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Getting More Than You Paid For: Unauthorized "Natural" Substances in Herbal Food Supplements on EU Market

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ABSTRACT

As the population in the industrialized world develops preference for what is perceived as a natural and holistic way of disease treatment, the popularity and the number of food supplements on the market, including herbal ones, is experiencing an unprecedented rise. However, unlike herbal medicinal products, intended for treating or preventing disease, current legislation classifies food supplements as products intended for achieving nutritional or physiological effect and to supplement the normal diet. Accordingly, most food supplements are not to be associated with specific health claims. However, either due to the subtle suggestions by the producers or the wishful thinking of the consumers, certain pharmacological effects from food supplements are often expected. Medicinal plants included in food supplements usually do not produce dramatic and instant pharmacological effects. Therefore, in order to meet the expectation of their customers, some producers have turned to the illicit and dangerous practice of adulterating their products with synthetic adulterants, including naturally occurring molecules, having the desired activity. Such practice is prevalent in, although not limited to, food supplements intended for use as weight-loss aids, as well as for sport performance and libido enhancement. The review is focusing on naturally occurring alkaloids, phenylethanolamines, and their semi-synthetic derivatives in food supplements in the European Union as reported by the Rapid Alert System for Food and Feed. Their desired and undesired pharmacological effects, as well as the methods for their detection and quantification in food supplements, will be reviewed.

Introduction

The popularity of herbal medicines and dietary supplements is increasing all over the world. This is partly due to the many side effects attributed to synthetic drugs, helped by the perception that herbal products are "natural" and therefore inevitably "safe". An average consumer is probably not aware that many synthetic drugs currently in use were developed from plants or derived from a naturally occurring molecule. However, numerous clinical trials to which synthetic drugs have been subjected revealed not only their activity but also their side effects. At the same time, most herbal products on the market have not been subjected to rigorous clinical trials and their potential side effects are therefore less known. Furthermore, for many consumers, all the "herbal preparations" belong to the same general group of "natural aids" with health-improving properties [1, 2]. They are also often combined with drugs or other herbal preparations [3]. In contrast to that, European legal framework draws a clear legal distinction between the two main types of the herbal products [4]. HMPs are defined as any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations or one or more such herbal substances in combination with one or more such herbal preparations [5]. HMPs, similarly to "chemical drugs", belong to the legal category of medicinal products for human use. They are, by the Directive 2001/83/EC (later amended by Directive 2004/27/EC), intended and having properties for treating or preventing disease in human beings, restoring, correcting, or modifying physiological functions by exerting a

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ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
CE	capillary electrophoresis
CNS	central nervous system
EC	European Commission
EU	European Union
FDA	US Food and Drug Administration
FS	food supplement
HMP	herbal medicinal product
PDA	photodiode array
QqQ	triple quadrupole detector
RASFF	Rapid Alert System for Food and Feed
RCT	randomized controlled trial

pharmacological, immunological, or metabolic action, or to making a medical diagnosis.

The other large category on the market is FSs. According to the Directive 2002/46/EC, FSs are 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. They are, by the same Directive 2002/46/EC, clearly distinguished from HMPs and other medicinal products. It is, however, specifically stated that various plants and herbal extracts might be present in FSs. Even though FSs have physiological (as opposed to pharmacological) function, in accordance with the EC Regulation No 1924/2006, some health claims are nevertheless permitted. Such claims must be based on generally accepted evidence and the claimed effect must be valid for the final product in relation to its composition, dose, and instructions of use. To be in conformity with food legislation and to respect the legal distinction with medicinal products, care should be taken that the product does not claim or possess properties of preventing, treating, or curing a human disease [4]. In this way, business operators can highlight the particular beneficial effects (related to health and nutrition) of their products on the product label or in its advertising [6]. The claims, however, can only be made if specifically approved by the authorities, ensuring that any claim made on a food's labeling, presentation, or advertising in the EU is clear, accurate, and based on scientific evidence. Both authorized and non-authorized health claims are published in a public EU register. Currently, the number of the non-authorized health claims largely exceeds the number of the authorized ones (2051 vs. 261 on June 26, 2017). For example, out of more than 100 claims related to weight management, only three have been authorized (e.g., the claim related to body weight loss has been authorized for glucomannan but not for chitosan or caffeine) [6]. It is important to know that the legislation of herbal products worldwide may significantly differ among countries. The interested reader is referred to a series of relevant reviews published in 2016 [7–10].

While the allowed herbal components in FSs [11, 12] are sometimes not potent enough to elicit the desired pharmacological effect (and consequently meet the criteria for approval of a health claim), the effect is nevertheless suggested by the producers and expected by the users of the product. Unfortunately, some of the producers meet the expectations of the users by adding synthetic compounds [11–13] or illicit herbal material [14, 15]. The number of cases where large amounts of adulterants, including undeclared synthetic substances, have been detected is increasing [12]. Many of the adulterants are registered drugs and their analogues intended to treat a number of conditions, such as hypoglycemic, antihypertensive, anti-inflammatory, and weight-loss agents, as well as anabolic steroids and drugs intended to treat erectile dysfunction. Use of drugs previously withdrawn from the market due to their serious adverse effects has also been recorded (e.g., fenfluramine in weight-loss products) [12]. This practice is intended to develop or intensify the effects of dietary supplements or herbal remedies. However, more often than not, the practice is also resulting in an increase of unwanted effects, sometimes with serious consequences [12, 13, 15]. Quality and safety of medicinal products, including HMPs, are strictly regulated by the Directive 2001/83/EC and Directive 2004/27/EC. FSs, on the other hand, are not subject to pharmacovigilance, nor is it necessary to demonstrate their quality and the batch-to-batch homogeneity in the same way as for HMPs and other medicinal products, which hinders the discovery of adulterations.

In addition to the synthetic substances, a practice has emerged among some producers to adulterate their FSs with molecules of natural origin. Once a natural plant source of a molecule has been published in a journal, producers of herbal supplements may misuse that finding to add the same substance of synthetic origin and often advertise such a product as "purely natural", a statement highly valued by many consumers [16, 17]. Even though the naturally occurring molecules are generally considered to have fewer side effects that the synthetic ones, at high concentration they too become evident. Furthermore, the concentration at which the "natural" component is found in an FS often largely exceeds its amount in natural source, making it highly unlikely that the substance in question was obtained by extraction techniques. Such large amounts in some FSs have led to serious consequences for their consumers. Perhaps the most infamous example was the irrational use of ephedrine-containing supplements as ergogenic aids [17]. Ephedrine is a naturally occurring phenylethanolamine contained in *Ephedra sinica* Stapf (Ephedraceae) and other *Ephedra* species with marked thermogenic and stimulant properties. Its ability to enhance energy expenditure and promote weight loss [18, 19] has made it a popular ingredient of various supplements [17]. Even though the ephedrine-containing plants have been used in traditional medicine for thousands of years, the introduction of synthetic ephedrine to the FS industry resulted in large number of serious adverse effects, including deaths, especially if ephedrine was combined with caffeine [17, 20, 21]. For example, by 2004, the FDA had received over 18,000 adverse event reports related to ephedrine-containing products, including instances of myocardial infarction, stroke, and death, all potentially related to the use of ephedra products [17]. Consequently, the use of ephedrine in FSs was banned in 2006 [17, 18].

To help ensure food (including FSs) safety, the EU has operated the RASFF. The RASFF is considered the key tool to ensure the cross-border flow of information of risks to public health in the food chain in EU [22]. It allows member states to inform one another of risks to health arising from food and feed. The information ex-

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▶ **Table 1** RASFF-registered occurrences of alkaloids, their derivatives, and the plants that contain them in food supplements.

Subject	Name	Occurrences	Date	
			First occurrence	Last occurrence
US	Yohimbine	47	27.02.2006	15.05.2017
US	Vinpocetine	22	02.03.2009	10.11.2016
UNFI	Higenamine (norcoclaurine)	8	23.12.2015	16.12.2016
US	Evodiamine	5	23.08.2011	27.02.2017
US	Huperzine A	5	17.06.2014	10.11.2016
US	Vincamine	3	26.05.2011	09.06.2011
US	Vinburnine	3	26.05.2011	09.06.2011
UI	Arecoline	2	12.01.2016	12.05.2016
US	11-hydroxyyohimbine	1	17.06.2014	
UNFI	Yohimbe bark extract	4	03.03.2015	10.11.2016
UNFI	*Evodia rutaecarpa*	2	02.12.2016	12.09.2016
UNFI	*Huperzia serrata*	1	09.06.2011	
UNFI	Corynanthe yohimbe bark	1	10.11.2016	

US: unauthorized substance; UI: unauthorized ingredient; UNFI: unauthorized novel food ingredient.

changed through the RASFF can lead to products being recalled from the market. In this way the detected food safety risks are averted from the consumers [15]. However, in spite of the precautions, the illegal practice of adulteration of FSs with substances possessing distinct pharmacological activity is, unfortunately, rather persistent. The occurrences of the most common synthetic adulterants in FSs has been reviewed elsewhere [11–13], but the awareness on the occurrence of natural compounds as adulterants in FSs is not so widespread. Thus, this review is focusing on naturally occurring alkaloids, phenylethanolamines, and their semisynthetic derivatives reported on the EU market as unauthorized substances and, in some cases, unauthorized (novel) food ingredients. Scientific literature on their desired and possible adverse effects will be reviewed. Furthermore, the methods for their detection and quantification in FSs will be summarized and reported.

RASFF Database Search

In order to search for the selected adulterants in the EU market, the RASFF database [22] was examined by a combination of electronic and manual means as follows. The database was accessed from the link https://webgate.ec.europa.eu/rasff-window/portal/?event=SearchForm&cleanSearch = 1, available on the RASFF website. The selected product category was "dietetic foods, food supplements, fortified foods". The period encompassed in the search was August 18, 1988, to May 29, 2017 (from the first entry in the database to the date of the search). The search results were exported in form of an Excel file. The file was searched electronically for unauthorized substances, unauthorized ingredients, and unauthorized novel food ingredients using the in-built "find" function of Microsoft Office Word. All the occurrences of alkaloids, phenylethanolamines, and their semi-synthetic derivatives were individually verified and counted. Amines other than phenylethanolamines were not included in the review.

The occurrence of natural alkaloids and phenylethanolamines in the RASFF database is presented in ▶ **Tables 1** and **2**, and their structures in ▶ **Figs. 1** and **2**, respectively. In the RASFF database, they were recorded as unauthorized substances or unauthorized ingredients, as well as unauthorized novel food ingredients, meaning that they did not comply with the EC Regulation No 258/97 concerning novel foods and novel food ingredients. The most common unauthorized alkaloid was yohimbine (47 occurrences), followed by vinpocetine (22) and higenamine (eight), while the most common phenylethanolamine was synephrine (48 occurrences), followed by its semisynthetic derivative oxilofrine (eight). The total number of occurrences of natural alkaloids and phenylethanolamines in the RASFF database (excluding crude plant material) was 169. Nine occurrences were related to food for particular use (mostly intended for sport and fat-burning purposes) and one was raw material for the production of supplements. The actual number of FSs is 137, which is lower than the sum of occurrences because some of the supplements contained more than one analyzed ingredient. The most frequent combination of the analyzed substances was yohimbine/synephrine (six), followed by vincamine/vinburnine/vinpocetine (three), synephrine/higenamine (three), yohimbine/oxilofrine (two), synephrine/halostachine (two), vinpocetine/huperzine A (two), and vinpocetine/evodiamine (two). In addition to that, natural alkaloids and phenylethanolamines were often combined with other stimulatory ingredients such as caffeine (36 combinations), various phenethylamine derivatives (e.g., eight combinations with hordenine), as well as stimulatory amines, such as 1,3-dimethylamylamine (nine combinations) and 1,3-dimethylbutylamine (five combinations). Such high number of combinations is alarming because it may bring unexpected side effects either due to an additive or synergistic effect of the combined substances. It is well known that the side effects of ephedrine and other phenylethanolamines can be potentiated by caffeine [20, 23]. Combinations

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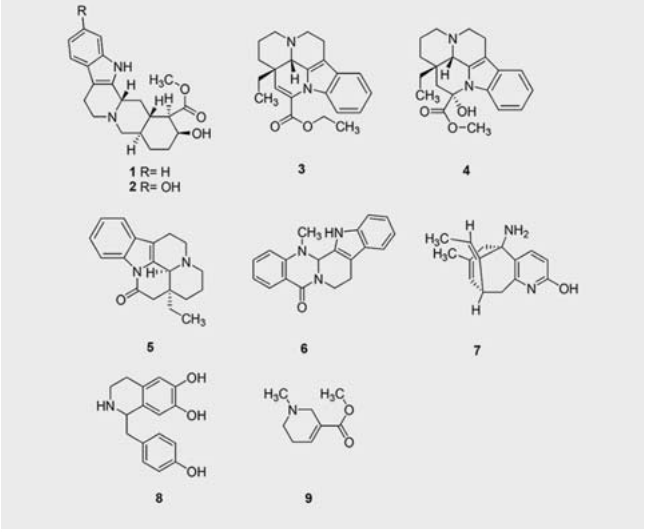
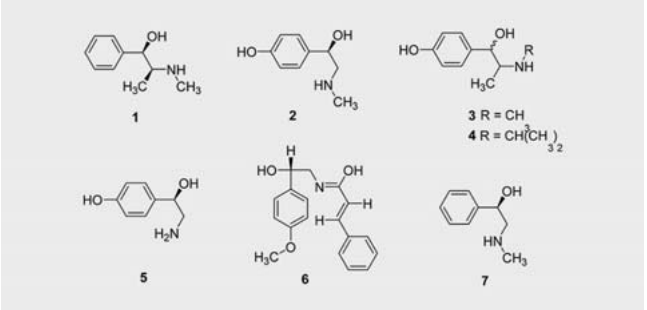
▶ **Table 2** RASFF-registered occurrences of phenylethanolamines, their derivatives, and the plants that contain them in food supplements.

Subject	Name	Occurrences	Date	
			First occurrence	Last occurrence
US	Synephrine	48	25.5.2007	01.9.2017
US	Oxilofrine	8	21.5.2014	13.04.2017
UNFI	Aegeline	6	16.2.2015	12.07.2016
US	Octopamine	4	25.3.2011	28.03.2014
US	Isopropyloctopamine	3	17.6.2014	26.04.2017
US	Halostachine	2	25.8.2016	12.06.2016
US	Ephedrine	2	03.06.2007	07.09.2010
PI	"Ephedra"[a]	3	22.10.2010	30.11.2016

[a] As reported in the RASFF database. US: unauthorized substance; UNFI: unauthorized novel food ingredient; PI: prohibited ingredient.



▶ **Fig. 1** Chemical structures of unauthorized alkaloids recorded in FSs: (**1**) yohimbine, (**2**) 11-hydroxyyohimbine, (**3**) vinpocetine, (**4**) vincamine, (**5**) vinburnine, (**6**) evodiamine, (**7**) huperzine A, (**8**) higenamine, (**9**) arecoline.



▶ **Fig. 2** Chemical structures of unauthorized phenylethanolamines recorded in FSs: (**1**) ephedrine, (**2**) synephrine, (**3**) oxilofrine, (**4**) isopropyloctopamine, (**5**) octopamine, (**6**) aegeline, (**7**) halostachine.

with common synthetic adulterants, such as sibutramine and phosphodiesterase-5 inhibitors [13], were not recorded. RASFF entries in general did not state the intended use of the recorded FSs. The few exceptions will be mentioned below, along with the respective compounds. However, the pharmacological action of the ingredients leads to conclusion that the products are mostly intended for use in sport and as weight-loss aids.

Even though the first entry in the database is from 1998, the number of records before 2002 is negligible, but after the Directive 2002/46/EC and harmonization of regulations in the EU member states in 2002 [15], the number of records starts to grow. Among the analyzed substances, the first record of unauthorized alkaloid in an FS is related to yohimbine (February 27, 2006), while the first phenylethanolamine recorded in the database is synephrine (May 25, 2007). Other compounds started appearing later, mostly after 2011. Most of them are probably used continually because most last occurrences are recorded relatively recently, during 2016 or 2017. Number of occurrences of individual substances was relatively low for a detailed statistical analysis, but preliminary analysis was possible in case of the two most common compounds, yohimbine and synephrine. Trends in the number of notifications recorded in the RASFF database for these two substances are shown in ▶ **Fig. 3**. It is evident that the number of records of both compounds is increasing exponentially. This trend could be the consequence of their increasing presence in FSs and/or the increasing number of analyses of the supplements in the market. ▶ **Fig. 3** also shows dense zones where the records are rather frequent. This is possibly the result of intense screening of similar FSs immediately after adulteration in one market has been detected. Most of the recorded FSs (97) originated from the United States, followed by the Netherlands (eight), which is in accordance with previously published review of RASFF data on food and FS contaminations [15].

It is interesting to note that the most frequently recorded synthetic adulterants in the RASFF database in the same period were erectile dysfunction drugs followed by the drugs used for weight control. For example, sildenafil and other phosphodiesterase-5 inhibitors were reported 144 times, while sibutramine and didesmethyl sibutramine were reported 67 times. Thus, it is evident that the number of occurrences of individual natural alkaloids

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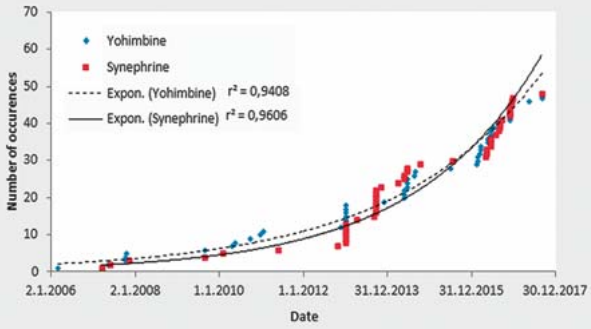
and phenylethanolamines was somewhat lower than the number of occurrences of synthetic adulterants. Even so, alkaloids and phenylethanolamines are frequent enough to pose a significant public health risk, especially when the serious side effects that these compounds may cause are taken into consideration.

Unauthorized Alkaloids in FSs

Yohimbine

Yohimbine (▶ **Fig. 1**) is an indole alkaloid isolated from the bark of the *Pausinystalia johimbe* (K.Schum.) Pierre ex Beille, Rubiaceae (syn. *Corynanthe johimbe* K.Schum.), traditionally used as an aphrodisiac in Africa [24, 25]. It was reported 47 times as unauthorized substance in the RASFF database, making it the most frequently reported alkaloid in this review. In addition to that, the presence of its metabolite 11-hydroxyyohimbine was reported once (▶ **Table 1**). The bark and the bark extract were reported as unauthorized novel food ingredients, adding to the amount of yohimbine in the market. Yohimbine is α_2-adrenergic receptor antagonist that has been used for treatment of erectile dysfunction before the era of phosphodiesterase-5 inhibitors [26], with the effect superior over placebo in clinical trials [25–27]. Yohimbine may also have anxiolytic effect, especially when combined with cognitive behavioral therapy [28]. In addition to that, yohimbine-containing products are advertised on the Internet as a fast weight-loss and body-building supplements [25]. The couple of times when an RASFF database entry stated the intended use of yohimbine products, it was found in "fat-burn capsules" and "nutritional fruit punch".

Along with its desired effects, medical use of yohimbine was known to cause a myriad of adverse reactions including gastrointestinal upset, increased blood pressure, headache, agitation, anxiety, manic reactions, bronchospasm, palpitations, insomnia, shivering, sweating, nausea, rash, tachycardia, and frequent urination [25]. Use of yohimbine in herbal and other supplements is also related to numerous adverse effects, such as agitation, anxiety, hypertension, tachycardia, priapism, and Raynaud's syndrome [29–31]. A bodybuilder developed severe acute neurotoxic effects (vomiting, loss of consciousness, and repeated seizures) 2 h after ingestion of 5 g of yohimbine. After 12 h and medical treatment, his state was normalized [32]. Furthermore, the FDA issued a warning of a supplement called LipoKinetix after receiving reports of at least six young people who developed acute hepatitis and/or liver failure. Supplement has been promoted for weight loss and, besides yohimbine, it contained norephedrine, caffeine, diiodothyronine, and sodium usniate [33]. Cases of death after acute yohimbine intoxication were also recorded [34]. Mixing of yohimbine with other stimulants may cause severe adverse events. A supplement called Dexaprine was removed from the Dutch market in 2014 because the ingestion of as little as half a tablet caused several cases of nausea, agitation, tachycardia, palpitations, and even one case of cardiac arrest. Analysis has shown that, besides yohimbine, the supplement contained a mixture of chemical stimulants, including synephrine, oxilofrine, isopropyloctopamine, caffeine, theophylline, and unidentified phenethylamines [35].



▶ **Fig. 3** Trends in the number of notifications recorded in the RASFF database for yohimbine and synephrine.

Vincamine derivatives

The Apocynaceae plant family contains so called eburnamine-vincamine alkaloids, substances that exert varied pharmacological activities. Among them, the most prominent ones are vincamine (▶ **Fig. 1**), vinburnine (▶ **Fig. 1**), vindeburnol, and apovincaminate. The plant sources of vincamine alkaloids are numerous: *Vinca minor* L., *Hunteria zeylanica* (Retz.) Gardner ex Thwaites, *Haplophyton cimicidum* A.DC., and *Leuconotis griffithii* Hook.f., to name a few. Vincamine derivatives display antihypoxic and neuroprotective potencies. They are considered to have modulatory effects on brain circulation and neuronal homeostasis [36], which is probably the reason for their addition to FSs. Vincamine derivatives (▶ **Fig. 1**) were used as unauthorized substances in several FSs, the most frequent one being vinpocetine, a semi-synthetic derivative of vincamine, with 22 occurrences in the RASFF database, while vincamine and vinburnine occurred three times each (▶ **Table 1**).

It has been reported that vinpocetine supplements were most commonly sold as sports supplements, weight-loss supplements, and brain enhancers [37]. The three RASFF entries where type of products was recorded also state that vinpocetine and other vincamine alkaloids were found in training supplements ("food for particular nutritional use", "food intended for sports people", "supplement to improve muscle growth", and "pre-training supplement"). Such applications are rather unexpected because ergogenic and weight-loss properties of vinpocetine are supported neither by clinical studies nor the traditional use of vincamine derivatives. The intended use of the other supplements was not recorded, but the combinations with huperzine A recorded in the RASFF database led to conclusion that at least some FSs were used as memory-loss aids. Vinpocetine use in supplements as a brain enhancer does have some basis in the results of the clinical trials that indicate the potential of vinpocetine as a neuroprotective, nootropic, and anticonvulsant agent [38–40]. The mechanism behind the observed positive effect of vinpocetine on memory impairment could be related to inhibition of phosphodiesterase type 1 and consequent increases in cAMP concentration [41]. However, most of the clinical studies had a small sample size and a short duration. Therefore, the actual therapeutic benefits are still unclear [38–40]. Similarly, no definite conclusions can be drawn regarding the efficacy of other eburnamine alkaloids, such as vincamine

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[42]. Trials aimed at assessing safety of vinpocetine did not report serious adverse effects [38,40]. Minor side effects such as gastrointestinal problems, flushing, rashes, headaches, and decreased blood pressure have been described [43,44]. No serious adverse effects have been reported in connection with use of FSs containing vinpocetine and other vincamine derivatives so far.

Evodiamine

Evodiamine (▶ **Fig. 1**) is a naturally occurring indole alkaloid from *Tetradium ruticarpum* (A.Juss.) T.G.Hartley (syn. *Evodia ruticarpa* [A.Juss.] Benth.) (Rutaceae) with potentially interesting effects displayed in preclinical studies such as anti-obesity, analgesic, anti-inflammatory, and thermoregulative effects [45], but the clinical evidence is lacking. Evodiamine was reported to improve cognitive abilities in the *in vivo* models of Alzheimer's disease. In many studies, the effects were achieved via anti-inflammatory activity such as inhibition of cyclooxygenase-2 expression and inflammatory cytokines production [45]. Studies involving human subjects with Alzheimer's disease have not been performed so far. Perhaps the most interesting application of evodiamine is due to its anti-obesity potential [45,46], an effect often advertised in the websites selling evodiamine supplements. This potential was demonstrated *in vivo* through induction of heat loss and heat production, as well as prevention of the accumulation of perivisceral fat and the body weight increase [47]. The possible mechanisms behind the effect are numerous, including β_3-adrenergic stimulation, improved leptin resistance, and insulin sensitivity [45]. Unfortunately, the initial clinical trials did not confirm that potential. In a small study with 11 participants, evodiamine was neither effective at inducing thermogenesis nor at increasing fat oxidation at rest or during exercise [48], while *E. ruticarpa* failed to prove a weight-reducing effect or resting metabolic rate [49]. However, renal, hepatic, or any other serious adverse effects were not recorded, neither in the studies nor related to higenamine-containing FS use.

Huperzine A

Huperzine A (▶ **Fig. 1**), ingredient of *Huperzia serrata* (Thunb.) Trevis., Lycopodiaceae, and other *Huperzia* Bernh. species, exerts a reversible and selective acetylcholinesterase inhibitory effect. Huperzine A can pass through the blood-brain barrier quickly and manifest a significant biological activity even after oral administration [50,51]. Numerous clinical studies, systematic reviews, and meta-analyses have found that huperzine A significantly improves memory, cognitive function, and daily living abilities of patients with Alzheimer's disease, without causing serious side effects [52,53]. On the other hand, a systematic review of RTCs of huperzine A for treatment of cognitive impairment in major depressive disorder, based on three low-quality RCTs from China, could not reach a definitive conclusion about its efficacy and safety [54], while a systematic review of interventions to delay functional decline in people with dementia based on two studies with 70 participants has established a relatively low activity for huperzine A [55]. Huperzine A may display mild peripheral cholinergic side effects, such as dry mouth, mild pain in abdomen, and diarrhea with no adverse effects on vital signs, blood test results, or electrocardiogram results. A slight propensity to induce nausea or vomiting was recorded [56]. Intoxication with huperzine A, characterized by sweating, vomiting, diarrhea, dizziness, cramps, and slurred speech, was recorded in two individuals consuming tea prepared from *Huperzia selago* (L.) Bernh. ex Schrank & Mart. The symptoms were suggestive of a cholinergic mechanism. Subsequent determination of acetylcholinesterase inhibitors revealed that the amount of huperzine A in the tea was sufficient to induce the observed intoxication symptoms [57].

Higenamine

Higenamine (norcoclaurine) (▶ **Fig. 1**) was first isolated from plants belonging to *Aconitum* (Ranunculaceae) genus, but it has also been found in *Tinospora crispa* (L.) Hook. f. & Thomson (Menispermaceae), *Nandina domestica* Thunb. (Berberidaceae), *Gnetum parvifolium* (Warb.) W.C.Cheng (Gnetaceae), *Nelumbo nucifera* Gaertn (Nelumbonaceae), and other species. The RASFF reported its presence in eight supplements (▶ **Table 1**), but unlike the other alkaloids in this text, classified as unauthorized substances, higenamine was classified as unauthorized novel food ingredient. The list of putative pharmacological effects includes positive inotropic and chronotropic effects, as well as antithrombotic, antiapoptotic, and antioxidative effects and anti-inflammatory and immunomodulatory activity [58]. It is potentially interesting as weight-loss aid [59] due to its potential to stimulate lipolysis and energy expenditure [60]. Out of eight entries in the RASFF database where higenamine was reported, two contained the type of products ("muscle feeder" and "food for sports people") that concurred with its lipolytic activity.

A small trial investigating safety profile of higenamine (50 and 150 mg/day) and its combination with caffeine and "yohimbe" bark did not find changes in metabolic parameters [61]. Another study, however, recorded dose-related heart in subjects receiving continuous intravenous infusion of higenamine at gradually escalating doses from 0.5 to 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The subjects' heart rates increased in parallel with increasing doses of higenamine [62]. This effect was confirmed in a study that recorded a moderate increase in heart rate and systolic blood pressure caused by supplement consisting of higenamine, caffeine, and yohimbe bark extract in comparison to placebo [60]. Although it is hard to be certain of the exact contribution of each of the three ingredients, caution should be advised. Higenamine use may potentially be related to skeletal muscle damage. A case of paraspinal muscle rhabdomyolysis in a young male in association with strenuous activity and the ingestion of an exercise supplement containing higenamine was recorded [63].

Arecoline

Arecoline (▶ **Fig. 1**) is a derivative of nicotinic acid, which can be found in betel (areca) nut, fruit of the palm *Areca catechu* L. (Arecaceae). It was recorded two times as an unauthorized ingredient in various supplements. Betel nut is one of the most widely consumed addictive substances in the world. It is often chewed wrapped inside betel leaves or with tobacco (betel quid). The effects of areca nut are mainly related to arecoline and its effect on the central and the autonomic nervous systems. It possesses parasympathomimetic properties, stimulating both muscarinic and nicotinic receptors. Habitual users claim euphoria, a sense of

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well-being, warmth, increased alertness, salivation, antimigraine properties, and enhanced capability to work [64,65]. Human trials have shown that betel quid chewing increases the heart rate and skin temperature with onset and duration, similar to a cardio-acceleratory response. Interestingly, although the parasympathomimetic arecoline has been thought to be responsible for most of the effects of betel quid chewing, studies have shown that plasma concentrations of noradrenaline and adrenaline were elevated, suggesting an additional sympathetic activation [64]. In folk medicine, chewing betel nut is considered to enhance the memory [66]. However, use of betel nut is also related to palpitation, oral submucous fibrosis, oral squamous cell carcinoma, and genotoxicity. Arecoline is reported to be the primary toxic constituent responsible for these effects [65,66].

Unauthorized Phenylethanolamines in FSs

Phenylethanolamines are found in many families throughout the plant kingdom. In higher animals and humans, they act as hormones (adrenaline) and sympathetic neurotransmitters (noradrenaline, dopamine). Due to their sympathomimetic activity, many phenylethanolamines can act as stimulants and display thermogenic properties, although to varying levels [18]. One of the most well-known phenylethanolamines to display such activity is ephedrine (▶ **Fig. 2**). It used to be widely used in weight-loss supplements, but it was later withdrawn due to many cases of misuse resulting in serious adverse effects [17]. In the search of the RASFF database, ephedrine occurred two times, while the term "Ephedra" occurred three times (▶ **Table 2**). However, due to its very well-known activity and adverse effects [67], ephedrine was not included in this review. Upon removal of ephedrine- and *Ephedra* sp.-containing supplements from most of the world markets, so called "Ephedra-free" products quickly filled this void. These products typically contain multiple botanical extracts and different natural products, either isolated from plants or synthetically produced. They are supposed to act as weight-loss aids, exercise performance enhancers, or energy boosters. The pharmacological properties of such mixtures may be difficult to predict, which brings again their tolerability, efficacy, but also safety into question [20]. The activities of individual phenylethanolamines and the recorded toxicities of the supplements that contained them are summarized below.

Synephrine

Synephrine (▶ **Fig. 2**) is a sympathomimetic phenylethanolamine derivative that occurs naturally in *Citrus aurantium* L. (Rutaceae). The presence of synephrine is also described in fruits of other citrus species such as *Citrus reticulata* Blanco, *Citrus. sinensis* (L.) Osbeck, *Citrus. limon* (L.) Osbeck, and *Tetradium ruticarpum* (A.Juss.) T.G.Hartley. However, *C. aurantium* is the major natural source for the dietary supplements industry [68]. The concentration of synephrine in natural sources is generally rather low [69]. Synephrine is often added to dietary supplements intended for weight loss and enhancement of sports performance. With 48 occurrences, synephrine was the most recorded phenylethanolamine in the RASFF database. The only three synephrine occurrences in the RASFF database where the type of synephrine products was described ("fat burning", "food for particular nutritional use for sportsmen", and "food for sports people") reflected the use of synephrine in sport. It is not uncommon that synthetic synephrine is used for "spiking" of FSs. In such supplements, besides naturally occurring *p*-synephrine, *m*-synephrine is often found. Even though some authors consider that both isomers can naturally be found in *Citrus* sp. [70], most agree that *m*-isomer does not occur naturally and that presence of *m*-synephrine, a sympathomimetic drug used primarily as a decongestant, indicates the presence of a synthetically added substance [68,71].

Use of synephrine in FSs became widespread when the FDA banned the use of ephedrine-containing dietary supplements. Unlike ephedrine, *p*-synephrine exhibits little or no binding to α_1, α_2, β_1, and β_2 adrenergic receptors. As a result, synephrine exhibits less CNS and cardiovascular stimulation as compared to ephedrine [72]. However, synephrine primarily binds to β_3 adrenergic and serotonergic receptors, as well as on trace-amine-associated receptors. These characteristics have given hope to FS producers that synephrine-containing products may display ergogenic and thermogenic effects and thus stimulate sports performance and weight loss without displaying ephedrine-like side effects [68,72]. The detailed analysis of pharmacological and side effects of synephrine can be found elsewhere [68,73], but the results of the performed studies are mildly positive with some exceptions [74]. It was demonstrated that *C. aurantium* and *p*-synephrine may increase resting metabolic rate and energy expenditure, lipolysis, and breakdown of fat during rest, as well as decrease weight when given for 6–12 weeks [68,75,76]. However, the growing use of synephrine-containing products has been accompanied by numerous reports of cardiac adverse events, such as thrombosis, coronary spasm, hypertension, tachyarrhythmia, variant angina, cardiac arrest, QT interval prolongation, ventricular fibrillation, myocardial infarction, and even sudden deaths [68,70,71,77–81]. Similar to a case of an ephedrine-containing FS [82], a weight-loss FS with synephrine was suspected to be the cause of severe exercise-induced rhabdomyolysis in a young male. Besides synephrine, the supplement also contained yohimbine and caffeine [83]. It is worth noting that this combination is particularly concerning because caffeine alone can cause rhabdomyolysis when taken in extremely high doses, and combination with synephrine appears to have a synergistic effect [23]. A supplement containing synephrine with other similar-acting substances was removed from the Dutch market due to the severe adverse events as described before [35]. Since *m*-synephrine has significantly stronger α-adrenergic receptor binding properties than *p*-synephrine [72], it is possible that undeclared *m*-isomer occasionally present in FSs at least partly contributes to the observed adverse effects.

Oxilofrine

Oxilofrine (▶ **Fig. 2**), a synephrine derivative, was reported eight times as an unauthorized substance in the RASFF (▶ **Table 2**). It is a pharmaceutical drug developed to stimulate the heart, increase blood pressure, and improve oxygen exchange. It is also prohibited for use in sports [84]. However, the use of oxilofrine, especially in a form of an FS, is not without risks. For example, one brand of supplements containing oxilofrine has been linked to

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serious adverse events including vomiting, agitation, and cardiac arrest [84]. The supplement in question contained multiple ingredients, so it is not possible to link the observed adverse effects to only one of them. Nevertheless, caution should be exercised, especially because studies on a single dose of oxilofrine have revealed that it may produce, albeit small, increase in systolic blood pressure and long-lasting positive inotropic effect [85]. Adverse effects such as cardiac arrest, heart palpitations, chest pain, nausea, and headache were also reported by the users of the products containing oxilofrine [86]. This is especially alarming because the adulteration of FSs with oxilofrine is not uncommon. A study that investigated presence of oxilofrine in FSs from people who had recently experienced adverse events has found it in more than half the supplements [84]. Combination of oxilofrine with synephrine, yohimbine, and other stimulatory substances was linked with severe adverse events as described previously [35].

Octopamine and isopropyloctopamine

Octopamine (*p*-octopamine) (▶ **Fig. 2**) is an adrenergic amine similar to synephrine first isolated from the salivary glands of octopus [87]. It occurs naturally in many animals, especially in invertebrates, and plants, including *Citrus* species [88–90]. Isopropyloctopamine (betaphrine) (▶ **Fig. 2**), on the other hand, is a synthetic derivative of octopamine and it is not present in *C. aurantium* [91]. Octopamine and isopropyloctopamine were recorded four and three times in the RASFF (▶ **Table 2**), respectively. In one record, octopamine was an ingredient of an FS intended for "fat burning".

While adrenergic receptor (α_1 and α_2) binding properties of octopamine and synephrine are similar [72], octopamine is a stronger β_1 and β_2 adrenoreceptor agonist than synephrine. Especially interesting are its β_3-adrenergic receptor binding properties [72], which may be related to enhancement of lipolysis in adipose tissue. Isopropyloctopamine is also a highly β-selective, direct-acting adrenergic agonist. *In vitro* studies in human subcutaneous adipose cells indicate that isopropyloctopamine is somewhat stronger lipolytic agent than octopamine and much stronger than synephrine or any other phenylethanolamine present in *C. aurantium* [92]. Even though no studies have ever assessed the effects of octopamine on sports performance, it is still considered to have stimulating and performance-enhancing properties. As a result, it is prohibited for use in professional sports [87]. Human or animal studies examining the activity of octopamine and isopropyloctopamine following oral administration are rare. Studies investigating its effects after parenteral administration have found that octopamine can raise systolic blood pressure by approximately 15 mmHg. No adverse effects were reported [87]. However, dietary supplements containing isopropyloctopamine were associated with serious side effects. A dietary supplement for energy and weight-loss containing isopropyloctopamine led to heart problems and hospitalizations in the Netherlands. The product was linked to 11 reported adverse reactions, including heart problems and in one case even a cardiac arrest. In the UK, a 20-year-old woman, said to have overdosed on this supplement, died. The levels of natural phenylethanolamines, although relatively high, could not explain the incidence of side effects, but the presence of isopropyloctopamine led to suspicion that isopropyloctopamine was the compound responsible for most of the observed side effects [93]. A supplement containing synephrine, octopamine, tyramine, and caffeine caused coronary spasm and thrombosis in a bodybuilder [78], while a series of adverse effects caused by a supplement containing multiple active ingredients, including isopropyloctopamine, was described before [35].

Other phenylethanolamines

Aegeline (▶ **Fig. 2**) was reported six times (▶ **Table 2**). It is a phenylethanolamine naturally occurring in bael tree, *Aegle marmelos* (L.) Corrêa (Rutaceae) [94]. Other sources include *Manekia naranjoana* (C.DC.) Callejas (Piperaceae) and *Zanthoxylum fagara* (L.) Sarg. (Rutaceae). *A. marmelos* is traditionally used as treatment for diabetes. Some of its antidiabetic activity has been confirmed by *in vivo* studies, with aegeline being one of the main antihyperglycemic agents [95]. It seems that aegeline and other *A. marmelos* constituents may show antiadipogenic activity, possibly related to its structural similarity with β_2-receptor agonists [96]. Aegeline and the supplements that contain it have gained a negative reputation due to a series of incidents that took place in Hawaii. Seven cases of nonviral acute hepatitis and fulminant hepatic failure among individuals exposed to the OxyELITE Pro, an aegeline-containing FS, were reported. The incidents took place between April 2013 and October 2013 [97, 98]. Even though it was not possible to directly implicate aegeline as the causative agent in the outbreak of hepatitis, the product was recalled [86]. It is interesting to note that later statistical analyses did not support the association between aegeline and acute hepatitis and liver failure [99]. Nevertheless, the case series indicates the need to assess for FS use in patients presenting with unexplained acute hepatitis [98].

Halostachine (▶ **Fig. 2**) is a naturally occurring phenylethanolamine first isolated from *Halostachys belangeriana* (Moq.) Botsch (Amaranthaceae) [100] and *Festuca arundinacea* Schreb (Poaceae). It is a partial β_2-receptor agonist with the ability to stimulate cAMP accumulation *in vitro* [101]. Halostachine occurred two times in FSs as an unauthorized substance in the RASFF database. Even though human trials aimed to investigate its pharmacological or adverse effects were not performed, due to its β_2-receptor agonist and cAMP-accumulating properties, it may be assumed that the addition of halostachine was intended to produce lipolytic effects. Clinical data on efficacy and safety of halostachine and halostachine-containing plants do not exist.

Analytical Methods for Quantification of Alkaloids and Phenylethanolamines in FSs

Contamination of FSs with substances showing distinct pharmacological activity may occur for various reasons, ranging from accidental to intentional. However, of most concern is deliberate adulteration or "spiking" of the supplement with the pharmacologically active ingredients. This practice is sometimes irresponsibly used to increase the effectiveness, and accordingly the sales, of the product. Such intentional adulteration is often distinguished from accidental contamination by the effect of the contaminant. In cases of deliberate adulteration, the effects of the adulterant usually enhance the effects claimed for the supple-

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ment [15]. Thus, when screening for the adulterants in FSs, the analytical methods should ideally focus on the compounds with the activity similar to the advertised activity of the FS. Since the number of potential adulterants in FSs is growing, development of advanced analytical methods for screening and simultaneous detection is of utmost importance [13]. As evident from ▶ **Tables 1** and **2**, the first occurrences of yohimbine and synephrine in FSs were recorded in 2006 and 2007, respectively. This review will therefore be aimed at reporting the methods used for the analysis of alkaloids and phenylethanolamines in FSs published in the last decade.

The majority of methods for analysis of selected alkaloids and phenylethanolamines in FSs were LC methods, with fast UHPLC methods being the most often used method for separation (▶ **Table 3**). Similar to the analysis of synthetic adulterants, LC-MS has become a key method in identifying compounds in FSs, as it is capable of providing data on both the quantities and structures [13]. Its particular value in the analysis of adulterants is that it provides a large amount of information about a complex mixture, enabling the screening, confirmation, and quantitation of hundreds of components with one analysis [102]. For the detection of the selected compounds in FSs, LC is usually combined with tandem mass spectrometers (e.g., QqQ or QTOF), sometimes with an added UV or PDA detector. Examples of UHPLC-QTOF-MS applications include quantification of yohimbine, synephrine, and oxilofrine [35, 84, 103, 104], while QqQ was mostly used for analysis of synephrine and octopamine [105–108]. Orbitrap, on the other hand, was used for analysis of yohimbine [104, 109], arecoline [110], and isopropyloctopamine [93]. LC with UV detection, either in form of a single-wavelength detection or PDA, was also used in several applications. For example, it was found suitable for quantification of yohimbine [111, 112], vincamine [44, 113], evodiamine [114–116], and synephrine [105, 117–121] in FSs. In addition to that, UV detection was used in CE and capillary electrochromatography methods for analysis of synephrine [122], octopamine [88], and yohimbine [111]. In order to increase the applicability of LC methods for analysis of phenylethanolamines, post-column derivatization was successfully applied on several occasions. Examples include HPLC-UV analysis of octopamine [123] and analysis of synephrine using chemiluminescence detection [124, 125]. Pre-column derivatization, on the other hand, was used for analysis of octopamine with a fluorescence detector [126].

As discussed before, many FSs contained more than one unauthorized ingredient. Therefore, new methods should ideally allow for the possibility of analyzing more than one adulterant, even when an appropriate standard is not available. Potentially very useful are ^{1}H NMR methods, which allow standardless identification and quantitative estimation. In the method aimed for analysis of vinpocetine, evodiamine, and similar substances in FSs, the identification was based on literature spectra or, if they were unavailable, by applying computational NMR spectra prediction. A simple peak-area comparison of the target compound with the appropriate reference was used for quantification with satisfying results [127]. ^{1}H NMR was also successfully applied for analysis of synephrine and other adulterants in FSs marketed for weight loss [132]. Even though the aforementioned ^{1}H NMR methods offer many advantages, such as reduced or eliminated need for standards and even separation of constituents, NMR instruments are bulky and not accessible in many laboratories. Due to the ubiquity of FSs, the need for screening techniques that may be adjusted for mobile applications, such as (HP)TLC, is becoming increasingly more apparent [17]. However, it seems that new (HP)TLC methods for analysis of

▶ **Table 3** Methods for analysis of alkaloids and phenylethanolamines in food supplements published since 2007.

Analyte	Method	Reference
Yohimbine	UHPLC-PDA-QTOF-MS	[103, 104]
	UHPLC-QTOF-MS	[35]
	UHPLC-UV-Orbitrap-MS	[104, 109]
	HPLC-UV	[111, 112]
	HPLC-PDA	[119]
	HPTLC densitometry	[128]
	CE-UV	[111]
Vinpocetine	UHPLC-PDA	[44, 113]
	^{1}H NMR	[127]
Evodiamine	UHPLC-PDA, UHPLC-UV	[114–116]
	^{1}H NMR	[127]
Arecoline	LC-Orbitrap-MS	[110]
Synephrine	UHPLC-QTOF-MS	[35]
	UHPLC-QqQ-MS	[107, 108]
	LC-SQD-MS	[129]
	LC-QqQ-MS	[106]
	LC-UV, LC-QqQ-MS	[105]
	HPLC-UV	[105, 120, 121]
	HPLC-PDA	[117–119]
	HPLC-FL	[121, 130]
	HPLC-chemiluminescence[a]	[124, 125]
	GC-MS	[131]
	CE-PDA	[122]
	Capillary electrochromatography-UV	[88]
	DOSY and DOSY-COSY ^{1}H-NMR	[132]
Oxilofrine	UHPLC-QTOF-MS	[35, 84]
Aegeline	UHPLC-PDA-SQD-MS, LC-TOF-MS	[133]
Octopamine	Simultaneous analysis with synephrine	[88, 106, 108, 117, 118, 121, 122, 125, 129, 130]
	LC-FL[b]	[126]
	HPLC-UV[c]	[123]
Isopropyl-octopamine	LC-Orbitrap-MS, LC-QqQ-MS, competitive radioligand β_2-adrenergic receptor binding assay, β-Agonist ELISA, multiplex bead-based assay for β-agonists	[93]

[a] After reaction with potassium permanganate; [b] After reaction with *o*-phthaldialdehyde; [c] After reaction with 2,5-dimethyl-1H-pyrrole-3,4-dicarbaldehyde.

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pharmacologically active adulterants of natural origin are not being continually developed. In the last 10 years, only one HPTLC method, intended for analysis of yohimbine in FSs, has been published [128].

A very interesting combination of biochemical and chemical methods in the analysis of an FS for energy and weight-loss was described. The use of product was associated with several cases of heart problems and hospitalizations in Netherlands. Since, according to the label, the product was an herbal mixture, initial LC-MS/MS analysis focused on the detection of naturally occurring substances. But the levels of natural phenylethanolamines, although relatively high, could not explain the incidence of side effects. The supplement was subsequently screened for the presence of the β-agonists using three different biosensor assays: competitive radioligand β_2-adrenergic receptor binding assay, β-agonists ELISA, and multiplex microsphere (bead)-based β-agonist assay with imaging detection. Positive results prompted subsequent LC-HRMS analysis, which confirmed the presence of isopropyloctopamine, leading to the suspicion that it was the compound responsible for most of the observed negative effects [93].

It is important to note that the number of published methods for quantification of alkaloids and phenylethanolamines in FSs was by no means proportional to the number of occurrences in the RASFF database (▶ **Table 3**). Most methods were developed or applied for the analysis of synephrine (18) and octopamine (12), followed by the methods for analysis of yohimbine (seven), evodiamine (four), and vinpocetine (three). Newer analytical methods for the other substances were scarce or nonexistent. This is especially worrying in case of substances in which use was associated with serious adverse events, such as isopropyloctopamine. The methods for simultaneous analysis of structural analogues (such as phenylethanolamines from citruses) are sometimes developed [106, 117, 121], but with few exceptions [35], most methods rather focused on a few compounds. Multiple occurrences of adulterants combinations, not only in the RASFF database, but also in scientific literature, as well as serious side effects that such combinations have been associated with, urge for the development of new methods capable of simultaneous analysis of a large number of structurally diverse adulterants in a short time.

Conclusions

Even though the number of FSs adulterated with naturally occurring alkaloids and phenylethanolamines is somewhat lower than the number of synthetic adulterants, preliminary analysis shows that their number is increasing exponentially. Due to the large number of FSs in the market and the fact that it is not always possible to detect all the adulterations even if the supplement is analyzed in the laboratory, the possibility exists that the number of discovered cases is only the tip of the iceberg. Generally, it can be concluded that the reported FSs were used for fat-burning, weight-loss, and bodybuilding purposes (e.g., yohimbine, vincamine, evodiamine, higenamine, phenylethanolamines), as well as libido- (e.g., yohimbine) and memory-enhancing (e.g., arecoline, huperzine A, vincamine derivatives) aids. The presented data have shown that, in spite of their natural origin, they can pose a significant threat to human health, especially if they are used in combinations. Dosing of such supplements and combining them with other supplements or drugs is often left to the better judgment of the consumers. Irresponsible practices of some FS producers combined with the lack of rigorous quality control sometimes results in serious health damage or even fatal outcomes. Due to the lack of pharmacovigilance procedures for FSs, it is possible that many adverse events related to their individual or combined use remain unnoticed. Given the lack of clinical evidence for the desired activity and possible side effects, the content and use of FSs should be more strictly controlled. In that process, the development of rapid analytical methods, suitable for fast screening and with capability of standardless detection of large number of potential adulterants, should be strongly encouraged.

Conflict of Interest

The author has no conflict of interest to declare.

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