gastric problems • Increased diuresis • Difficulty in swallowing	• C	• NR
• *Ginkgo biloba*	• Haemorrhagic complications • Ventricular arrhythmia • Acute generalized exanthematous pustulosis • Toxic epidermal necrolysis • Convulsions • Drug interactions	• C	• Discomfort • Insomnia • Constipation • Dizziness	• C	• Cardiovascular adverse effects
• *Glycine max*	• Allergic reactions • Pseudohormonal activity • Gastrointestinal disorders • Thyroid dysfunction • Bladder cancer • Others • Nutrients and drug interactions	• C	• Gastric problems	• Allergic reactions • Hypercalcemia	• C
• *Glycyrrhiza glabra*	• Hypokalaemia • Hypertension • Drug interactions	• Disorientation • Hypertensive crisis • Severe hypokalemia	• NR	• C	• C
	• Review from literature	• Poison Centers	• PlantLIBRA PFS Consumer survey	• ANSES	• FDA

(*continued on next page*)

Table 4 (*continued*)

	Review from the literature	Poison Centers	PlantLIBRA PFS Consumer Survey	ANSES	FDA
• *Hypericum perforatum*	• Convulsions • Confusion • Manic attack • Hypertension • Delirium • Sexual dysfunction • Serotonin syndrome-like symptoms • Increase of transaminases • Drug interactions	• C	• NR	• C	• C
• *Ilex paraguariensis*	• NR	• Transient ischemic attack	• NR	• C	• NR
• *Melissa officinalis*	• Drug interactions	• C	• Allergic reactions • Dizziness	• Erythema	• C
• *Mentha × piperita*	• NR	• Disorientation • Hypertensive crisis • Severe hypokalemia	• NR	• C	• NR
• *Olea europaea*	• C	• NR	• Diarrhoea • Allergic symptoms • Gastric problems (nausea)	• C	• NR
• *Panax ginseng* C.A.Mey.	• Stimulant effects, • Maniacal episode • Metrorrhagia • Allergic reactions • Drug interactions	• Transient ischemic attack	• Gastric problems • Constipation • Tachycardia	• Aphthae	• C
• *Passiflora incarnata*	• Drug interactions	• C	• Insomnia	• C	• NR
• *Paullinia cupana*	• NR	• Myocardial infarction • Transient ischemic attack	• Constipation • Diarrhoea • Insomnia • Tachycardia • Dizziness	• Insomnia • Anxiety	• NR
• *Piper nigrum*	• NR	• C	• NR	• Hepatotoxicity	• C
• *Red rice*	• NR	• NR	• Hepatotoxicity • Headache • Dizziness • Heartburn • Gas • Digestive tract discomfort • Dry skin • Difficulty in swallowing	• Drug interactions	• NR
• *Ribes nigrum*	• NR • Review from literature	• NR • Poison Centers	• Gastric problems • PlantLIBRA PFS Consumer survey	• Itchy erythema • ANSES	• NR • FDA
• *Serenoa repens*	• NR	• C	• Discomfort	• NR	• Gastrointestinal disorders • Cardiovascular adverse effects
• *Silybum marianum*	• NR	• NR	• NR	• C	• Hepatotoxicity • Cardiovascular adverse effects
• *Taraxacum officinale*	• NR	• C	• Dizziness	• Drug interactions	• C
• *Trigonella foenum-graecum*	• NR	• C	• Discomfort	• C	• C
• *Vaccinium macrocarpon*	• NR	• NR	• Discomfort	• Neutropenia • Purpura	• C
• *Valeriana officinalis*	• Hepatotoxicity • Drug interactions	• Somnolence • Drowsiness • Gastrointestinal disorders	• Dizziness • Insomnia • Constipation • Migraine • Flatulence	• C	• C

(*continued on next page*)

Table 4 (*continued*)

	Review from the literature	Poison Centers	PlantLIBRA PFS Consumer Survey	ANSES	FDA
• *Vitex agnus castus*	• Intermenstrual bleeding or disorders • Gastrointestinal disorders • Acneiform facial inflammation • Headache • Weight gain • Dizziness • Allergic reactions • Arteriospasm (less frequent) • Hepatitis (less frequent)	• NR	• NR	• C	• C
• *Vitis vinifera*	• Allergic reactions	• C	• NR	• C	• C
• *Zingiber officinalis*	• NR	• C	• Gastric problems	• Purpura	• NR

C: Cited, but the specific adverse effect was not described; NR: Not Reported.

the causality was not assessable.

Fig. 3 illustrates the organ/system most frequently target of adverse effects according to the different data sources.

Generally speaking, gastrointestinal tract was the main target system of adverse effects, as shown by its involvement in 35–60% of cases of all data sources. Nervous system was associated with 45% and 43% of cases collected by the European Poison Centers and ANSES, respectively. Liver was the organ most frequently affected (67% of cases) according to ANSES database, followed by nervous system and skin/mucosa. Data from FDA (not reported in Fig. 3) and Pavia Poison Centre showed that cardiovascular adverse reactions were the most important effects observed.

Gastrointestinal effects regarded some of the most cited plants; one of them was *Camellia sinensis* (included in the top list in five out of six data sources). These effects, described in different papers, could be mediated by the polyphenol content, which can interfere with food digestibility by inhibiting digestive enzyme alpha-amylase, pepsin, trypsin and lipase (He, Lv, & Yao, 2007; NCCIH, 2012). *Glycine* max (cited in three of the six data sources) was responsible for enterocolitis, vomiting, abdominal pain and diarrhea, as described in the scientific literature. High consumption of fibres , especially raffinose oligosaccharides, could cause intestinal bloating, pain, flatulence or diarrhea (Wongputtisin, Ramaraj, Unpaprom, Kawaree, & Pongtrakul, 2015). Similar effects were observed in adverse effects due to *Cynara scolymus* (cited in three data sources) including diarrhea, abdominal spasm, epigastric complaints like nausea. These effects are described in the literature and has been associated with phenolic acids and fructo-oligosaccharides (EMA, 2019).

6. Conclusion

Both growing market of PFS and the parallel increasing botanical use by consumers have raised serious concerns about their quality, efficacy and safety. These aspects were faced during the PlantLIBRA project (2010–2014), where the different aspects of PFS have been explored. The analysis of adverse effects from different sources was an important part of the project: adverse effects were analyzed and assessed when possible for causality. Some plants were more frequently involved in adverse effects than others: *Camellia sinensis, Valeriana officinalis, Panax ginseng, Citrus aurantium, Ginkgo biloba, Glycine max, Glycyrrhiza glabra, Melissa officinalis and Paullina cupana*. For some of them (e.g. *Camellia sinensis* and *Valeriana officinalis*), the frequency of reported adverse effects was comparable, as shown by their inclusion in the top list of plants of 3/6 data sources. In Table 4 are reported the plants mostly involved in adverse effects and the symptoms described in the different studies. Some adverse effects were quite similar in the different studies (e.g. *Camellia sinensis, Citrus aurantium, Paullinia cupana),* other ones were reported only by specific sources (e.g *Cimicifuga racemosa*, *Cinnamomum verum*, *Echinacea* spp., *Equisetum arvense, Foeniculum vulgare, Hypericum perforatum, Vitex agnus castus, Vitis vinifera, Zingiber officinalis)* and others were reported by different studies but the symptoms described were different *(*e.g. *Ginkgo biloba, Melissa officinalis, Valeriana officinalis)*.

Gastrointestinal disorders and central nervous symptoms were the most frequent clinical signs. Among gastrointestinal symptoms, the most cited were abdominal and gastric pain, diarrhea and constipation. The severity of adverse effects was generally classified as mild/moderate, but some severe or fatal cases were reported. For this reason, both consumers and physicians must be aware about the possible risks associated with PFS consumption, including interactions with drugs. In this sense, the need of a higher number of available and reliable sources of scientific information on PFS – other than health-care professionals – should be underlined. Finally, data collected from Poison Centers should be regularly published, in order to continuously increase the knowledge about the possible risks associated with botanicals consumption, contributing, in parallel, to avoid their underestimation.

7. Ethics statement

Authors declare that neither human nor animal experimentations were included in the paper

CRediT authorship contribution statement

Francesca Colombo: Investigation, Writing - original draft. **Chiara Di Lorenzo:** Visualization, Writing - review & editing. **Simone Biella:** Visualization, Data curation. **Sarah Vecchio:** Investigation, Writing - original draft. **Gianfranco Frigerio:** Investigation, Data curation. **Patrizia Restani:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank all PlantLIBRA partners involved in WP4 activities and Dr. A. Dopter for providing data from ANSES.

This research was supported by grants from Progetto Eccellenza.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Bailey, R. L., Saldanha, L. G., Gahche, J. J., & Dwyer, J. T. (2014). Estimating caffeine intake from energy drinks and dietary supplements in the United States. *Nutrition Reviews, 72*, 9–13. https://doi.org/10.1111/nure.12138.

Barnes, P. M., Bloom, B., & Nahin, R. L. (2009). Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Statistics Reports, 12*, 1–23.

Bouchard, N. C., Howland, M. A., Greller, H. A., Hoffman, R. S., & Nelson, L. S. (2005). Ischemic stroke associated with use of an ephedra-free dietary supplement containing synephrine. *Mayo Clinic Proceedings, 80*, 541–545. https://doi.org/10.4065/80.4.541.

Di Lorenzo, C., Ceschi, A., Kupferschmidt, H., Lüde, S., De Souza Nascimento, E., Dos Santos, A., ... Restani, P. (2015). Adverse effects of plant food supplements and botanical preparations: A systematic review with critical evaluation of causality. *British Journal of Clinical Pharmacology, 79*, 578–592. https://doi.org/10.1111/bcp.12519.

Di Lorenzo, C., Dopter, A., Vecchio, S., Lüde, S., Colombo, F., Orgiu, F., & Restani, P. (2018). The other face of the moon: Side effects, INTERACTIONS and molecules of concerns. In P. Restani (Ed.). *Food supplements containing botanicals: benefits, side effects and regulatory aspects: The scientific inheritance of the EU Project PlantLIBRA* (pp. 141–176). Springer International Publishing AG. https://doi.org/10.1007/978-3-319-62229-3_5.

Dunnick, J. K., & Nyska, A. (2013). The toxicity and pathology of selected dietary herbal medicines. *Toxicologic Pathology, 41*, 374–386. https://doi.org/10.1177/0192623312466451.

EFSA Ans Panel (2018). Scientific opinion on the safety of green tea catechins. *EFSA Journal, 16*. https://doi.org/10.2903/j.efsa.2018.5239.

EFSA Scientific Committee (2009). Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. *EFSA Journal, 7*(9), 1249. https://doi.org/10.2093/j.efsa.2009.1249.

Egan, B., Hodgkins, C., Shepherd, R., Timotijevic, L., & Raats, M. (2011). An overview of consumer attitudes and beliefs about plant food supplements. *Food and Function, 2*, 747–752. https://doi.org/10.1039/c1fo10109a.

EMA (2012). Assessment report on Paullinia cupana Kunth ex H.B.K. var. sorbilis (Mart.) Ducke, semen. Retrieved February 27, 2020, from https://www.ema.europa.eu/en/documents/herbal-report/draft-assessment-report-paullinia-cupana-kunth-ex-hbk-var-sorbilis-mart-ducke-semen_en.pdf.

EMA (2013). Community herbal monograph on Camellia sinensis (L.) Kuntze, non fermentatum folium. Retrieved February 27, 2020, from https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-camellia-sinensis-l-kuntze-non-fermentatum-folium_en.pdf.

EMA (2016). European Union herbal monograph on Valeriana officinalis L., radix. Retrieved February 28, 2020, from https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-valeriana-officinalis-l-radix_en.pdf.

EMA (2019). European Union herbal monograph on Cynara cardunculus L. (syn. Cynara scolymus L.), folium. Retrieved February 27, 2020, from https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-cynara-cardunculus-l-syn-cynara-scolymus-l-folium_en.pdf.

Ernst, E., & Thompson Coon, J. (2001). Heavy metals in traditional Chinese medicines: A systematic review. *Clinical Pharmacology and Therapeutics, 70*, 487–504. https://doi.org/10.1067/mcp.2001.120249.

European Commission (2002). Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002. Official Journal of the European Communities, (June), 51–57. https://doi.org/10.1016/j.jclepro.2010.02.014.

Federico, A., Tiso, A., & Loguercio, C. (2007). A case of hepatotoxicity caused by green tea. *Free Radical Biology and Medicine, 43*, 474. https://doi.org/10.1016/j.freeradbiomed.2007.05.010.

Garcia-Alvarez, A., Egan, B., De Klein, S., Dima, L., Maggi, F. M., Isoniemi, M., ... Serra-Majem, L. (2014). Usage of plant food supplements across six european countries: Findings from the plantlibra consumer survey. *PLoS ONE, 9*, Article e92265. https://doi.org/10.1371/journal.pone.0092265.

He, Q., Lv, Y., & Yao, K. (2007). Effects of tea polyphenols on the activities of α-amylase, pepsin, trypsin and lipase. *Food Chemistry, 101*, 1178–1182. https://doi.org/10.1016/j.foodchem.2006.03.020.

Kaiser, S., Carvalho, Â. R., Pittol, V., Dietrich, F., Manica, F., Machado, M. M., ... Ortega, G. G. (2016). Genotoxicity and cytotoxicity of oxindole alkaloids from Uncaria tomentosa (cat's claw): Chemotype relevance. *Journal of Ethnopharmacology, 189*, 90–98. https://doi.org/10.1016/j.jep.2016.05.026.

Kupiec, T., & Raj, V. (2005). Fatal seizures due to potential herb-drug interactions with Ginkgo biloba. *Journal of Analytical Toxicology, 29*, 755–758. https://doi.org/10.1093/jat/29.7.755.

Li, N., Xia, Q., Ruan, J., Fu, P., & Lin, G. (2012). Hepatotoxicity and tumorigenicity induced by metabolic activation of pyrrolizidine alkaloids in herbs. *Current Drug Metabolism, 12*, 823–834. https://doi.org/10.2174/138920011797470119.

Lombardi, N., Crescioli, G., Bettiol, A., Menniti-Ippolito, F., Maggini, V., Gallo, E., ... Firenzuoli, F. (2019). Safety of complementary and alternative medicine in children: A 16-years retrospective analysis of the Italian Phytovigilance system database. *Phytomedicine, 61*, Article 152856. https://doi.org/10.1016/j.phymed.2019.152856.

Lüde, S., Vecchio, S., Sinno-Tellier, S., Dopter, A., Mustonen, H., Vucinic, S., ... Ceschi, A. (2016). Adverse effects of plant food supplements and plants consumed as food: results from the poisons centres-based PlantLIBRA study. *Phytotherapy Research, 30*, 988–996. https://doi.org/10.1002/ptr.5604.

Mazzanti, G., Menniti-Ippolito, F., Moro, P. A., Cassetti, F., Raschetti, R., Santuccio, C., & Mastrangelo, S. (2009). Hepatotoxicity from green tea: A review of the literature and two unpublished cases. *European Journal of Clinical Pharmacology, 65*, 331–341. https://doi.org/10.1007/s00228-008-0610-7.

Menniti-Ippolito, F., Mazzanti, G., Santuccio, C., Moro, P. A., Calapai, G., Firenzuoli, F., ... Raschetti, R. (2008). Surveillance of suspected adverse reactions to natural health products in Italy. *Pharmacoepidemiology and Drug Safety, 17*, 626–635. https://doi.org/10.1002/pds.1566.

Ministero della Salute, 2018. Disciplina dell'impiego negli integratori alimentari di sostanze e preparati vegetali. Gazzetta Ufficiale Serie Generale n. 224, 26/09/2018 (Accessed 16 June 2020).

Miller, L. G., & Freeman, B. (2002). Possible subdural hematoma associated with Ginkgo biloba. *Journal of Herbal Pharmacotherapy, 2*, 57–63. https://doi.org/10.1300/J157v02n02_06.

NCCIH (2012). Green tea. Retrieved February 27, 2020, from https://www.nccih.nih.gov/health/green-tea.

Owens, C., Baergen, R., & Puckett, D. (2014). Online sources of herbal product information. *American Journal of Medicine, 127*, 109–115. https://doi.org/10.1016/j.amjmed.2013.09.016.

Pedroso, J. L., Henriques Aquino, C. C., Escórcio Bezerra, M. L., Baiense, R. F., Suarez, M. M., Dutra, L. A., ... Povoas Barsottini, O. G. (2011). Ginkgo biloba and cerebral bleeding: A case report and critical review. *Neurologist, 17*, 89–90. https://doi.org/10.1097/NRL.0b013e3181f097b4.

Polatoglu, K. (2013). "Chemotypes"– A fact that should not be ignored in natural product studies. *The Natural Products Journal, 3*, 10–14. https://doi.org/10.2174/2210315511303010004.

Poli, F., Appendino, G., Sacchetti, G., Ballero, M., Maggiano, N., & Ranelletti, F. O. (2005). Antiproliferative effects of daucane esters from Ferula communis and F. arrigonii on human colon cancer cell lines. *Phytotherapy Research, 19*, 152–157. https://doi.org/10.1002/ptr.1443.

RASFF (2018). The Rapid Alert System for Food and Feed — 2018 annual report. https://doi.org/10.2875/914558.

Restani, P., Di Lorenzo, C., Garcia-Alvarez, A., Badea, M., Ceschi, A., Egan, B., ... Serra-Majem, L. (2016). Adverse effects of plant food supplements self-reported by consumers in the PlantLIBRA survey involving six european countries. *PLoS ONE, 11*, Article e0150089. https://doi.org/10.1371/journal.pone.0150089.

Restani, P. (2019). Integratori a base di erbe. In Review scientifica sull'integrazione alimentare: stato dell'arte alla luce delle evidenze scientifiche e nuove frontiere di sviluppo (II Ed., pp. 17–36). Edra.

Rubiolo, P., Matteodo, M., Riccio, G., Ballero, M., Christen, P., Fleury-Souverain, S., ... Bicchi, C. (2006). Analytical discrimination of poisonous and nonpoisonous chemotypes of giant fennel (Ferula communis L.) through their biologically active and volatile fractions. *Journal of Agricultural and Food Chemistry, 54*, 7556–7563. https://doi.org/10.1021/jf061592t.

Schilter, B., Andersson, C., Anton, R., Constable, A., Kleiner, J., O'Brien, J., ... Walker, R. (2003). Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. *Food and Chemical Toxicology, 41*, 1625–1649. https://doi.org/10.1016/S0278-6915(03)00221-7.

Schulz, M., Meins, J., Diemert, S., Zagermann-Muncke, P., Goebel, R., Schrenk, D., ... Abdel-Tawab, M. (2015). Detection of pyrrolizidine alkaloids in German licensed herbal medicinal teas. *Phytomedicine, 22*, 648–656. https://doi.org/10.1016/j.phymed.2015.03.020.

Smith, T., Lynch, M. E., Johnson, J., Kawa, K., Bauman, H., & Blumenthal, M. (2015). Herbal dietary supplement sales in US rise 6.8% in 2014. Retrieved February 28, 2020, from http://cms.herbalgram.org/press/2015/HerbalDietarySupplementSalesinUSRisein2014.html.

Sharma, Tarun, Wong, Linda, Tsai, Naoky, & Wong, Russel D. (2010). Hydroxycut(®) (Herbal Weight Loss Supplement) Induced Hepatotoxicity: A Case Report and Review of Literature. *Hawaii Medical Journal, 69*(8), 188–190.

Tankeu, S., Vermaak, I., Chen, W., Sandasi, M., & Viljoen, A. (2016). Differentiation between two "fang ji" herbal medicines, Stephania tetrandra and the nephrotoxic Aristolochia fangchi, using hyperspectral imaging. *Phytochemistry, 122*, 213–222. https://doi.org/10.1016/j.phytochem.2015.11.008.

Timbo, B. B., Ross, M. P., Mccarthy, P. V., & Lin, C. T. J. (2006). Dietary supplements in a national survey: Prevalence of use and reports of adverse events. *Journal of the American Dietetic Association, 106*, 1966–1974. https://doi.org/10.1016/j.jada.2006.09.002.

Tucker, J., Fischer, T., Upjohn, L., Mazzera, D., & Kumar, M. (2018). Unapproved pharmaceutical ingredients included in dietary supplements associated with US *food and drug administration w*arnings. *JAMA Network Open, 5*(1), Article e183337. https://doi.org/10.1001/jamanetworkopen.2018.3337.

Vargas-Murga, L., Garcia-Alvarez, A., Roman-Viñas, B., Ngo, J., Ribas-Barba, L., Van Den Berg, S. J. P. L., ... Serra-Majem, L. (2011). Plant food supplement (PFS) market structure in EC Member States, methods and techniques for the assessment of individual PFS intake. *Food and Function, 2*, 731–739. https://doi.org/10.1039/c1fo10075k.

Vitalone, A., Menniti-Ippolito, F., Moro, P. A., Firenzuoli, F., Raschetti, R., & Mazzanti, G. (2011). Suspected adverse reactions associated with herbal products used for weight loss: A case series reported to the Italian National Institute of Health. *European Journal of Clinical Pharmacology, 67*, 215–224. https://doi.org/10.1007/s00228-010-0981-4.

WHO (2004). WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. Retrieved February 28, 2020, from https://apps.who.int/iris/handle/10665/43034.

Wongputtisin, P., Ramaraj, R., Unpaprom, Y., Kawaree, R., & Pongtrakul, N. (2015). Raffinose family oligosaccharides in seed of Glycine max cv. Chiang Mai60 and potential source of prebiotic substances. *International Journal of Food Science and Technology, 50*, 1750–1756. https://doi.org/10.1111/ijfs.12842.

Zickuhr, K. (2010). Generations 2010 - A Project of the Pew Research Center. Retrieved from http://pewinternet.org/Reports/2010/Generations-2010/Overview.aspx.