

Do We Need Plant Food Supplements? A Critical Examination of Quality, Safety, Efficacy, and Necessity for a New Regulatory Framework

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ABSTRACT

Given the expanding market of plant food supplements (PFSs) not undergoing any pre-marketing authorization, the overall quality, safety and efficacy of PFSs were subjected to a critical examination. Although many high-quality PFSs exist on the legal market, quality concerns are in general justified. Besides economic adulteration, active ingredients dramatically differing from label claims and among products were reported in several studies. In addition, PFSs sold via the Internet may be intentionally adulterated with undeclared prescription drugs. Compared to PFSs with only one single herb, PFSs containing herbal mixtures were more involved in moderate and severe clinical courses. Although prohibited by regulation, misleading labels on PFSs are common. Above all, only vague evidence for the efficacy of PFSs exists. Notwithstanding the unproven efficacy and insufficient safety assessment, PFSs represent a relevant source for consumers to get access to herbal preparations in the United States and meanwhile also in Europe, as launching of licensed/registered European herbal medicinal products (HMPs) has steadily decreased. However, being non-vitamin, non-mineral products, PFSs are neither food nor drugs. In terms of protecting public health and providing the consumer with high-quality, effective, and safe PFSs, possibilities are shown how to deal with the many challenges of PFSs. Last but not least, suggestions are made for assigning PFSs a separate regulatory category being less regulated compared to HMPs but more strictly regulated compared to food laws including implementation of good manufacturing practices and a scientific pre-marketing review process by an expert commission.

Introduction

Since the early history of medicine and up until today, phytotherapy represents a regular part of medical treatment and health maintenance. According to the WHO, approximately 80% of the world population still relies on herbal medicines for health-related benefits. Hence, it is not surprising that botanicals are available in the form of different types of products, including HMPs, PFSs, homeopathic products, foods (teas and juices), and cosmetics. Whereas up to 20 years ago herbal medicines in the EU were mainly authorized on the basis of their WEU and submitted evi-

dence for preclinical safety, clinical trials results, and extensive quality control, herbal preparations today are mostly available as PFSs with no guaranteed efficacy and much less controlled quality [1, 2]. This shift is mainly attributed to the large expenses and the long duration associated with the registration of HMPs in the highly regulated pharmaceutical market. While the authorization and registration of new HMPs steadily declined over the last decades, the global herbal supplements and remedies market exhibited a robust growth and is expected to reach \$107 billion by 2017 according to the Global Industry Analysts Report [3]. The factors that fueled this growth include an increasing awareness about

ABBREVIATIONS

AKBA	acetyl-11-keto-boswellic acid
BA	boswellic acid
cGMP	current good manufacturing practice
DSHEA	Dietary Supplement Health and Education Act
EC	European Commission
ECG	electrocardiogram
EGCG	epigallocatechin-3-O-gallate
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESCOMP	European Scientific Cooperative on Phytotherapy
EU	European Union
FDA	U.S. Food and Drug Administration
GMP	good manufacturing practice
HMP	herbal medicinal product
HMPC	Committee of Herbal Medicinal Products
IL	interleukin
5-LO	5-lipoxygenase
MA	market authorization
MC	multi-component
NIH	National Institute of Health
NF- κ B	nuclear factor "kappa-light-chain-enhancer" of activated B-cells
PA	pyrrolizidine alkaloids
PDE-5	phosphodiesterase-5
PFS	plant food supplement
THMP	traditional herbal medicinal product
TNF- α	tumor necrosis factor- α
TU	traditional use
TUR	traditional use registration
USP	United States Pharmacopoeia
WEU	well-established use
WHO	World Health Organization

general health and well-being and the general widespread acceptance of food supplements by consumers and their confidence to include herbs in preventive health [3]. However, this development is accompanied with the increase of different grades and qualities of PFSs in the European and U.S. market. Based on that background, a closer look will be taken in this paper on the regulatory aspects, quality, efficacy, and safety of PFSs, ending up with proposals to optimize consumer safety.

Overview on HMPs in Europe

Similar to medicinal products, HMPs need a pre-MA and can be manufactured only according to GMP by companies in possession of a manufacturing license. They must include full tests on pharmaceutical quality and sufficient evidence for safety and efficacy. Hence, they may be granted authorization based on a "full application" in which the efficacy and safety are shown by data from product-specific clinical and preclinical trials in the same way as for conventional drugs. In addition, two classes of HMPs are legally recognized in Europe: WEU and the THMPs [4]. WEU is

granted MA based on at least 10 years use in the EU and bibliographical evidence on efficacy and safety [5,6]. As WEU cannot be demonstrated for many plant products because of lack of sufficient scientific data, Directive 2004/24/EC allowed a simplified pharmaceutical registration for HMPs with a history of TU for at least 30 years, of which at least 15 years are in the EU [7]. According to this directive, THMPs have to provide all information also required for the MA of a medicinal product with the exception of preclinical and clinical data. Hence, efficacy and safety can be demonstrated by referring either to HMPC monographs, to ESCOP monographs, to WHO monographs, to EC list entries or to expert reports [8]. Registered THMPs must indicate their therapeutic effect in a specific way: "Traditional herbal medicinal product used ..." They must also bear the following sentence in the labeling and package leaflet: "The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use".

As of March 2017, the EMA adopted 142 monographs for TU, 26 monographs for WEU, and 15 monographs for simultaneous TU and WEU. At the same time, 13 community list entries were finalized and published in the Official Journal of the European Union. Other list entries are pending because of incomplete genotoxicity data [2].

The total number of WEU, MA, and TUR applications since national implementation of Directive 2004/24/EC until December 31, 2016, received, under assessment, granted, refused, and withdrawn in EU member states are presented in ► **Table 1** [9].

The maximum number of TURs reaching 374 was observed in 2011, which was the deadline to bring to conformity existing THMPs already on the market with the new legal framework. After that, the number of TURs declined, not exceeding 139 TURs in 2015. The number of WEU MA granted ranged between 57 in 2005 and 92 in 2015.

When looking at the different countries in Europe, a high heterogeneity between the individual countries may be observed. As of December 31, 2016, there were 348 TURs granted in the United Kingdom, 285 in Germany, 215 in Poland, 209 in Austria, 100 in Spain, and 65 in Hungary while the majority of countries like France, Norway, Italy, Belgium, Portugal, and many others had only registered a handful of TU products [9].

The same applies when reviewing the number of WEU authorizations granted since the implementation of Directive 2004/24/EC until December 31, 2016. Again, Germany stands out with 286 authorizations, followed by Austria (56), Slovakia (49), and Sweden (46) [9]. Historical reasons, different medical and nutritional practices, and different national regulatory and administrative approaches can explain some but not all the heterogeneity between the individual countries. Moreover, lack of resources or dedicated herbal experts as well as lack of political will in favor of herbal medicines may be other reasons for the observed disparity [2].

EU-wide, a total of 61 different herbal substances were included in 694 WEU MA applications for mono-component HMP products by December 31, 2016. The main therapeutic area for which WEU MA have been granted are cough and cold, other, mental stress and mood disorders, urinary tract and genital disorders, constipation and sleep disorders, and temporary insomnia. The category "other" includes cardiovascular indications, improv-

ing liver function and mild cerebral insufficiencies. The largest number of WEU MA were given to the following five herbal substances in descending order: ivy (*Hedera helix* L., Araliaceae), ginkgo (*Ginkgo biloba* L., Ginkgoaceae), valerian (*Valeriana officinalis* L., Valerianaceae), St. John's wort (*Hypericum perforatum* L., Clusiaceae), and milk thistle (*Silybum marianum* L., Asteraceae) [9].

With regard to TURs, a total of 162 different herbal substances were included in 1066 mono-component THMPs in the EU by December 31, 2016, with the following five herbal substances receiving the largest number of TURs in descending order: devil's claw (*Harpagophytum procumbens* DC., Pedaliaceae), umckaloabo (*Pelargonium sidoides* DC., Geraniaceae), valerian (*V. officinalis*), St. John's wort (*H. perforatum*), and thyme (*Thymus vulgaris* Sm., Lamiaceae). The main therapeutic area addressed by mono-component and combination THMPs were cough and cold, mental stress and mood disorders, gastrointestinal disorders, urinary tract and genital disorders, and sleep disorders and temporary insomnia [9].

Whereas HMPs are characterized by their pharmacological effect, which is scientifically evaluated, herbal products available as PFSs are marketed to supplement the normal diet and exert only a physiological (or nutritional) effect. However, being consumed in form of tablets, capsules, and sugar-coated pills, PFSs become more and more drug-like in the perception of the consumer. As they may pose the risk of misleading consumers if they are assigned qualities that they do not have, a closer look will be taken at the PFS market in Europe [8].

Overview on PFSs in Europe

In general, food supplements are regulated in the EU under Directive 2002/46/EC. However, PFSs are not covered by this directive, as Directive 2002/46/EC addresses mainly vitamins and minerals and does not clarify what is meant with the term "other substance with a nutritional or physiological effect", although it is generally understood that this could include botanicals and botanical extracts. Hence, there is currently no EU legislation specifically for PFSs other than the general EU food legislation Regulation 178/2002. Therefore, member states' competent authorities supervise the PFS market according to their own criteria [10]. Some EU member states have adopted lists of authorized plants and plant parts in their legislation, like the so-called BELFRIT list used in Belgium, France, and Italy. Other member states work with guidelines and/or unofficial lists.

In July 2007, the Regulation (EC) No 1924/2006 entered into force. It lays down harmonized rules on nutritional (Art. 8) and health-related claims (Art. 13 and 14) applicable to food supplements. According to this regulation, health claims must be based on and substantiated by generally accepted scientific evidence and must not mislead the consumer. They need to be authorized by the European Commission and member states under the scrutiny of the European Parliament and Council following an assessment of their scientific substantiation by the EFSA [8]. As the EFSA, however, considers human studies, besides monographs, to be essential for the substantiation of health claims, evidence of TU was not considered sufficient to prove the substantiation of a health claim for PFSs. In this point, the EFSA reveals to be even

► **Table 1** Total number of WEU applications and the total number of TUR applications received, under assessment, granted, refused and withdrawn in EU Member States since national implementation of Directive 2004/24/EC until 31 December 2016.

WEU MA	applications received	1354
	applications under assessment	303
	granted	803
	refused	64
	applications withdrawn by the applicant	181
TUR	applications received	2730
	applications under assessment	574
	granted	1719
	refused	240
	applications withdrawn by the applicant	197

stricter than the regulatory authorities registering THMPs solely on the base of bibliographic evidence of TU. For that reason, no claim on botanicals based on TU alone has obtained a positive assessment so far by the EFSA. In addition, following a request by the European Commission, the evaluations of health claims concerning botanicals are kept "on hold".

Hence, different approaches exist among member states on which botanicals can be used in plant foods and under which conditions. Furthermore, the same botanicals are sometimes used in both foods and medicines, and consumers may sometimes struggle to perceive the difference between certain indications found on HMPs and health claims on PFSs (e.g., "relief of minor articular pain" vs. "maintenance of normal joints" or "treatment of common cold" vs. "supports immune system"). Furthermore, since member states have the right to classify, on a case-by-case basis, a product as food or as medicine, it is possible that the same product is classified as food in one member state and as a medicinal product in another. Hence, the current market in Italy is almost completely represented by food supplements, whereas in countries like Germany or France, the botanical market is represented by HMPs and food supplements [10]. Again, in other countries like Portugal, mostly THMPs are sold. This may lead to important differences in the level of information that is provided to consumers on products apparently similar. Based on that background, the European Commission decided to launch a reflection on whether this difference should be maintained or not. It is expected that a final report on how to deal with the botanical claim situation will be published by the end of 2017.

In general, PFS usage data in the EU is scarce. The only data addressing the type and frequency of PFS usage emphasizing a clear distinction between PFSs, HMPs, and other dietary supplements or complementary and alternative medicines are available from a retrospective survey of consumers in six European countries carried out by Garcia-Alvarez et al. [11]. Based on a questionnaire completed by 2359 consumers, the estimated weighted overall PFS usage prevalence rate was 18.8% and the per-country rate was 22.7% in Italy, 19.1% in the United Kingdom, 18.0% in Spain, 17.6% in Romania, 16.9% in Germany, and 9.6% in Finland. The

11 most frequently used botanicals (number of consumers included in this study ranging from 194 to 100) in descending order are ginkgo, evening primrose (*Oenothera biennis* L., Onagraceae), artichoke (*Cynara scolymus* L., Asteraceae), ginseng (*Panax ginseng* C.A.Mey., Araliaceae), aloe (*Aloe barbadensis* Mill., Gard. Dict., Aloaceae), fennel (*Foeniculum vulgare* Mill., Apiaceae), valerian, soy bean (*Glycine max* [L.] Merr., Fabaceae), lemon balm (*Melissa officinalis* L., Lamiaceae), echinacea (*Echinacea purpurea*, [L.] Moench, Asteraceae), and bilberry (*Vaccinium myrtillus* L., Ericaceae). The overall prevalence rates reported in Europe can be compared to rates from surveys conducted in the United States, where data on usage of dietary supplements, including herbal supplements, are collected more routinely [11].

Overview on the Herbal Market in the United States

In the United States, there is no separate category for traditional herbal medicine, as the FDA does not accept bibliographic evidence for efficacy but prefers randomized controlled clinical trials [10]. In general, herbal products are not marketed as drugs but are regulated in the United States by the DSHEA of 1994, which classifies herbs as dietary supplements that are not to be used for treating any condition or disease state but only as support for maintaining and promoting good health. Herbal dietary supplements can be thus produced, sold, and marketed without first demonstrating safety and efficacy, as is required for pharmaceutical drugs. Also, herbal dietary supplements do not need approval from the FDA before being marketed. Only companies that distribute or manufacture dietary supplements containing “new dietary ingredients” are required to submit pre-market safety notifications. According to the DSHEA, the manufacturer is responsible to determine safety and to demonstrate evidence for the claims made. In 2006, Congress passed the Dietary Supplement and Non-Prescription Drug Protection Act, which obligates manufacturers of dietary supplements to report serious adverse effects to the FDA [12]. In case a dietary supplement has to be removed from the market, the FDA bears the regulatory burden of proving that the product is unsafe. As a company does not have to provide the FDA with the evidence it relies on to substantiate their claims, dietary supplement manufacturers frequently use certain “structure/function claims”, which are often vaguely worded claims of health benefits. For example, an echinacea product (often used to treat or to prevent common cold) might claim to support the body’s natural defenses. In contrast to Europe, each dietary supplement package must state that the product is a “dietary supplement” and that “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease” [13]. It is interesting that regardless of these warning statements mandatory for dietary supplements in the United States, many herbal dietary supplements are nevertheless consumed to manage symptoms and treat specific conditions [14].

Another major difference exists between dietary supplement products in the United States and food supplement products in Europe. In contrast to Europe, dietary supplement products in

the United States must be manufactured under cGMP, requiring that manufacturers verify that specifications are met for identity, purity, strength, and composition of their dietary supplements [15, 16].

According to the American Botanical Council, sales of herbal dietary supplements increased by 7.7% in 2016, totaling an estimated \$7.45 billion, which is the second highest rate of growth for these products in more than a decade [17]. Among the top-selling herbal dietary supplements was horehound (*Marrubium vulgare* L., Lamiaceae) used to relieve upper respiratory symptoms. Also, frankincense (*Boswellia serrata* Roxb., Burseraceae) and turmeric (*Curcuma longa* L., Zingiberaceae), used in Ayurvedic medicine for its anti-inflammatory benefits, experienced a sales increase of more than 50% in 2016, being + 118.7% for frankincense and + 85.5% for turmeric. This reflects the general rise of Ayurvedic herbs and the increased focus on inflammation currently observed in the United States. In addition, many herbal dietary supplements are used by the U.S. population for the treatment and prevention of a wide array of ailments including common cold, depression, and other non-life-threatening medical conditions, although they are not regulated for this purpose. Other popular indications for use of herbal dietary supplements include bone health, menopause or hot flashes for women, prostate health for men, mental health, and weight loss [14]. Older adults tended to use PFSs chronically to maintain long-term organ-specific functions (e.g., preservation of bone, heart, prostate), whereas younger adults rather used PFSs for short-term gains, such as enhancing energy or boosting immune function [18].

Aside from the fact that marketing a PFS is definitely easier and cheaper than marketing an HMP, several other factors led to the increasing utilization of PFSs for self-medication.

Factors Responsible for the Overall Increased PFS Intake

The rising significance of health issues in daily life, together with an increased possibility to self-medicate, and the aging of the population seem to be the major reason for the success of PFSs [19–21]. Additional factors that promote the consumption of products of plant origin is the belief that botanicals are natural and “natural is good” and consequently safe [19,22]. Therefore, PFSs are used more and more to improve quality of life and well-being, support “natural” healing, boost the immune system, lose weight, or enhance muscle growth during body building. Furthermore, PFSs are usually excluded from tight prescription regulations and thus can be easily purchased in pharmacies, in health stores, in gyms, and from Internet sources. Hence, people suffering from lack of time to see a physician and patients experiencing unsuccessful treatments with conventional drugs or feeling uncomfortable about discussing their medical problems have easy access. Moreover, manufacturers pursue systematic marketing strategies to increase consumers’ awareness, assigning PFSs undue respectability and credibility [23].

However, an imbalance exists between the increasing number of PFSs, representing a relevant source to benefit from natural substances on the one hand and the development of policies to

regulate their application and safety on the other hand. Based on that background, quality, safety, and efficacy of PFSs should be all the more subjected to a closer examination.

Quality Aspects of PFSs

European and U.S. regulations pertaining to food supplements address issues including upper limits of safe intake, types and substantiation of claims, availability of safe ingredients, increased consumer information about use, and appropriate technical requirements addressing food additives and contaminants [24]. Mandatory quality control for PFSs features in particular the analysis of heavy metals such as lead, mercury, cadmium, and arsenic, and the determination of microbial load, aflatoxins, pesticides, residual solvents, and radioactivity [1]. In addition, supplement manufactures in the United States are required to follow cGMP to ensure the identity, purity, quality, strength, and composition of their products. This is not obligatory for PFS manufacturers in Europe. They are also not required by law to carry out content analysis quantifying surrogate marker compounds or active principles in their products except in the case of pre-established daily intake limits (as required, for example, for hypericin or synephrine). On the other hand, manufacturers of HMPs including THMPs using extracts complying with pharmacopoeial standards have to perform standardized extraction procedures and comprehensive quality-control testing. In order to avoid safety concerns, PFSs in Europe are often under-dosed compared to the corresponding HMPs.

Based on the results of studies published so far on the quality of PFSs, quality concerns are in general justified. Often, manufacturers of finished PFSs, whether in Europe or in the United States, do not handle the unprocessed botanicals by themselves but buy herbs that have been already processed into powders or extracts. Thus, they have no opportunity to authenticate the material they bought by morphology [25]. Hence, certain segments of the herbal supplement market may easily practice so-called economic adulteration, substituting a less-expensive for a more-expensive ingredient, including related substitute species and cheap fillers [26, 27]. In a study conducted by Booker et al., 33 out of 35 tested ginkgo products sold as food supplements in health food stores, supermarkets, and pharmacies in the Central London area and via the Internet were found to contain elevated levels of rutin and/or quercetin or low levels of ginkgo metabolites compared with the reference samples. Such samples with disproportional levels of rutin or quercetin compared with other ginkgo metabolites are likely to be adulterated, either by accident or intentionally, and those samples with low or non-existing ginkgo metabolites are likely to have been produced using poor extraction techniques [27]. Also, a study of the Central Laboratory of German Pharmacists reported disproportional levels of quercetin in 7 out of 10 ginkgo supplements obtained from German health food stores, drug stores, and pharmacies. In light of the high production costs, these findings are not surprising, as 50 kg dried ginkgo leaves are needed to obtain 1 kg of pharmacologically active ginkgo extract complying with pharmacopoeial standard [28]. Similar observations were made in the United States. In order to save costs but nevertheless accounting for achieving the desired 24% flavonol

glycoside content, some extract providers or supplement manufacturers manipulated the extract composition or stretched ginkgo extracts with pure flavonols (e.g., rutin, quercetin, kaempferol) or flavonoid-rich material as the fruit/flower of Japanese sophora (*Styphnolobium japonicum* L., Burseraceae), pretending a quality that does not exist [29]. It is also apparent that black raspberry dietary supplement producers and sellers are not able to differentiate between black raspberry and blackberry, as often wrong images are posted on the supplements packaging [30].

Regarding the consistency of chemical contents, several studies documented dramatically different levels of labeled active ingredients in PFSs [13]. Hence, a study on the quality of frankincense containing PFSs including 17 top-selling products from Europe and the United States revealed that 41% of the products did not comply with the label declaration. Hence, one product from Italy did not contain any of the six characteristic BAs (KBA, AKBA, α BA, β BA, A α BA, A β BA) at all, and another U.S. product contained only traces, suggesting the absence of frankincense or the use of another species like *Boswellia frereana* Birdw. (Burseraceae) instead of *Boswellia serrata* Roxb. (Burseraceae). In another product, the ratios of the individual BAs were different from *B. serrata* gum resin, indicating also the use of another species such as *Boswellia sacra* Flueck. (Burseraceae) or *Boswellia carterii* Birdw. (Burseraceae). Furthermore, two products revealed different BA contents from those declared on the label. Further, two products did not declare the use of manipulated *Boswellia* gum resin extract being enriched in AKBA content reaching up to 66% [31]. A further study on 25 products from the genera *P. ginseng* and *Eleutherococcus senticosus* Rupr. et Maxim. (Araliaceae) obtained from a local U.S. health food store found a 15- to 200-fold variation in the concentration of ginsenosides and eleutherosides [32]. Another study showed that the ginsenoside contents of 232 *P. ginseng* and 81 *Panax quinquefolius* L. (Araliaceae) products marketed as commercial ginseng products in North America ranged from 0.00% to 13.54% and from 0.009% to 8.00%, respectively, and that \approx 26% of these products did not meet label claims. Also, the eleutherosides B and E content of eleuthero root powder and other formulated extract products showed large variation [33–35]. Studies on the quality of St. John's wort products showed hypericin content ranging from 47% to 165% of label claim [36]. Similarly, silymarin was detected at 58–116% of label claim [33]. Also, 7 of 19 black raspberry (*Rubus occidentalis* L. Rosaceae) products purchased in the time from May to July 2013 from Amazon.com contained no anthocyanin from black raspberry fruit, while three of those seven had no anthocyanins of any kind. The remaining products revealed a wide range of anthocyanin concentration ranging from 0.1 to 145.2 mg per capsule [30].

Moreover, FDA inspections of manufacturing facilities have revealed GMP violations in about two-thirds of all inspections. Commonly identified problems include failure to verify that a finished batch meets product specifications for identity, purity, strength, and composition, failure to verify the identity of a dietary ingredient prior to use, and failure to establish and to follow written procedures for quality-control operations [26].

In addition, a large number of PFSs sold via the Internet are intentionally adulterated, especially those that carry claims about weight loss and male sexual performance containing undeclared

prescription drugs or synthetic analogues of them [10]. The amounts of these undeclared synthetic ingredients may even exceed the therapeutic dose of the particular pharmaceutical [24]. Hence, weight-loss products frequently contain sibutramine, which has been withdrawn from the European and U.S. market because of its association with strokes and cardiovascular events. According to the FDA list of tainted food supplements from a total of 416 public alerts launched between 2010 and 2015, 37% corresponded to adulterated weight-loss products, from which most cases (87%) involved the illegal addition of sibutramine [37]. Illicit weight-loss products have also been reported to contain stimulants and other anorexics, benzodiazepines, antidepressants, diuretics, and laxatives [38, 39]. As a result of the weight-loss-inducing side effects of the hypoglycemic drug metformin, this compound can also be found in weight-loss supplements, often with other adulterants such as sibutramine and phenolphthalein [40]. Nutritional supplements advertised as metabolic activating agents and fat burners revealed to contain high amounts of caffeine, ephedrine (and its analogues pseudoephedrine, methylephedrine), methylenedioxymethamphetamine, or β -methylphenylethylamine [41, 42]. Many supplements for the enhancement of athletic performance contain analogues of amphetamines, and herbal supplements for sexual health frequently contain sildenafil or other PDE-5 inhibitors [43]. It has been estimated that in Europe, six million illicit products containing PDE-5 inhibitors have been purchased outside the official health system. In the Netherlands alone, 75% of sexual enhancement supplements seized contained PDE-5 analogues [44]. Also, own test purchases carried out by the Central Laboratory of German Pharmacists revealed that every other PFS obtained from illegal Internet sites was adulterated with synthetic PDE-5 inhibitors. The presence of various hypoglycemic drugs like glibenclamide, rosiglitazone, and metformin has been also reported in PFSs claiming to regulate the concentration of blood sugar or to treat diabetes mellitus [45, 46]. Other studies have revealed adulteration of herbal supplements claiming to be effective in lowering or maintaining optimal blood pressure with various antihypertension drugs like amlodipine, indapamide, valsartan, clonidine, and hydrochlorothiazide [47]. Considering the analgesic, antipyretic, and anti-inflammatory effects of glucocorticoids and nonsteroidal anti-inflammatory drugs, these compounds (e.g., phenylbutazone, aminopyrine, indomethacin, hydrocortisone, dexamethasone, ibuprofen, diclofenac, salicylic acid, and naproxen) have been also found in herbal products intended for management of rheumatoid arthritis, eczema, or chronic back pain [48].

Therefore, it may be difficult for patients to ascertain with certainty the precise contents of the PFS they may be interested in taking [13]. This applies not only for products bought from illegal Internet websites but also for products obtained from the official health system. Of course, the insights obtained above in the quality of PFSs cannot be generalized and it is beyond question that also high-quality PFSs exist in the legal market and that many PFS manufacturers are beginning to significantly improve their quality standards. Nevertheless, the quality of PFSs still varies from one product to another and still many companies sell low-quality products, some containing unknown/unreported ingredients not to speak of missing efficacy and safety.

Safety Aspects of PFSs

The common misconception that botanicals are harmless and devoid of adverse effects often leads to improper use and unrestricted intake, resulting in increased incidence of side effects and drug interactions [49, 50]. Hence, the growing use of PFSs is accompanied by an increasing concern particularly because no pre-marketing safety assessment is required. Being considered as foods in Europe, PFSs are subjected to the disposition of the General Food Law (Regulation [EC] 178/2002), with the responsibilities for food safety issues mainly relying on the food business operator [51, 52]. Nevertheless, the EFSA issued a guidance, in which a general framework for safety assessment of botanicals and botanical preparations is presented [51]. Also, in the United States PFSs do not require any approval from the FDA before being introduced in the market. Hence, manufacturers do not have to provide evidence for safety and effectiveness of their products, but they are prohibited to market unsafe or ineffective products. In general, data on safety and adverse effects of PFSs in Europe and the United States are scarce, mainly because PFSs are still not covered well under the pharmacovigilance scheme and only individual case reports or case series on single plants are reported in the literature [19, 53].

Based on the Annual Report of the American Association of Poison Control Centers in the United States, no death cases could be attributed to dietary supplements [54]. The most common calls involving PFSs represented minor problems involving caffeine-containing dietary supplements (often the content of caffeine is not listed on the label) followed by yohimbine products [55].

In order to fill the gap of scarce data in Europe, a multicenter retrospective review of data from selected European and Brazilian poison centers involving human cases of adverse effects due to plants consumed as food or ingredients of food supplements between 2006 and 2010 was performed as part of the EU project PlantLIBRA (Levels of Intake, Benefit, and Risk Assessment) [19, 56]. Ten poison centers provided a total of 75 cases originating from all over Europe (Finland 9, France 31, Germany 4, Italy 13, Serbia 4, Sweden 5, Switzerland 5) and Brazil (4). In 57 cases (76%), a PFS was involved, and in 18 (24%), a plant was ingested as food. Whereas the number of involved PFSs containing only one ingredient was comparable to that with more than one ingredient, the latter were more frequently associated with moderate and severe clinical courses (33.3%) compared to PFSs with one ingredient (10%). The most frequently observed clinical effects were neurotoxicity ($n = 34$) and gastrointestinal symptoms ($n = 24$). This is in accordance with data from the Italian pharmacovigilance center on spontaneously reported adverse effects of natural health products including homeopathics [57]. Other organs/organ systems reported in the PlantLIBRA project to be involved in adverse effects were the cardiovascular system ($n = 13$), skin/mucosa ($n = 8$), the liver ($n = 4$), the respiratory system ($n = 2$), the kidney ($n = 1$), and other organ systems ($n = 5$). In total, 58 different plants were consumed as ingredients of PFSs or as food. The 15 plants in this study involved in three or more cases of adverse effects are listed in ► **Table 2** [19].

► **Table 2** Overview of the fifteen plants involved in three or more cases of adverse effects after ingestion of a PFS or a plant as food in the 75 cases recorded by Lüde et al. according to data from [19].

Latin name	Common name	As food	In PFS	Total
<i>Valeriana officinalis</i> L., Valerianaceae	Valerian	1	22	23
<i>Camellia sinensis</i> (L.) Kuntze, Theaceae	Green tea	1	9	10
<i>Melissa officinalis</i> L., Lamiaceae	Lemon balm		7	7
<i>Mentha piperata</i> L., Lamiaceae	Peppermint		7	7
<i>Passiflora incarnata</i> L., Passifloraceae	Passionflower	1	6	7
<i>Paullinia cupana</i> Kunth, Sapindaceae	Guarana		7	7
<i>Glycyrrhiza glabra</i> L., Fabaceae	Licorice	5	1	6
<i>Ilex paraguariensis</i> A.St.-Hil., Aquifoliaceae	Yerba mate		6	6
<i>Panax ginseng</i> C. A.Mey., Araliaceae	Ginseng		5	5
<i>Citrus aurantium</i> L., Rutaceae	Bitter orange		4	4
<i>Cynara scolymus</i> L., Asteraceae	Artichoke	4		4
<i>Dioscorea villosa</i> L., Dioscoreaceae	Wild yam		4	4
<i>Allium ursinum</i> L., Alliaceae	Wild garlic	3		3
<i>Carum carvi</i> L., Apiaceae	Caraway		3	3
<i>Taraxacum officinale</i> L., Asteraceae	Common dandelion	2	1	3

In 59 (79%) of the 75 cases, only one organ/organ system was involved. In 14 cases, two organs/organ systems were involved, and two cases had more than two organs/organ systems involved. The signs and symptoms observed in the 75 cases with adverse effects after the ingestion of a PFS or a plant are summarized in ► **Table 3** [19].

The plant most commonly involved in cases of adverse effects in this study was valerian (*V. officinalis*). The observed adverse reactions included somnolence, drowsiness, and gastrointestinal symptoms. The neurological symptoms can be well explained by valerian's properties as a relaxant and sleep aid [19,58]. Only two cases, using a multi-ingredient PFS were severe. In one case, a 30-year-old man, who recovered completely, was using a product containing bitter orange (*Citrus aurantium* L., Rutaceae), green tea (*Camellia sinensis* [L.] Kuntze, Theaceae), guarana (*Paullinia cupana* Kunth, Sapindaceae), and coleus (*Coleus forskohlii* [Willd.] Briq., Lamiaceae), which he combined with a product containing golden root (*Rhodiola rosea* L., Crassulaceae) to lose weight. Besides a weight loss of 18 kg in two months, he suffered a myocardial infarction during sexual activity. In the other case, a 40-year-old man suffered a transient ischemic attack a few hours after the ingestion of a single recommended dose of a PFS containing ginseng (*P. ginseng*), guarana (*P. cupana*), yerba mate (*Ilex paraguariensis* A.St.-Hil., Aquifoliaceae), maca (*Lepidium meyenii* Walp, Brassicaceae), damiana (*Turnera diffusa* Willd.ex Schult, Turneraceae), oat (*Avena sativa* L., Poaceae), and chili pepper (*Capsicum annuum* L., Solanaceae) [19]. As, however, the origin of the ingested PFS is not known, it cannot be excluded that these PFSs were obtained from the Internet and have been adulterated with synthetic drugs. Most cases, however, showed a benign clinical course with mild outcome. The symptoms most commonly recorded in the moderate cases of this study were—apart from gastrointestinal symptoms—edema and hypokalemia sometimes ac-

companied by hypertension or ECG changes. In all of these cases, licorice (*Glycyrrhiza glabra* L., Fabaceae) was involved. These observations correspond well to the known effect of glycyrrhetic acid, which influences the electrolyte balance by inhibiting the 11 β -hydroxysteroid dehydrogenase type 2 enzyme, leading to an aldosterone-like effect. Consequently, the renin-angiotensin-aldosterone axis is suppressed, which causes volume expansion, hypertension, hypokalemia, and metabolic alkalosis [19,53,59,60].

In general, most reported adverse events in the literature might be associated with green tea (*C. sinensis*), black cohosh (*Cimicifuga racemosa* L. Nutt, Ranunculaceae), bitter orange (*C. aurantium*), licorice (*G. glabra*), and soy bean (*G. max*) [53]. In cases where no clear assignment of the reported effects to a PFS or HMP can be made because of the different classifications in different countries, the reported effects will be assigned in the following to the respective herb in general.

While green tea infusion is widely consumed and may be considered generally safe, PFSs with green tea extracts have shown to have a hepatotoxic potential. This is attributed to the different composition of infusion and extracts. Whereas infusions and aqueous extracts contain mostly hydrophilic compounds, hydroalcoholic extracts contain both hydrophilic and lipophilic components, and powdered leaves contain all of the tea active components [53]. In total, 19 cases of hepatotoxicity related to the consumption of PFSs containing green tea were identified until 2015, mostly in women (16/19). The causality assessment between consumption of herbal preparations and hepatic reaction resulted as “probable” in eight cases and as “possible” in 11 cases. In seven cases, patients used preparations containing only green tea, while 12 reactions involved patients who took MC preparations. Compared to single ingredient products, the reactions induced by MC were more serious, with four cases involving liver transplantation. As the MC preparations contained numerous other components

► **Table 3** Observed signs and symptoms in the 75 cases with adverse effects after ingestion of a PFS or a plant as food according to data from [19].

Signs/symptoms		N
Nervous system	Drowsiness	16
	Somnolence	8
	Dizziness	7
	Headache	5
	Restlessness	2
	Tremor	2
	Transient ischemic attack	1
Gastrointestinal system	Nausea	14
	Vomiting	14
	Abdominal pain	13
	Diarrhea	11
Cardiovascular system	Tachycardia	5
	Hypertension	4
	ECG changes	3
	Chest pain	2
	Hypotension	1
	Myocardial infarction	1
Skin/mucosa	Skin or mucosa inhibition	5
	Angioedema	2
	Urticaria	2
Liver	Hepatitis	3
	Elevated liver enzymes	1
	Icterus	1
Respiratory system	Respiratory insufficiency	2
Kidney	Renal insufficiency	1
Other	Hypokalemia	3
	Edema	2
	Miosis	1

also suspected to induce liver damage, it is difficult to ascribe the hepatotoxicity to one specific component as, for example, green tea [61]. Patients experienced acute hepatotoxicity following the intake of green tea (*C. sinensis*) in the form of a PFS containing hydroalcoholic extracts revealed clinical symptoms with different severity ranging from a mild increase in serum aminotransferases to fulminant hepatitis requiring liver transplantation [19,62,63]. The mechanism of hepatotoxicity remains unclear, but many factors may be related to the patient and to catechins and their gallic esters, in particular EGCG, which can induce oxidative stress and liver damage in certain conditions as fasting. The association with EGCG seems further confirmed by the lack of adverse effects in case of fermented teas as black tea, in which the content of EGCG is significantly reduced [53,61]. In summary, the present data considering the great use of this supplement confirm a certain safety concern with green tea, even if the number of hepatic reactions is low. A major safety concern exists when green tea is asso-

ciated with other ingredients that may additionally enhance the risk of liver damage [61].

In case of black cohosh (*C. racemosa*), 19 papers describe specific adverse effects, among which 14 were classified as “certain/probable” and five were classified as “possible”. The adverse reactions resulted from the chronic ingestion of black cohosh extracts as such or as ingredient of a PFS [53,64–70]. In the case of hepatotoxicity, the event was quickly reversible after discontinuation, except in two cases where liver transplantation became necessary and in one case where the event was fatal [64,69]. Also, when ingested as an HMP, black cohosh (*C. racemosa*) was associated with five serious reports related to the liver as described by Svedlund et al. in their study on spontaneously reported adverse reactions resulting from HMPs and natural remedies in Sweden in the time from 2007 to 2015 [71]. Despite the limited available nonclinical and clinical data, liver toxicity has been also associated with the use of black cohosh by the European Community, as discussed in the assessment report pertinent to the European Community herbal monographs on *C. racemosa* rhizome [72,73].

PFSs with bitter orange (*C. aurantium*) contain *p*-synephrine, which has many of the pharmacological properties as ephedrine and therefore the potential to cause many of the same side effects [13]. Hence, adverse effects associated with bitter orange dietary weight-loss supplement concern mainly the cardiovascular system [53,74]. Ischemic colitis was also reported [75]. In combination with caffeine, statistically significant increases in systolic and diastolic blood pressure (approximately 9 mmHg) and pulse (16.7 beats per minute) were observed in healthy adults [76]. Patients taking such products also reported insomnia or feeling jittery [13]. Often, bitter orange extracts used in herbal weight-loss formulas have higher concentrations of *p*-synephrine than reported for the traditional extracts of the dried fruit or peel [77]. This reflects another important issue to be taken into account when assessing the safety of PFSs—that is, that some preparations of a botanical may be marketed containing significantly higher levels of active (toxic) principles than those normally occurring in historical food of the same botanical [78]. Nevertheless, the adverse effects cases with regard to bitter orange were mainly classified as “possible” due to the frequent presence of accompanying conditions, such as obesity, hypothyroidism, asthma, diabetes, hypertension, and hyperlipidemia. Although products containing widely used plants for weight loss such as green tea (*C. sinensis*), sea grape (*Ephedra distachya* L., Ephedraceae), hoodia (*Hoodia gordonii* [Masson] Sweet ex Decne, Asclepiadaceae), bitter orange (*C. aurantium*) and brindleberry (*Garcinia cambogia* [Gaertn.] Desr., Clusiaceae) are marketed as highly effective, adverse events were only rarely recorded. Reasons for this observation might be the difficulty of finding these products in legal shops due to regulatory restrictions based on their negative safety profiles or the fear of cardiotoxic side effects attributed to the presence of stimulant amines as synephrine and octapamine [19,74,79].

The adverse effects due to soy bean (*G. max*) are mainly associated with the well-known allergic potential of soy bean, which is included in the major allergens requiring specific labeling. The second most important group of side effects is associated with the postulated pseudohormonal activity of the isoflavone fraction and include ureteral Müllerian carcinosarcoma associated with en-

dometriosi s [53,80]. Other case reports associated with soy bean with satisfactory demonstration of causality are gastrointestinal adverse effects including enterocolitis, vomiting, abdominal pain, and diarrhea [81]. Because of contradictory findings from *in vitro* and animal studies, a definitive safety assessment of isoflavone intake can still not be made. However, according to Wolters and Hahn, a daily oral dose of 50 mg isoflavones may be regarded as safe and it may be assumed that a short-term intake of soy bean is not associated with significant adverse effects [82]. However, women with breast cancer should avoid long-term use of soy products or isolated isoflavones [83]. Interestingly, some manufacturers advertise the presence and others the absence of isoflavones in their PFS products.

Other herbs like echinacea (*E. purpurea*, Asteraceae), ginkgo (*G. biloba*), St. John's wort (*H. perforatum*), Devil's claw (*H. procumbens*), ginseng (*P. ginseng*), grape (*Vitis vinifera* L., Vitaceae), and vitex/chaste tree (*Vitex agnus castus* L., Lamiaceae) appear to be relatively safe, with observed adverse effects not exceeding individual reports [53].

Generally speaking, in spite of some fatal cases, given the large number of plants and the widespread use of PFSs, the occurrence of adverse effects by PFSs is relatively low and the number of severe clinical reactions is very limited. Nevertheless, these findings should be handled with care, as it cannot be excluded that adverse effects are detected only to a small extent by poison centers, as can be deduced from a one-year poison center surveillance project [19,55]. According to this study conducted in the United States, only 0.4% of the calls concerned dietary supplements, of which 33% were due to adverse effects. Moreover, it has been confirmed that people do not think of poison centers as information centers and often do not report their use of dietary supplements to the physician [20,84]. In addition, adverse effects caused by PFSs may be underestimated because most PFSs do not provide safety information encouraging consumers to consider PFSs as safe, which results in not reporting their use when admitted to hospital or emergency service [53]. Hence, the true frequency of side effects for most herbs is not known in particular because most have not been tested in large clinical trials.

Of concern are also PFSs contaminated with pesticides, heavy metals such as lead, mercury, and arsenic, microbial agents, and mycotoxins as well as PAs, alkenylbenzenes, or aristolochic acids [78,85–87]. PAs are converted by cytochromes P450 to pyrrolic dehydro-alkaloid metabolites that alkylate DNA and other macromolecules, causing liver cell necrosis and liver cancer [78]. Besides PAs detected recently in commercially available medicinal teas, six batches of St. John's wort tablets have been precautionary recalled in the United Kingdom because of potentially toxic PA levels due to product contamination [88,89]. Similarly, alkenylbenzenes including apiole, β -asarone, elemicin, estragole, emthyleugenol, myristicin, and safrole are converted by cytochromes P450 and sulfotransferase-mediated biotransformation to genotoxic and carcinogenic 1'-sulfoxy-metabolites that bind to DNA and cause liver cancer. Aristolochic acid I and II undergo reductive metabolic activation by cytochromes P450 and/or other enzymes, resulting in formation of reactive nitrenium ion metabolites that cause Chinese herb nephropathy and urethelial cancers [78]. Because of sloppy control measures, it cannot be excluded that products con-

taining these plant constituents are offered on the market, thus presenting a considerable safety concern.

Whereas contamination of PFSs is generally an unintentional event that results from growing, spraying, and harvesting of the herbal plant, adulteration with prescription drugs is typically driven by a desire to increase or alter the claimed effect of the PFS to gain a commercial advantage. Hence, the most significant safety concern results from the sale of adulterated PFSs. Adulterants that should not be present in PFSs may be introduced into the supply chain at any step between the planting, production, and packaging phase of the marketed formulation. In weight-loss supplements, drug adulterants that have been identified include sibutramine, fenfluramine, and phenolphthalein [39,90]. All of these drugs have been removed from the market due to safety concerns. Other adulterants that have been identified in weight-loss products include diethylpropion, 1,3-dimethylamine, fenproporex, furosemide, rimonabant, and cetilistat [18,91]. On the basis of reports from a nationally representative sample of emergency departments from 2004 through 2013, it was estimated that weight-loss products causing cardiac symptoms (palpitations, chest pain, or tachycardia), headache, dizziness, nausea, vomiting, or mild or moderate allergic reactions were implicated in 25.5% of emergency department visits [92]. In the case of supposedly pure herbal sexual performance-enhancing supplements, high rates of product adulteration with PDE-5 inhibitors, including sildenafil, tadalafil, and vardenafil as well as their analogues ranging between 37% and 81%, have been observed [37,93,94]. For a more detailed insight into the adulteration rate of dietary supplements the review of Rocha et al. may be consulted [37]. The use of these compounds and analogues can pose considerable dangers to consumers, as they may contain toxic constituents or substances whose safety has never been examined before and whose interaction with medication may be unpredictable and lethal. Considering that these adulterated products are, beyond that, consumed without medical supervision by consumers without knowing that these ingredients are present, they represent a significant threat to consumer health. In fact, the FDA received numerous reports of serious adverse events associated with consumer use of these tainted products including strokes, acute liver injury, kidney failure, pulmonary embolisms, and even death [95].

Not surprisingly, muscle-building supplements have also often been found to be adulterated with anabolic steroids or aromatase inhibitors, both classified as prescription drugs. Also *de novo* synthesized androgenic compounds, so-called designer steroids, that have structural similarities to testosterone and are more difficult to detect by standard chromatographic and spectroscopic techniques may be included. With the exception of dehydroepiandrosterone, most anabolic steroids are designated as Schedule-3 controlled substances. As a consequence of consumer usage of supplements that are illegally spiked with anabolic steroids, hepatotoxicity continues to be reported [18]. Although the FDA has issued warnings about 300 tainted products that can cause serious adverse events including stroke, organ failure, and death, some adulterated products remain in the marketplace even after recalls. Hence, 27 supplements recalled because of adulteration were tested at least six months after being recalled. Sixty-three percent (17/27) contained the same pharmaceutical adulterant identified

previously by the FDA, and six contained one or more additional banned ingredients [37,96].

In summary, safety of PFSs may be compromised by several factors including the use of wrong species of plant by mistake, adulteration of herbal products with other undeclared medicines, contamination with toxic or hazardous substances, overdosages, misuse and long-term use of multi-ingredient PFSs by consumers, and use of PFSs concomitantly with other medicines.

Interaction Aspects of PFSs

An important but mainly under-investigated safety concern is the potential for popular PFSs to interact with drugs. Although the potential for drug-drug interactions must be investigated for all new drugs, and many interactions have been documented, drug-PFS interactions remain underexplored [97]. Drug-PFS supplement interactions can include inhibition or induction of P450 enzymes, UDP-glucuronosyltransferases, other phase I and II enzymes involved in drug metabolism, drug transporters and drug-efflux proteins. By inhibiting the action of specific drug-metabolizing enzymes, PFSs may prolong the half-lives of drugs, which may result in prolonged action and even toxicity. On the other hand, inhibition of enzymes can also prevent prodrugs from exerting their pharmacological effects. Moreover, if herbal compounds are highly bound to serum proteins, they may displace other drugs from this protein, which may lead to an increase in the concentration of the free drug to toxic levels. An example of a well-documented interaction is the induction of CYP3A4 by St. John's wort, leading to lower efficacy of many drugs like oral contraceptives and the anticoagulant warfarin [98–100]. Although St. John's wort has generated the most publicity regarding safe use, nearly two-thirds of 15 preparations (13 unlicensed PFSs and two THMPs) obtained from British health food shops, pharmacies, and supermarkets failed to mention any of the possible interactions with conventional medicines such as the oral contraceptive or warfarin. Only the two registered THMPs and two unlicensed products obtained from pharmacies informed the consumer about eight possible interactions [101]. This is consistent with findings in the United States, indicating that manufacturers of the vast majority of St. John's wort preparations failed to adequately address clinically relevant safety issues [102]. Also, for green tea supplements, interactions have been reported with conventional drugs, especially with statins, where an increase in plasma concentrations and a worsening of the related side effects, such as rhabdomyolysis, were observed [54,103]. For many other herbs like black cohosh, ginkgo, ginseng, milk thistle, saw palmetto, and valerian, preclinical assays predicted drug interactions that revealed, however, to be of no clinical relevance when tested in humans [97]. In general, there are considerable discrepancies between preclinical data and corresponding clinical responses. In the case of ginseng, for example, preclinical studies with human liver cells predicted drug interactions that were not manifested in a clinical trial [97,104]. A similar outcome was observed for ginkgo, when preclinical work with both recombinant protein and liver microsomes predicted inhibition of several P450 enzymes, but no drug-ginkgo interactions were observed in a clinical trial [97,105–107]. These examples indicate that a clinical

trial often fails to confirm drug-herb interactions that were predicted by common preclinical experiments. A possible reason for that might be the use of different extract types and different doses. Another reason for these inconsistencies might be that preclinical assays do not take into account the bioavailability of different natural substances. If substances are not absorbed after oral administration, then they would be unlikely to have any effects on phase I metabolism in humans. The frequency of botanical natural products showing P450 inhibition in preclinical studies without similar effects in humans suggests that most preclinical methods are overestimating inhibition [97]. Similar concerns about disagreements across literature resources and databases for drug interaction have been raised before [108,109]. This increases the difficulty of implementing an evidence-based clinical practice for PFS products. Another limitation is the concern of publication bias, which might arise as only evidence-based herbal products are predominantly published in the literature. Therefore, there might be many more PFS-drug interactions that exist but are simply without documented outcomes [108]. In general, however, for PFSs with a long history of use without incident, the risk for drug interactions is likely to be low.

In summary, it may be concluded that the safety of using most herbs with drugs is not well established and most of the current evidence for interactions is based on case reports while systematic investigations are missing. Therefore, it is difficult for consumers to make an informed decision. Hence, health-care professionals and consumers should pay more attention toward interactions between any PFSs and a drug, especially those patients using medications that have a narrow therapeutic range (i.e., warfarin, digoxin), as they are at greater risk for adverse outcomes because of PFS-drug interactions. Furthermore, health-care professionals must always question patients about use of herbal products.

Efficacy Aspects of PFSs

PFSs cover a wide range of applications involving, therefore, a wide range of plants. Some preparations contain only one ingredient, which may be either an extract (or concentrate) of a single plant, while other PFSs are combinations of several plants. In general, the number of studies carried out in the field of dietary supplements for non-vitamin, non-mineral products, especially herbs, is significantly fewer than those for vitamin-mineral supplements [13]. Systematic reviews and meta-analyses supported efficacy for St. John's wort for mild but not severe depression, ginkgo for existing dementia, garlic for hypercholesterimia, and saw palmetto for benign prostate hyperplasia. Moreover, ginger was found to be effective for nausea, hawthorn leaf/flower for mild heart failure, and feverfew for migraines. On the other hand, the efficacy evidence was mixed for echinacea for cold, ginseng for physical performance, and green tea for cancer [13,110–123]. With regard to PFSs used for menopausal symptom relief, including black cohosh and plant extracts with supposed estrogenic activities as soy bean, the scientific evidence of efficacy is scarce and highly variable [124]. Hence, black cohosh revealed not to be superior to placebo for menopausal symptoms and relief of hot flashes in recent clinical trials [125]. In case of soy bean, the North American Menopause Society concluded that soy-based isofla-

vones are modestly effective in relieving menopausal symptoms. On the other hand, a meta-analysis of the use of soy bean supplements for hot flashes showed a statistically significant decrease in hot flashes, in spite of questionable clinical efficacy [126, 127]. In turn, another review published by the Cochrane Collaborative on 43 randomized controlled trials concluded that there was no conclusive evidence that soy supplements reduced menopausal hot flashes [128]. However, it should be pointed out that the proven efficacy or non-efficacy can only be assigned to the composition of the herb included in that specific study and cannot be generally extended to another extract of the same species properly with a different composition and different preparation procedure. Therefore, scientific studies on the effects of a specific PFS can differ according to the species of plants used in the product, the sources of the botanical, how the botanicals are prepared, how the product is formulated, and how the product is standardized. Each of these variables can affect the biologic effects of PFSs and the outcome of a scientific study. As much scientific evidence often suffers from poor methodology, inconsistent outcome measures, and conflicting results, larger placebo-controlled clinical trials are needed with fully standardized extracts before questions of efficacy can be reliably answered [13, 97].

In a study on Internet marketing carried out in the United States, more than half of the products were found to have misleading labels illegally claiming to treat, prevent, diagnose, or cure specific diseases, indicating that although prohibited by regulations, illegal and erroneous marketing claims for PFSs are common [13, 129, 130]. In this context, the FDA has cited manufacturers of hundreds of products for promising relief from a wide variety of diseases including diabetes, heart disease, HIV/AIDS, and cancer in recent years [26]. However, there are also reports of deceptive marketing of products sold in European retail stores and on websites [129]. This is reflected in the health claims made for ginkgo promising improved blood circulation, effects on symptoms of age, and improved memory with statements like the following that could not be substantiated for Dutch PFSs containing *G. biloba*: “helps for cold hands and feet”; “improves memory”; “natural memory booster”; “protects against symptoms of old age”. In fact, the WHO monographs indicates the use of *G. biloba* for symptomatic treatment of mild to moderate cerebrovascular insufficiency, improvement of pain-free walking distance in patients with peripheral arterial occlusive disease, and treatment of inner ear problems like tinnitus. However, these are medical claims supported only by the most widely cited two extracts in the scientific literature—EGb761 and LI1370 (being standardized extracts of dry *G. biloba* leaves extracted with acetone and water containing 22–27% of flavones glycosides and 5–7% of terpene lactones with 2.8–3.4 ginkgolide A, B, and C, and 2.6–3.2% of bilobalide as well as concentrations of ginkgolic acids below 5 ppm)—and are prohibited for PFSs. In the study assessing the health claims of 29 herbal supplements containing ginkgo, conducted in the time from August to September 2005 in the Netherlands, 25 products mentioned claims for positive influence on memory and/or concentration or improvement of blood circulation. Only four products did not have any claims on the label. For 16 products, the detailed content and the recommended dose was declared on the label, whereas the declaration for the other 13 products was unclear insofar that the rec-

ommended dose was stated, but not the amount of flavonoid and terpene lactone. When the components of the PFSs were evaluated according to the guideline for pharmaceuticals that requires the presence of 90–110% of the declared amount, only one out of the 29 PFSs met this criterion. Moreover, 16 products did not meet the dose range for terpene lactones and flavonoids for a 24% standardized extract [131]. Such unauthorized claims mislead consumers into buying the advertised products and subject them to unknown risk with no clear evidence of efficacy.

Consumers may be also misled by outdated literature or references to *in vitro* studies performed at dosages that can never be achieved in humans following oral administration. This was particularly evident for some studies cited by the manufacturers in the case of PFS products using an AKBA-enriched extract. Hence, the literature referred to highlighted the 5-LO inhibitory effect of AKBA *in vitro*, although it was recently shown that AKBA never approaches the concentrations needed to modulate the addressed target even when large dosages of AKBA were administered due to lack of sufficient absorption [36].

Furthermore, the potential for toxicity originating from certain herbs is compounded by the frequent use of misleading marketing information. For example, a systematic review of bitter orange for weight loss identified only one methodologically flawed study examining the effect of the herb, which incorrectly reported a statistically significant benefit for weight loss, whereas the herb was not more effective than placebo. This misleading article was often cited as “published scientific evidence” of the efficacy of bitter orange for weight loss without mentioning the side effects [13, 132].

In summary, there is vague evidence for the efficacy of PFSs [133]. Nevertheless, consumers are not held back from consuming PFSs even by the warning statements mandatory for PFSs in the United States and the negative reports from market analysts regarding adulteration and poor quality of some PFSs on the market [52]. Therefore, measures have to be taken to increase the quality and the reliability of these products in spite of the challenges generally associated with PFSs.

Challenges Associated with PFSs

In view of the increasing use of PFSs, it is essential to understand that, being botanicals, there are in fact very different challenges for PFSs that need to be resolved [134], as can be depicted from the above with regard to the following.

Quality

- The quality of the products on the market may be a great issue.
- In the absence of standardization, comprehensive product analysis cannot ensure batch-to-batch product reproducibility.
- Different parts of the plant, stem, leaf, or root provide different quantities of active ingredients.
- The composition of products derived from the same botanical drug will differ unless very similar extraction and processing steps are followed. Moreover, other factors like environmental conditions (e.g., soil type, year of growth, geographic location, climate, plant selection, and cultivation) play an important role, leading to content variability.

- The general lack of knowledge about the active ingredients in herbal material makes it difficult to anticipate which individual components are critical for product characterization and reproducibility.
- Often, supplements are standardized to the content of single irrelevant phytoconstituents, while the contents of nonstandardized constituents may vary widely between products and even within manufactured lots.
- Unless active ingredients are known, any dissolution or shelf life testing would have to rely on marker compounds with probably different solubility or stability profiles compared to unidentified bioactive constituents.
- Clear, well-established reference standards are missing for chemical fingerprinting.
- Whereas some marker/bioactive compounds are commercially available for some of the major PFSs, many others are not.
- Methods for the quality control of finished PFSs remain far more complex than for other synthetic pharmaceuticals; especially for mixture products, it is difficult to ascertain the inclusion of all plants. Multiple analytical approaches may be required to provide sufficiently comprehensive information.
- Analysis for the absence of all undeclared pharmaceutical compounds is difficult to perform because of the large number of pharmaceuticals and novel analogues.
- Penalties imposed for adulteration are not proportionate to the infringements committed, so they do not have a deterring effect.

Nevertheless, despite these hurdles, it has to be mentioned that there has been already a notable progress in the development of advanced methods to qualitatively and quantitatively measure ingredients and screen for contaminants and adulterants in PFSs [18,135]. With a more routine application of such methods in conjunction with the emergence of accessible product-specific fingerprint databases, it is expected in the future that the scientific authentication of botanical products and identification of candidate compounds, adulterants, or contaminants will become much easier.

Discrepancy between *in vitro* results and observed *in vivo* effects

- The use of high concentrations of single constituents in *in vitro* studies, although in fact the PFS is a complex mixture, can result in exposing the *in vitro* system to exaggerated and unrealistic conditions, as compounds in a mixture may have additive or antagonistic activities that may not be apparent when an entity is tested in isolation [136].
- Testing PFS components in cell culture for metabolism or transport studies can prove extremely difficult when single components are essentially insoluble in different solvents.
- The potential influence of excipients, generally regarded as inert, which are added into various oral dosage formulations including lactose, starch, microcrystalline cellulose, stearate lubricants, and others when performing *in vitro* or *in vivo* assessments of drug interactions, are seldom considered [137].
- Additionally, the variability between what are supposed to be the same products, the lot-to-lot variability, and the differ-

ences in recommended dosage, dose frequency, and duration of dosing regimens make extrapolations of *in vitro* findings to the *in vivo* situation exceedingly difficult [138].

Safety assessment

- Poor quality of data reported to regulatory agencies is a common challenge. This pertains especially to questionnaires of adverse drug reactions regarding liver toxicity that are not specific for toxic liver diseases and the uncertainty associated with unregulated PFSs with regard to the ingredients actually included as well as the dosage regimen and comedication [139].
- As a specific and valid diagnostic laboratory marker for herb-induced liver injury and drug-induced liver injury is lacking, the diagnosis of herb-induced liver injury and drug-induced liver injury requires a thorough clinical assessment and an appropriate diagnostic algorithm like the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method scale that considers specific hepatotoxicity characteristics. Often insufficient efforts are made to assess and exclude alternative causes [140].
- A frequent problem encountered in the conduction of *in vitro* studies for possible interactions is the uncertainty in assigning conclusive hepatic concentrations of multiple constituents and their potential metabolites, accounting for oral bioavailability and first-pass metabolism. Consequently, the evaluation of existing literature turns out to be difficult in view of using inappropriately high concentrations of single isolated constituents in *in vitro* studies when only a small fraction may be actually bioavailable [138].
- There is lack of scientific evidence to evaluate safety and efficacy of PFSs.
- The long history of safe use of botanicals does not include society's current use of prescription and over-the-counter medications [134].
- There is currently more speculation than fact in the area of safety assessment of PFSs [137].
- In some instances, safety issues can arise from confusion due to similarity in the popular names used for certain plants. A prominent example is the potential for confusion of black cohosh (*C. racemosa*) and blue cohosh (*Caulophyllum thalictroides* [L.] Michx., Berberidaceae) [134].
- No sufficient safety information is provided with the products.

Clinical data

- The same complexity valid for dissolution testing applies also to the determination of the bioavailability of PFSs [134].
- For almost all PFSs, there is little or no adequate pharmacokinetic data available, and of the small numbers that are available, overall conclusions are limited because of the use of different formulations, different or unknown dosages, and differences in measured analytes [138].
- Publication bias resulting from positive studies receiving preferential treatment may lead to a selective overestimation of the health benefits of some PFSs.
- Clinical trials on PFSs are often small in size and of short duration.

- A great variability between published outcomes from apparently similar studies is often seen in meta-analysis of randomized controlled trials due to differences in the study design, in the doses administered, in the products tested, in the product delivery, in outcome assessment methods, or in the participant population [141].
- Additional critical issues include nonlinear dose response curves for many products and inter-and intra-individual differences in bioavailability and other responses to PFSs and their constituents [142].
- Consumers are inundated by flyers, pamphlets, and books promoting specific herbs or products that are often laden with considerable hyperbole or exaggeration in the claims made for anticipated benefit [134].

Vigilance

- Meaningful, functional, and effective adverse events reporting and post-marketing surveillance systems are absolutely critical. Primarily reports and whatever data are received are recorded, but often, follow-up investigations are necessary to establish or eliminate linkage of the reported adverse effect to the PFSs in question [134].
- Potential acute toxicity remains a potentially serious risk in case of unregulated products.

Given these challenges and scarce data on efficacy and safety of PFSs, the overall usefulness of PFSs may be put into question. However, it has to be taken into consideration, that in times of declining licensing of herbal medicines in Europe because of regulatory constraints and the dietary supplement status of herbal products in the United States, PFSs often represent the only way to enable the consumer access to promising herbal products.

Exemplary Herbs of Encouraging Benefits

An example is frankincense, which is experiencing a continuous increase in sales due to its anti-inflammatory properties in times of growing prevalence of symptoms like joint pain in a progressively aging Western population [143, 144]. In fact, it was shown that a number of pivotal enzymes in inflammation like 5-LO, cathepsin G, and microsomal prostaglandin E synthase-1 as well as NF- κ B and several cytokines like TNF- α , IL-1 β , and IL-6 are inhibited by BAs, the main active ingredients of *Boswellia serrata* Roxb. ex Colebr. [143]. Moreover, the reputation of BAs as potential pharmaceutical candidates found support in numerous studies [145]. A search in the frame of the EC-funded PlantLIBRA project retrieved six human studies reporting positive effects of *B. serrata* on several biomarkers such as nitric oxide, malondialdehyde, leukotriene C4, metalloprotease-3, eosinophil counts, leukocyte infiltration, etc. versus two studies with no observed benefit for erythrocyte sedimentation rate and leukocyte count. Moreover, positive results on hard endpoints like pain, ulceration, and disability score were reported in nine human studies versus two studies without benefits on joint score and knee circumference. Of course, the studies carried out so far with *B. serrata* are insufficient, and there are many drawbacks hampering the assessment of the beneficial health effect like insufficient characterization of

the *Boswellia* extract administered and heterogeneity in dosing and time of exposure between the studies as well as small sample size and incomplete reporting of data. However, all outcomes support the positive effects of *B. serrata* [146]. This is in agreement with the outcome of a previous review on all randomized clinical trials with *B. serrata* extracts, suggesting that the evidence for the effectiveness is encouraging [147].

Other promising PFSs are those containing curcuminoids or curcumin that are considered the active principles of the golden spice turmeric (*C. longa*). Extensive research over the past half-century has shown that curcumin (diferuloylmethane) can modulate numerous signaling molecules such as apoptotic proteins, pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, NF- κ B, cyclooxygenase-2, 5-LO, C-reactive protein, prostaglandin E2, adhesion molecules, phosphorylase kinase, transforming growth factor- β , triglyceride, creatinine, aspartate amino transferase, and alanine amino transferase) in human participants. The clinical trials conducted thus far have indicated promising effects of curcumin in patients with various pro-inflammatory diseases including arthritis, atherosclerosis, cardiovascular diseases, and cancer, just to mention a few. Also, the beneficial effect of curcumin in improving lipid profiles in patients with acute coronary syndrome, as well as its protective action against hepatic conditions and alcohol intoxication, has been demonstrated. Common to all these studies have been the safety, tolerability, and nontoxicity of this polyphenol, even at doses up to 12 g/d. However, poor bioavailability was revealed to be a major limitation to the therapeutic efficacy [148]. Hence, various formulations of curcumin have been developed for PFSs, including nanoscaled micellar formulations that have resulted in enhanced bioavailability combined with better therapeutic activity [149]. Last but not least, the FDA has approved curcumin as being generally recognized as safe. Meanwhile, it is being used as a supplement in several countries, often in combination with *Boswellia* [148]. Based on these findings, it may seem that curcumin's clinical efficacy is too good to be true. Nevertheless, the pharmaceutical industry remains reluctant in carrying out further clinical studies essentially needed to provide a deeper understanding of curcumin's therapeutic potential that might help placing this molecule at the forefront of novel therapeutics.

The main reason for this reluctance on the part of the pharmaceutical industry is the strict regulation environment for the registration of HMPs, which, on the one side, results in a high level of consumer protection but, on the other side, represents major burdens for applicants often connected with high costs in times of a rapidly growing competition with the supplement sector. As long as this regulation environment remains unchanged, the tendency remains and will even increase to position the majority of potential phytoactive principles in the food area as PFSs or other registration tracks [4, 8, 150]. Consequently, many promising multitargeted, innocuous, inexpensive, and readily available PFSs will remain under-investigated, never finding their way in being acknowledged as medicinal products.

PFSs Caught in the Trap between Diet and Drugs

From the analysis in the present paper, it is clear that, on the one side, the current regulatory and legal situation in the EU is still far away from harmonization that would make it possible for all European citizens to benefit from traditional medicinal products and food supplements under, if not identical, at least comparable conditions [10]. On the other side, most of the problems associated with the use of traditional and herbal medicines arise mainly from shifting these products as PFSs into the food sector. Although it is a general obligation of EU food law that all foods placed on the market are safe, there is no harmonized requirements for foods containing botanicals to comply with specific safety and quality standards (e.g., GMP) as it is common practice for THMPs or botanical dietary supplements in the United States. Adhering to the food law that is not as strictly regulated as the drug law, which contains additional regulatory provisions for protection of the consumer's health, PFSs are not subject to a strict pre-market and post-market control. As such, evidence of quality, efficacy, and safety of these PFSs is not required before marketing and no proper vigilance is carried out after marketing.

In fact, herbs and similar nutritional substances are consumed differently from conventional food and are not authentic supplements like multivitamins or minerals that have nutritional value. Being composed of phytoactive principles extracted from herbs that are concentrated and administered in a suitable pharmaceutical form such as tablets or capsules, they are rather used worldwide in daily practice as medicine. In reality, however, they represent an intermediate stage between diet and drugs. From a personal point of view, there is hence an urgent need for modifying the regulatory framework for PFSs enabling a more stringent control of product's quality and safety, which in turn should also ultimately result in more evidence-based uses. Insofar a new class of regulation requirements being facilitated compared to HMPs but more strictly regulated compared to PFSs may be defined and qualified for these intermediate stage products in order to compensate for the lack of regulation in this area. These regulations should focus on providing the consumer with high-quality PFSs and accurate and transparent information about the contents, efficacy, and safety of PFSs.

However, despite calls for change from many quarters, including industry, there has been little progress in the regulation of herbal supplements. This is in part because the perspective and interests of various parties are in direct conflict; whereas some manufacturers support a weakening of standards, medical professional groups would like to see them strengthened [26]. Nonetheless, the consumer has the right to obtain and the industry has an unquestionable responsibility to provide consumers with truthful, meaningful, understandable, and not misleading information about PFSs.

Proposals for immediate and long-term actions

Of course, there are a lot of reputable PFS companies, but the consumer is unable to cope with the different qualities of PFSs on the market. In addition, misleading products of poor quality undercut

legitimate manufacturers and distributors who painstakingly provide high-quality products. Based on that background, the utmost priority should be to furnish the general public including health-care professionals with adequate information to facilitate better understanding of the benefits and risks associated with the use of these products and to ensure that all PFSs are safe and of suitable quality.

Therefore, in terms of the consumer's health and safety, the following immediate actions, proposed previously by Kapoor and Sharfstein and strongly supported by the author, should be mandatory [26]:

- Implementation of standard manufacturing procedures for PFSs accompanied by standardized laboratory techniques for quality control.
- Truthful, not misleading, labeling providing an accurate list of all ingredients.
- Stronger disclaimers on the outer package clearly highlighting that PFSs are not intended to diagnose, treat, cure, or prevent any disease and pointing to the consumer missing scientific evidence for propagated effects using declarations like "this statement has not been evaluated by the regulatory authority".
- Inclusion of a detailed, approved leaflet in each package.
- Strengthened surveillance of potential adverse effects.

By this way, the public might be able to expect full disclosure of key safety information when purchasing a PFS. In addition, from a personnel point of view, the following aspects should be considered at a minimum on the longer run in terms of quality, safety, and efficacy as well as vigilance.

Quality

In response to concerns regarding quality assurance, the FDA recently instituted the requirement that, in the United States, botanical dietary supplements be prepared using GMP [135]. Similar to the United States, the industry of PFSs in Europe should also implement and adhere to GMP. This is necessary because the final quality of the product on the shelf is dependent on the quality of raw material and the quality of the extraction, formulation, and manufacturing process. Also, the safety and benefits of a product are directly related to its quality. In view of the fact that an analysis screening for all undeclared pharmaceutical compounds cannot be easily performed because of the large number of pharmaceuticals and novel analogues, quality-control standards must be defined for dietary supplements made from plant sources to ensure and verify the content and consistency of products. This in turn precludes the development of standardized validated analytical methods. Compendial standards may serve as appropriate references for conducting tests or examinations. Therefore, whenever possible, quality control should be performed according to pharmacopoeial monographs like the Dietary Supplements Compendium or the Herbal Compendium in the USP that establishes standards for the identity, strength, quality, and purity of herbal products. The current revision of the USP-NF includes almost 500 monographs for dietary supplement ingredients and finished dietary supplements. They may be referred to as specifications agreed in contractual agreements between buyers and sellers in

international trade and serve as uniform points of reference for regulators and manufacturers, thus promoting consumer confidence [95]. Another measure of the quality of finished goods that should be considered is whether the product breaks down, dissolves, and is bioavailable after oral ingestion. Hence, PFS manufacturers must also test their formulations for disintegration and dissolution prior to marketing.

Moreover, any anticipated changes of extraction or cleanup procedures must be made only with due consideration of the fact that these changes may significantly alter the content of a preparation and may obviate reliance on any history of the botanical's safe use because of different levels of physiologically active ingredients. Hence, the safety and benefit of new preparations, if significantly different from established preparations, should be verified by appropriate testing.

In summary, PFS manufacturers should pay close attention to the following:

- Good agricultural practice for cultivated herbs in order to reduce the risk of contamination by pesticides, heavy metals etc.
- Implementation of GMP from the moment the ingredients are harvested from the ground in order to reduce the likelihood of contaminants like pesticides or heavy metals to the minimum.
- Accurate identification and authentication of the starting material by their scientific names (latin binomial) in the form of voucher specimen in order to ensure chemical uniformity. This is important because common names are inadequate and often refer to more than one species.
- Verification of identity, integrity, and homogeneity of any PFS raw material supply, whether fresh, dried, or ground powder using taxonomic, chemotaxonomic, macroscopic, organoleptic, microscopic, and/or chromatographic analysis and DNA tests.
- Implementation of quality-control measures ensuring the correct levels of active and/or marker compounds in the raw material/extract and the absence of unacceptable or unlawful levels of pesticides, heavy metals, and contaminants using standardized reliable, rugged, reproducible, and validated methods prior to formulation of the PFS. Further, the plant material or extract must be checked for the absence of adulterant plant species. DNA techniques complemented with other orthogonal techniques may be powerful tools for authentication of plant material at the early stages of processing. It is also advisable to use several screening techniques to maximize the potential for adulteration detection, because no single methodology is universally applicable as described in the General Chapter <2251> Adulteration of Dietary Supplements with Drugs and Drug Analogs in the USP.
- Use of pharmaceutical-grade or standardized herbal material.
- Implementation of quality-control measures ensuring homogeneous composition of formulation batches and dosage forms through entire manufacturing runs and between runs in order to ensure consistency and proper quantity of content in the product reaching the consumer.
- Inclusion of a shelf life stability testing program for finished products.
- Ensuring good practice along the entire supply chain that should be verified by repeated vendor audits, as supply chain transparency when properly documented provides stringent quality assurance at each link of the supply chain.
- Implementation of a PFS adulteration database based on the incidences of PFS adulterations to provide an easily searchable public database of the risks of adulteration and the available detection methods.

As not all PFSs represent the same quality, the establishment of a voluntary third-party verification program may represent a powerful tool to demonstrate the quality of a product. Like the USP dietary supplement verification service, such a voluntary third-party verification program should include an on-site facility audit for compliance with GMP, a thorough review of manufacturing and quality-control product documentation, comprehensive laboratory testing for conformance to dietary supplement standards found in the USP-NF, continuous change control monitoring, and off-the-shelf surveillance testing of randomly selected samples of products to confirm that USP-verified products continue to meet the USP's stringent standards [95]. High-quality PFSs meeting the stringent requirements of the verification process could be provided with a quality seal similar to the USP seal given to dietary supplements in the United States that have been proven to:

- contain the ingredients listed on the label in the declared potency and amount
- not contain harmful levels of specified contaminants
- break down and release into the body within a specified amount of time
- have been manufactured according to GMP

Such third-party verification can thus add another level of security and can help the consumer distinguish between high- and low-quality products.

Besides improving quality and consistency of its products, the PFS industry should also invest in research and in developing a stronger foundation of credible data to support its products. Hence, studies on PFSs as single or combined phytocomplexes, as well as the need for assessing their mechanism of action, are very much needed. At the same time, there is a need of clinical data substantiating any health-related claim. This aspect and the evaluation of safety, possible unwanted side effects, and possible interactions with prescriptions drugs or with food should become a major issue. The EC-funded project PlantLIBRA, which aims to foster the safe use of food supplements containing botanicals or their preparations by evaluating the quality and health benefits of PFSs and by increasing science-based decisions by regulators and food-chain operators, marks a first step in the right direction.

Efficacy

If not yet realized, clinical trials using PFSs should be supported by rigorous preclinical data on molecular mechanisms and better data on safety, pharmacokinetics, and metabolism in both healthy and, where appropriate, more application-relevant human populations. The mechanistic data should include strong evidence pinpointing the key bioactive components and the critical molecular targets in the organism [151]. Of course, the most critical element will be to define specific standards for PFSs to ensure consistency

between studies. As it might be difficult to identify the active constituents in a complex mixture, a comprehensive characterization is particularly important in case of complex mixtures, where identities of the bioactive components and their mechanism of action are not fully understood. In this case, considering a well-characterized mixture *in toto* instead of isolated compounds might represent the shortest road to success. In any case, however, a proper selection of the formulation and dosage as well as careful identification and control of significant variables is indispensable in terms of the so much needed better design of clinical trials.

In order to deal with the backlog of several thousand of herbal products that have limited evidence of safety and efficacy, more funding should be provided for more studies focusing on the efficacy and safety of herbs, not vitamins and minerals that have often established efficacy. It is also advisable to make use of modern techniques like the Internet to recruit subjects for clinical studies faster [13]. Hence, in a recent study conducted entirely of the Internet, investigators were able to recruit and enroll 391 patients in just one week [152].

As PFS manufacturers do not have the resources to conduct these costly studies needed to secure approval of a claim, some form of patent protection should exist so that manufacturers who invest in expensive studies and document the efficacy of their products could be rewarded financially. This approach might leverage large research investments for PFS manufacturers.

Based on the background that consumers do not make the anticipated distinction between substantiated and non-substantiated health claims, it might be helpful to create online efficacy tables monitored and evaluated by expert scientists to facilitate for the consumer the grading of a certain PFSs.

Safety

Altogether, it is clear, that “natural” does not equal “safe” and that PFSs may contain compounds of concern at levels far above those found in the regular diet. On top of this comes the fact that the TU of a PFS compound as a herb or tea does not guarantee its safety when used as a supplement. Nevertheless, a formalized framework for the safety assessment of PFSs is not in place yet, and safety assessments are performed rather on a national and *ad hoc* basis or by dedicated bodies like, for example, the EMA. The latter, however, judges the safety of medicinal preparations and does not refer to the safety of PFSs in the field of food use. Besides, even when regulatory measures are in place, PFSs containing compounds of concern may still be offered for sale on the Internet [78].

Therefore, given the expanding market of PFSs, clear criteria for control and safety assessment of PFSs should be established and prohibited, and restricted herbs should be clearly defined. This might include, where justified, mandating safety tests similar to those required for over-the-counter drugs including the Ames test, 90-day feeding studies during which the animal receives very high doses of the supplement, a two-generation feeding study that determines if the supplement is likely to have adverse effects on the next generation of the animal ingesting the product, and long-term studies lasting more than two years. On the other hand, botanicals or botanical preparations for which an adequate body of knowledge exists could benefit from a “presumption of

safety” without any need for further testing as proposed by the EFSA guidance on safety assessment of botanicals and botanical preparations [51]. For food supplements consisting of complex mixtures of different botanicals, safety assessment could be carried out on the levels of individual substances of concern known to be present, taking into consideration the limitation that such an approach does not generally allow the assessment of possible synergistic or antagonistic effects. Any data on possible herb-drug interaction should be also carefully considered [51].

Vigilance

There is a great need for more careful vigilance to identify, clarify, and elaborate any unwanted side effects or important PFS-drug interactions. Therefore, the establishment of an industry independent vigilance system should be given top priority, ensuring that data are reported comprehensively and transparently.

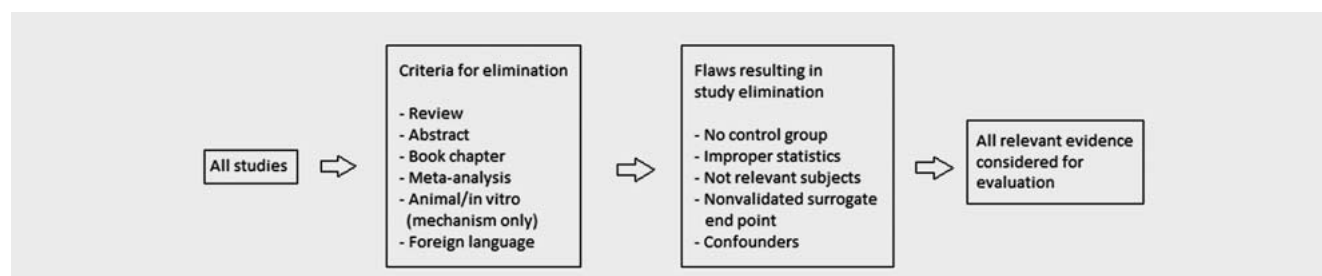
Hence, following the example of the United States, supplement manufacturers should be urged to report, including information about the reporter, the injured party, the product, the adverse event, and the manufacturer of the PFS, serious adverse events like death, life-threatening experiences, in-patient hospitalization, persistent or significant disability, congenital anomalies, and medical or surgical interventions to prevent an adverse outcome within 15 business days [18]. This information should be collected in suitable databases that are digitally interconnected in order to be able to process large amounts of global data quickly. In addition, all serious adverse effects of a supplement should be listed on a website so that consumers can have immediate access to this information.

Moreover, consumers should be encouraged to tell their health-care professionals about the use of PFSs, and practitioners should consider initiating such discussions. However, all these measures do not take away from the necessity for accurate and complete written information about precautions, interactions, and side effects to be provided to consumers when buying PFSs.

Last but not least, significant consequences should be levied against manufacturers whose supplements are misbranded or adulterated so that manufacturers are motivated to follow a stricter regulatory system as such described above.

Proposal for a new regulatory framework

In the end, there is no scientific basis for calling herbals supplements. Being non-vitamin, non-mineral ingredients, PFSs are neither food nor drugs. Therefore, from a personnel point of view, they should be liberated from either designation and assigned a separate regulatory category. Such a new regulatory category, which might be called “phytoceuticals”, “botaceuticals”, or “herbaceuticals”, should be restricted to herbal substances and products thereof that are not considered an essential or conditionally essential nutrient in the human diet but are believed to have beneficial effects on health. These beneficial health effects may be based on promoting human health by way of amplifying specifically relevant bodily functions through their ability to mimic natural human related biochemical substances or preventing the onset of pathologic conditions, which in turn helps to avoid or delay the need to use pharmaceuticals. Also, THMPs might be assigned to this new category, as from a legal point of view the plausibility of



► **Fig. 1** Exemplarily overview for filtering out not qualified studies following an evidence-based review process proposed by the FDA [154].

TU associated with THMPs alone may be insufficient to support a certain pharmacological effect. Hence, the actually available THMPs are in fact not medicinal products by function but by presentation only [8]. This suggested new product category could be also implemented in the United States if the DSHEA is reformed accordingly, restricting the definition of dietary ingredients to vitamins and minerals intended to supplement the diet.

In deviation from the current situation for PFSs, this new regulatory product category, which is referred to in the following for simplicity reason as “phytoceuticals”, should undergo a pre-marketing review and approval process, whereby manufacturers have to submit safety and effectiveness data. Ideally, the review and approval process should be carried out by a specially designated scientific commission set up of experts in this field for this purpose, and the fees should be sufficiently low compared to drug authorization.

Evaluations of scientific evidences for any claimed health benefits for “phytoceuticals” should preferably proceed according to an evidence-based review process as described by the FDA, which is already increasingly applied for the evaluation of the strength of scientific evidence for nutrition-related topics [153]. An exemplarily overview how to filter out non-qualified studies following such an evidence-based review process is demonstrated in ► **Fig. 1** [154].

By this way, the totality of scientific evidence is only derived from qualified studies suitable for scientific conclusions to be drawn, thus ensuring an objective, transparent, and rigorous process for evaluating scientific evidence.

Moreover, periodic tests should be initiated by this commission to ensure the contents match those listed on the label. While such stricter regulations would surely help the safety of PFSs, additional efforts are needed, as mentioned above, to improve and promote high-quality research. Therefore, this commission should preferably also develop programs specifically addressed to encourage well-designed clinical research in this new area. A similar approach is already pursued in the United States in the form of the Office of Dietary Supplements established at the NIH, the mission of which is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public [155]. The realization of a comparable perspective plan in Europe could thus trigger new insights in the field of “phytoceuticals”, a new product category, acting beyond the diet and before drugs and encouraging the use of proactive medicine to

prevent better than to cure pathological conditions arising from wrong diet and lifestyle.

The above-mentioned possible measures may help protecting public health by ensuring safe PFSs of suitable quality. Until, however, the above proposed modifications in handling of PFSs are implemented in total or in part, the consumer is still spoilt for choice of the right PFSs. Hence, the questions arise for the consumer how to judge on the great variety of PFSs available on the market and how to distinguish between high- and low-quality products, especially as the number of well-researched, high-quality products on the market continues to grow!

What is a Good PFS?

A trustworthy PFS should have a short ingredient list to ensure the ingredients have the chance to be present in physiologically relevant amounts. This is important because supplement manufacturers are namely required to list ingredients in order of fractional content—that is, the first listed ingredient is present in the highest amount. Furthermore, providing voluntary chemical composition data may help to demonstrate that the manufacturer has attempted quality control. Package claims referencing reliable peer-reviewed journal articles can be another marker of quality [156]. Last but not least, the principle applies “hands off of PFSs that sound too good to be true”, as they in fact probably are.

Conclusion

The use of PFSs has grown steadily over the last 20 years despite incomplete information regarding active constituents, mechanisms of action, efficacy, and safety. Hence, PFSs have become an integral part of health management, which may be attributed to the current consumer perception that “natural is good”, the greater costs of many HMPs, the insistent marketing campaign, and the increasing perception of the need of a healthy diet. However, lack of product quality and the adulteration of PFSs, especially those sold via the Internet remain a question of concern. Furthermore, safety issues such as possible PFS-drug interactions remain unaddressed for most PFSs, and only few rigorously designed clinical trials have shown efficacy.

Assigning PFSs a new regulatory category in between drugs and diet can help protecting the consumer’s right, and enforcing the industry to provide high-quality, effective, and safe PFSs with truthful not misleading labels. Such newly regulated “phytoceuti-

cals”, “herbaceuticals”, or “botaceuticals” may then become a key player as a tool for expanding proactive medicines, representing a promising approach to prevent disease onset and a money saving tool for national health systems facing more and more long-term chronic health conditions.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Biagi M, Pecorari R, Appendino G, Miraldi E, Magnano AR, Governa P, Cettolin G, Giachetti D. Herbal products in Italy: the thin line between phytotherapy, nutrition and parapharmaceuticals; a normative overview of the fastest growing market in Europe. *Pharmaceuticals* 2016; 9: E65
- [2] Cranz H, Anquez-Traxler C. TradReg 2013: regulation of herbal and traditional medicinal products-European and global strategies-international symposium. *J Ethnopharmacol* 2014; 158: 495–497
- [3] Global Industry Analysts, Inc. Global herbal supplements and remedies market to reach USD\$107 billion by 2017, according to new report by Global Industry Analysts, Inc. PRWeb. Available at http://www.prweb.com/releases/herbal_supplements/herbal_remedies/prweb9260421.htm. Accessed May 30, 2017
- [4] Minghetti P, Franzè S, Zaccara V, Raso F, Morazzoni P. Innovation in phytotherapy: is a new regulation the feasible perspective in Europe? *Planta Med* 2016; 82: 591–595
- [5] Council of the European Economic Community. Directive 65/65/EEC, 1965. Council Directive 65/65/EEC of 26. January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. *Official Journal* 1965; 22: 369–373 (09.02.1965)
- [6] Council of the European Economic Community. Directive 87/21/EEC, 1987. Council Directive 87/21/EEC of 22. December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. *Official Journal* 1987; 15: 36–37 (17.01.1987)
- [7] European Parliament, Council of the European Union. Directive 2004/24/EC, 2004. Commission Directive 2004/24/EC of the European Parliament and of the Council of 31. March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal* 2004; 136: 85–90 (30.04.2004)
- [8] Quintus C, Schweim HG. European regulation of herbal medicinal products on the border area to the food sector. *Phytomedicine* 2012; 19: 378–381
- [9] European Medicines Agency. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106706.pdf. Accessed December 6, 2017
- [10] Silano V, Coppens P, Larranaga-Guetaria A, Minghetti P, Roth-Ehrang R. Regulations applicable to plant food supplements and related products in the European Union. *Food Funct* 2011; 2: 710–719
- [11] García-Alvarez A, Egan B, de Klein S, Dima L, Maggi FM, Isoniemi M, Ribas-Berba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from PlantLIBRA consumer survey. *PLoS One* 2014; 9: e92265
- [12] Dietary Supplement and nonprescription Drug Consumer Protection Act. Public Law 109–462. Washington D.C.: United States Government Printing Office; 2006. Available at <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentsToTheFDCA/ucm148035.htm>. Accessed December 4, 2017
- [13] Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation. *J Gen Intern Med* 2008; 23: 854–859
- [14] Jiratchariyakul W, Mahady GB. Overview of botanical status in EU, USA, and Thailand. *Evid Based Complement Alternat Med* 2013; 2013: 480128
- [15] Food and Drug Administration. Dietary Supplement Current Good Manufacturing Practices (CGMPs) and Interim Final Rule (IFR) Facts. Available at <https://www.fda.gov/Food/GuidanceRegulation/CGMP/ucm110858.htm>. Accessed July 17, 2017
- [16] Pawar RS, Handy SM, Cheng R, Shyong N, Grundel E. Assessment of the authenticity of herbal dietary supplements: comparison of chemical and DNA barcoding methods. *Planta Med* 2017; 83: 921–936
- [17] Smith T, Kawa K, Eckl V, Morton C, Stredney R. Herbal supplement sales in US increase 7.7% in 2016. Consumer preferences shifting toward ingredients with general wellness benefits, driving growth of adaptogens and digestive health products. *HerbalGram* 2017; 115: 56–65
- [18] Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. *Int J Mol Sci* 2016; 17: 331
- [19] Lüde S, Vecchio S, Sinno-Tellier S, Dopter A, Mustonen H, Vucinic S, Jonsson B, Müller D, Veras Gimenez Fruchtingarten L, Hraby K, De Souza Nascimento E, Di Lorenzo C, Restani P, Kupferschmidt H, Ceschi A. Adverse effects of plant food supplements and plants consumed as food: results from the poisons centres – based PlantLIBRA study. *Phytother Res* 2016; 30: 988–996
- [20] Kennedy J. Herb and supplement use in the US adult population. *Clin Ther* 2005; 27: 1847–1858
- [21] Peters CL, Shelton J, Sharma P. An investigation of factors that influence the consumption of dietary supplements. *Health Mark Q* 2003; 21: 113–135
- [22] Egan B, Hodgkins C, Shepherd R, Timotijevic L, Raats M. An overview of consumer attitudes and beliefs about plant food supplements. *Food Funct* 2011; 2: 747–752
- [23] Brevort P. The booming US botanical market: a new overview. *HerbalGram* 1998; 44: 33–48
- [24] Václavík L, Krynský AJ, Rader JI. Mass spectrometric analysis of pharmaceutical adulterants in products labeled as botanical dietary supplements or herbal remedies: a review. *Anal Bioanal Chem* 2014; 406: 6767–6790
- [25] Walker KM, Applequist WL. Adulteration of selected unprocessed botanicals in the U.S. retail herbal trade. *Econ Bot* 2012; 66: 321–327
- [26] Kapoor A, Sharfstein JM. Breaking the gridlock: regulation of dietary supplements in the United States. *Drug Test Anal* 2016; 8: 424–430
- [27] Booker A, Frommenwiler D, Reich E, Horsfield S, Heinrich M. Adulteration and poor quality of *Ginkgo biloba* supplements. *J Herb Med* 2016; 6: 79–87
- [28] Tawab M, Krzywon M, Schubert-Zsilavecz M. Nahrungsergänzungsmittel mit Ginkgo unter der Lupe. *Pharm Ztg* 2010; 155: 86–91
- [29] Avula B, Sagi S, Gafner S, Upton R, Wang YH, Wang M, Khan IA. Identification of *Ginkgo biloba* supplements adulteration using high performance thin layer chromatography and ultra high performance liquid chromatography-diode array detector-quadrupole time of flight-mass spectrometry. *Anal Bioanal Chem* 2015; 407: 7733–7746
- [30] Lee J. Marketplace analysis demonstrates quality control standards needed for black raspberry dietary supplements. *Plant Foods Hum Nutr* 2014; 69: 161–167
- [31] Meins J, Artaria C, Riva A, Morazzoni P, Schubert-Zsilavecz M, Abdel-Tawab M. Survey on the quality of the top-selling European and American botanical dietary supplements containing boswellic acids. *Planta Med* 2016; 82: 573–579

- [32] Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in commercial ginseng products: an analysis of 25 preparations. *Am J Clin Nutr* 2001; 73: 1101–1106
- [33] Khan IM. Issues related to botanicals. *Life Sci* 2006; 78: 2033–2038
- [34] Fitzloff J, Yat P, Lu Z, Awang DVC, Amason JT, van Breemen RB, Hall T, Blumenthal M, Fong HHS. Perspectives on the Quality Assurance of Ginseng Products in North America. In: Huh H, Choi KJ, Kim YC, eds. *Advances in Ginseng Research: Proceedings of the 7th International Symposium on Ginseng*. Seoul: The Korean Society of Ginseng; 1998: 138–145
- [35] Awang DVC, Yat PN, Amason JT, Lu ZZ, Fitzloff JF, Fong H, Hall T, Blumenthal M. The American Botanical Council's program of evaluation of 'ginseng' products on the North American market. *International Ginseng Conference 99. Ginseng: its science and its markets. Advances in biotechnology, medicinal applications and marketing*. Hong Kong, China: 1999; abstract No A17
- [36] Constantine GH, Karchesy J. Variations in Hypericin Concentrations in *Hypericum perforatum* L. and commercial Products. *Tunica: American Society of Pharmacognosy Interim Meeting*; 1999
- [37] Rocha T, Amaral JS, Oliveira MBPP. Adulteration of dietary supplements by illegal addition of synthetic drugs: a review. *Compr Rev Food Sci Food Saf* 2016; 15: 43–62
- [38] Wang J, Chen B, Yao S. Analysis of six synthetic adulterants in herbal weight-reducing dietary supplements by LC electrospray ionization-MS. *Food Addit Contam A* 2008; 25: 822–830
- [39] Carvalho LM, Martini M, Moreira AL, de Lima APS, Correia D, Falcao T, Garcia SC, de Bairos AV, do Nascimento PC, Bohrer D. Presence of synthetic pharmaceuticals as adulterants in slimming phytotherapeutic formulations and their analytical determination. *Forensic Sci Int* 2011; 204: 6–12
- [40] Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin dependent diabetes. *Obes Res* 1998; 6: 47–53
- [41] Deventer K, van Thuijn W, Mikulcikova P, Van Ecnou P, Delbeke FT. Detection of selected stimulants as contaminants in solid nutritional supplements by liquid chromatography-mass spectrometry. *Food Chem* 2007; 103: 1508–1513
- [42] Pawar RS, Grundel E, Fardin-Kia AR, Rader JI. Determination of selected biogenic amines in *Acacia rigidula* plant materials and dietary supplements using LC-MS/MS method. *J Pharm Biomed Anal* 2014; 88: 457–466
- [43] Cohen PA, Venhuis BJ. Adulterated sexual enhancement supplements: more than mojo. *JAMA Inter Med* 2013; 173: 1169–1170
- [44] Venhuis BJ, de Kaste D. Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements. *J Pharm Biomed Anal* 2012; 69: 196–208
- [45] Bogusz MJ, Hassan H, Al-Enazi E, Ibrahim Z, Al-Tufail M. Application of LC-ESI-MS-MS for detection of synthetic adulterants in herbal remedies. *J Pharm Biomed Anal* 2006; 41: 554–564
- [46] Wang J, Yang D, Wang Z, Chen B, Yao S. Simultaneous determination of illegal additives in dietary supplements and traditional medicines by high performance liquid-chromatography-electrospray ionization mass spectrometry. *Chromatographia* 2009; 70: 1353–1359
- [47] Lu YL, Zhou NL, Liao SY, Su N, He DX, Tian QQ, Chen B, Yao SZ. Detection of adulteration of anti-hypertension dietary supplements and traditional Chinese medicines with synthetic drugs using LC/MS. *Food Addit Contam A* 2010; 27: 893–902
- [48] Kim HJ, Lee JH, Part HJ, Kim JY, Cho S, Kim WS. Determination of non-opioid analgesics in adulterated food and dietary supplements by LC-MS/MS. *Food Addit Contam A* 2014; 31: 973–978
- [49] Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 2014; 4: 177
- [50] Heinrich M. Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chain. *Br J Clin Pharmacol* 2015; 80: 62–66
- [51] European Food Safety Authority. Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. 2009. Available at <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1249/epdf>. Accessed July 28, 2017
- [52] Nicoletti M. Nutraceuticals and botanicals: overview and perspectives. *Int J Food Sci Nutr* 2012; 63 (Suppl. 1): 2–6
- [53] Di Lorenzo C, Ceschi A, Kupferschmidt H, Lude S, De Souza Nascimento E, Dos Santos A, Colombo F, Frigerio G, Nørby K, Plumb J, Finglas P, Restani P. Adverse effects of plant food supplements and botanical preparations: a systematic review with critical evaluation of causality. *Br J Clin Pharmacol* 2015; 79: 578–592
- [54] Mowry JB, Spyker DA, Cantilena LR Jr., McMillan N, Ford M. 2013 annual report of the American Association of Poison Control Centers' national poison data system (NPDS): 31st annual report. *Clin Toxicol (Phila)* 2014; 52: 1032–1283
- [55] Haller CA, Kearney T, Bent S, Ko R, Benowitz NL, Olson K. Dietary supplement adverse events: report of a one-year poison center surveillance project. *JMT* 2008; 4: 84–92
- [56] Bucchini L, Rodarte A, Restani P. The PlantLIBRA project: how we intend to innovate the science of botanicals. *Food Funct* 2011; 2: 769–773
- [57] Menniti-Ippolito F, Mazzanti G, Santucio C, Moro PA, Calapai G, Firenzoli F, Valeri A, Raschetti R. Surveillance of suspected adverse reactions to natural health products in Italy. *Pharmacoepidemiol Drug Saf* 2008; 17: 626–635
- [58] Taibi DM, Landis CA, Petry H, Vitiello MV. A systematic review of valerian as a sleep aid: safe but not effective. *Sleep Med Rev* 2007; 11: 209–230
- [59] Isbrucker RA, Burdock GA. Risk and safety assessment on the consumption of licorice root (*Glycyrrhiza* sp.) its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. *Regul Toxicol Pharmacol* 2006; 46: 167–192
- [60] Leitolf H, Dixit KCS, Higham CE, Brabant G. Licorice – or more? *Exp Clin Endocrinol Diabetes* 2010; 118: 250–253
- [61] Mazzanti G, Di Sotto A, Vitalone A. Hepatotoxicity of green tea: an update. *Arch Toxicol* 2015; 89: 1175–1191
- [62] Gloro R, Hourmand-Ollivier I, Mosquet B, Mosquet L, Rousselot P, Salamé E, Piquet MA, Dao T. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. *Eur J Gastroenterol Hepatol* 2005; 17: 1135–1137
- [63] Vial T, Bernard G, Lewden B, Dumortier J, Descotes J. [Acute hepatitis due to Exolise, a *Camellia sinensis*-derived drug]. *Gastroenterol Clin Biol* 2003; 27: 1166–1167
- [64] Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl* 2006; 12: 989–992
- [65] Vannaci A, Iapi F, Gallo E, Vietri M, Toti M, Menniti-Ippolito F, Raschette R, Firenzoli F, Mugelli A. A case of hepatitis associated with long-term use of *Cimicifuga racemosa*. *Altern Ther Health Med* 2009; 15: 62–63
- [66] Zimmermann R, Witte A, Voll RE, Strobel J, Frieser M. Coagulation activation and fluid retention associated with the use of black cohosh: a case study. *Climacteric* 2010; 13: 187–191
- [67] Minicullo PL, Saija A, Patafi M, Marotta G, Ferlazzo B, Gangemi S. Muscle damage induced by black cohosh (*Cimicifuga racemosa*). *Phyto-medicine* 2006; 13: 115–118
- [68] Ingrassia A, Donohue K, Wilkel C, Falanga V. Cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh. *J Am Acad Dermatol* 2007; 56: S124–S126
- [69] Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatotoxicity. *Med J Aust* 2002; 177: 440–443

- [70] Meyer S, Vogt T, Obermann EC, Landthaler M, Karrer S. Cutaneous pseudolymphoma induced by *Cimicifuga racemosa*. *Dermatology* 2007; 214: 94–96
- [71] Svedlund E, Larsson M, Hägerkvist R. Spontaneously reported adverse reactions for herbal medicinal products and natural remedies in Sweden 2007–15: report from the Medicinal Products Agency. *Drugs Real World Outcomes* 2017; 4: 119–125
- [72] European Medicines Agency. European Community on *Cimicifuga racemosa* (L.) Nutt., rhizoma (EM/HMPC/600717/2007 Corr.). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2011/01/WC500100981.pdf. Accessed August 4, 2017
- [73] European Medicines Agency. Assessment report on *Cimicifuga racemosa* (L.) Nutt., rhizome (EMA/HMPC/3968/2008). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/05/WC500106358.pdf. Accessed August 4, 2017
- [74] Vitalone A, Menniti-Ippolito F, Moro PA, Firenzuoli F, Raschetti R, Mazzanti G. Suspected adverse reactions associated with herbal products used for weight loss: a case series reported to the Italian national Institute of Health. *Eur J Clin Pharmacol* 2011; 67: 215–224
- [75] Sultan S, Spector J, Michell RM. Ischemic colitis associated with use of bitter-orange-containing dietary weight-loss supplement. *Mayo Clin Proc* 2006; 81: 1630–1631
- [76] Haller CA, Benowitz NL, Jacob P 3rd. Hemodynamic effects of ephedra-free weight loss supplements in humans. *Am J Med* 2005; 118: 998–1003
- [77] Speijers G, Bottex B, Dusemund B, Lugasi A, Tóth J, Amberg-Müller J, Galli CL, Silano V, Rietjens IM. Safety assessment of botanicals and botanical preparations used as ingredients in food supplements: testing an European Food Safety Authority-tiered approach. *Mol Nutr Food Res* 2010; 54: 175–185
- [78] Van den Berg SJPL, Serra-Majem L, Coppens P, Rietjens IM. Safety assessment of PFS. *Food Funct* 2011; 2: 760–768
- [79] Rietjens IM, Martena MJ, Boersma MG, Spiegelberg W, Alink GM. Molecular mechanism of toxicity of important food-borne phytochemicals. *Mol Nutr Food Res* 2005; 49: 131–158
- [80] Noel JC, Anaf V, Fayt I, Wespes E. Uteral mullerian carcinosarcoma (mixed mullerian tumor) associated with endometriosis occurring in a patient with a concentrated soy isoflavones supplementation. *Arch Gynecol Obstet* 2006; 274: 389–392
- [81] Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006; 295: 2057–2071
- [82] Wolters M, Hahn A. Soy isoflavones – a therapy for menopausal symptoms? *Wien Med Wochenschr* 2004; 154: 334–341
- [83] Fritz H, Seely D, Flower G, Skidmore B, Fernandes R, Vadeboncoeur S, Kennedy D, Cooley K, Wong R, Sagar S, Sabri E, Fergusson D. Soy, red clover, and isoflavones and breast cancer: a systematic review. *PLoS One* 2013; 8: e81968
- [84] Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the US adult population: a comparison of the 2002 and 2007. *Clin Ther* 2011; 33: 1749–1758
- [85] Van der Voet GB, Sarafonov A, Todorov TI, Centeno JA, Jonas WB, Ives JA, Mullick FG. Clinical and analytic toxicology of dietary supplements: a case study and review of the literature. *Biol Trace Element Res* 2008; 125: 1–12
- [86] Stickel F, Droz S, Patsenker E, Bögli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife contaminated with *Bacillus subtilis*. *J Hepatol* 2009; 50: 111–117
- [87] Veprikova Z, Zachariasova M, Dzuman Z, Zachariasova A, Fenclova M, Slavikova P, Vackavikova M, Mastovska K, Hengst D, Hajslova J. Mycotoxins in plant-based dietary supplements: hidden health risk for consumers. *J Agric Food Chem* 2015; 63: 6633–6643
- [88] Schulz M, Meins J, Diemert S, Zagermann-Muncke P, Goebel R, Schrenk D, Schubert-Zsilavecz M, Abdel-Tawab M. Detection of pyrrolizidine alkaloids in German licensed herbal medicinal teas. *Phytomedicine* 2015; 22: 648–656
- [89] Medicines and Healthcare Products Regulatory Agency. Precautionary recall – six batches of St. John's wort tablets. Available at <https://www.gov.uk/government/news/precautionary-recall-six-batches-of-st-johns-wort-tablets>. Accessed August 7, 2017
- [90] Mathon C, Ankli A, Reich E, Bieri S, Christen P. Screening and determination of sibutramine in adulterated herbal slimming supplements by HPTLC-UV densitometry. *J Chromatogr B Anal Technol Biomed Life Sci* 2014; 967: 174–182
- [91] da Justa Neves DB, Caldas ED. Dietary supplements: international legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market. *Regul Toxicol Pharmacol* 2015; 73: 93–104
- [92] Geller AI, Shehab N, Weidle NJ, Maribeth C, Lovegrove MPH, Wolpert BJ, Babgaleh B, Timbo MD, Mozersky RP, Budnitz DS. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med* 2015; 373: 1531–1540
- [93] Reeuwijk NM, Venhuis BJ, de Kaste D, Hoogenboom LA, Rietjens IM, Martena MJ. Sildenafil and analogous phosphodiesterase type 5 (PDE-5) inhibitors in herbal food supplements sampled on the Dutch market. *Food Addit Contam A Chem Anal Control Expo Risk Assess* 2013; 30: 2027–2034
- [94] Damiano F, Silva C, Gregori A, Vacondio F, Mor M, Menozzi M, Di Giorgio D. Analysis of illicit dietary supplements sold in the Italian market: identification of a sildenafil thioderivative as adulterant using UPLC-TOF/MS and GC/MS. *Sci Justice* 2014; 54: 228–237
- [95] Sarma N, Giancaspro G, Venema J. Dietary supplements quality analysis tools from the United States Pharmacopeia. *Drug Test Anal* 2016; 8: 418–423
- [96] Cohen PA, Maller G, DeSouza R, Neal-Kaback J. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA* 2014; 312: 1691–1693
- [97] Sprouse AA, van Breemen R. Pharmacokinetic interactions between drugs and botanical dietary supplements. *Drug Met Dispos* 2016; 44: 162–171
- [98] Tirona RG, Bailey DG. Herbal product-drug interactions mediated by induction. *Br J Clin Pharmacol* 2006; 61: 677–681
- [99] Hall SD, Wang Z, Huang SM, Hamman MA, Vasaveda N, Adigum AQ, Hilligoss JK, Miller M, Gorski JC. The interaction between St. John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003; 74: 525–535
- [100] Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. Effect of St. John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2004; 57: 592–599
- [101] Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? *BMC Med* 2011; 9: 94
- [102] Clauson KA, Santamarina ML, Rutledge JC. Clinically relevant safety issues associated with St. John's wort product labels. *BMC Complement Altern Med* 2008; 8: 42
- [103] Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, Mastrangelo S. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009; 65: 331–341

- [104] Anderson GD, Rosito G, Mohustsy MA, Elmer GW. Drug interaction potential of soy extract and *Panax ginseng*. *J Clin Pharmacol* 2003; 43: 643–648
- [105] Yale SH, Glurich I. Analysis of the inhibitory potential of *Ginkgo biloba*, *E. purpurea*, and *Serenoa repens* on the metabolic activity of cytochrome P450 3A4, 2D6 and 2C9. *J Altern Complement Med* 2005; 11: 433–439
- [106] Ohnishi N, Kusuhara M, Yoshioka M, Kuroda K, Soga A, Nishikawa F, Koishi T, Nakagawa M, Hori S, Matsumoto T, Yamashita M, Ohta S, Takara K, Yokoyama T. Studies on interactions between functional foods or dietary supplements and medicines. I. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics of diltiazem in rats. *Biol Pharm Bull* 2003; 26: 1315–1320
- [107] Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin Pharmacol Ther* 2002; 72: 276–287
- [108] Tsai HH, Lin HW, Pickard AW, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. *Int J Clin Pract* 2012; 66: 1056–1078
- [109] Vitry AL. Comparative assessment of four drug interactions compendia. *Br J Clin Pharmacol* 2007; 63: 709–714
- [110] Bent S, Ko R. Commonly used herbal medicines in the United States: a review. *Am J Med* 2004; 116: 478–485
- [111] Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM. A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. *Phytother Res* 2016; 30: 691–700
- [112] Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. *Nutr Rev* 2013; 71: 282–299
- [113] Alali FQ, El-Eimat T, Khalid L, Hudaib R, Al-Shehabi TS, Eid AH. Garlic for cardiovascular disease: prevention or treatment. *Curr Pharm Des* 2017; 23: 1028–1041
- [114] Alkanjari O, Vitalone A. What do we know about phytotherapy of benign prostatic hyperplasia? *Life Sci* 2015; 126: 42–56
- [115] Ooi SL, Pak SC. *Serenoa repens* for lower urinary tract symptoms/benign prostatic hyperplasia: current evidence and its clinical implications in naturopathic medicine. *J Altern Complement Med* 2017; 23: 599–606
- [116] Russo A, Capgrossio P, La Croce G, Ventimiglia E, Boeri L, Briganti A, Damiano R, Montorsi F, Salonia A. *Serenoa repens*, selenium and lycopene to manage lower urinary tract symptoms suggestive for benign prostatic hyperplasia. *Expert Opin Drug Saf* 2016; 15: 1661–1670
- [117] Novara G, Giannarini G, Alcaraz A, C  zar-Olmo JM, Descazeaud A, Montorsi F, Ficarra V. Efficacy and safety of hexanic lipidosterolic extract of *Serenoa repens* (Permixon) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: systematic review and meta-analysis of randomized clinical trials. *Eur Urol Focus* 2016; 2: 553–561
- [118] De Smet P. Herbal remedies. *NEJM* 2002; 347: 2046–2056
- [119] Karsch-V  lk M, Barrett B, Linde K. Echinacea for preventing and treating the common cold. *JAMA* 2015; 13: 618–619
- [120] Giles JT, Palat CT 3rd, Chien SH, Chang ZG, Kennedy DT. Evaluation of *Echinacea* for treatment of the common cold. *Pharmacotherapy* 2000; 20: 690–697
- [121] Lee NH, Son CG. Systematic review of randomized controlled trials evaluating the efficacy and safety of ginseng. *J Acupunct Meridian Stud* 2011; 4: 85–89
- [122] Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. Anticancer efficacy of polyphenols and their combinations. *Nutrients* 2016; 8: E552
- [123] Sinha D, Biswas J, Nabavi SM, Bishayee A. Tea phytochemicals for breast cancer prevention and intervention: from bench to bedside and beyond. *Semin Cancer Biol* 2017; 46: 33–54
- [124] Dietz BM, Hajirahimkhan A, Dunlap TL, Bolton JL. Botanicals and their bioactive phytochemicals for women’s health. *Pharmacol Rev* 2016; 68: 1026–1073
- [125] Tanmahasamut P, Vichinsartvichai P, Rattanachaiyanont M, Techatrak K, Dangrat C, Sardod P. *Cimicifuga racemosa* extract for relieving menopausal symptoms: a randomized controlled trial. *Climacteric* 2015; 18: 79–85
- [126] North American Menopause Society. The role of soy isoflavones in menopausal health: report of the North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). *Menopause* 2011; 18: 732–753
- [127] Bola  os R, Del Castillo A, Francia J. Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis. *Menopause* 2010; 17: 660–666
- [128] Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev* 2013; 12: CD001395
- [129] Morris CA, Avorn J. Internet marketing of herbal products. *JAMA* 2003; 290: 1505–1509
- [130] US Government Accountability Office. Herbal dietary supplements: examples of deceptive or questionable marketing practices and potentially dangerous advice. Available at <http://www.gao.gov/products/GAO-10-662>. Accessed August 7, 2017
- [131] Franssen HP, Pelgrom SMGJ, Stewart-Knox B, de Kaste D, Verhagen H. Assessment of health claims, content, and safety of herbal supplements containing *Ginkgo biloba*. *Food Nutr Res* 2010; 54: 5221
- [132] Miracleburn with Hoodia and patented Advantra-Z. Available at <http://www.4diamaxol.com/miracleburn.htm>. Accessed August 9, 2017
- [133] Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. *Arch Toxicol* 2015; 89: 851–865
- [134] Cardellina JH 2nd. Challenges and opportunities confronting the botanical dietary supplement industry. *J Nat Prod* 2002; 65: 1073–1084
- [135] van Breemen RB. Development of safe and effective botanical dietary supplements. *J Med Chem* 2015; 58: 8360–8372
- [136] Markowitz JS, Zhu HJ. Limitations of *in vitro* assessments of the drug interaction potential of botanical supplements. *Planta Med* 2012; 78: 1421–1427
- [137] Chen ML, Straughn AB, Sadrieh N, Meyer M, Faustino PJ, Ciavarella AB, Meibohm B, Yates CR, Hussain AS. A modern view of excipient effects on bioequivalence: case study of sorbitol. *Pharm Res* 2007; 24: 73–80
- [138] Markowitz JS, von Moltke LL, Donovan JL. Predicting interactions between conventional medications and botanical products on the basis of *in vitro* investigations. *Mol Nutr Food Res* 2008; 52: 747–754
- [139] Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity – challenges and pitfalls of causality assessment. *Maturitas* 2009; 63: 302–304
- [140] Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. *Eur J Gastroenterol Hepatol* 2013; 25: 1093–1098
- [141] Zheng XX, Xu YL, Li SH, Hui R, Wu YJ, Huang XH. Effects of green tea catechins with or without caffeine on glycemic control in adults: a metaanalysis of randomized controlled trials. *Am J Clin Nutr* 2013; 97: 750–762
- [142] Nahrstedt A, Butterweck V. Lessons learned from herbal medicinal products: the example of St. John’s wort. *J Nat Prod* 2010; 73: 1015–1021
- [143] Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. *Boswellia serrata*: an overall assessment of *in vitro*, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet* 2011; 50: 349–369
- [144] Nieman DC, Shanely RA, Luo B, Dew D, Meaney MB, Sha W. A commercialized dietary supplement alleviates joint pain in community adults: a

- double-blind, placebo-controlled community trial. *Nutr J* 2013; 12: 154
- [145] Du Z, Liu Z, Ning Z, Liu Y, Song Z, Wang C, Lu A. Prospects of boswellic acids as potential pharmaceuticals. *Planta Med* 2015; 81: 259–271
- [146] Di Lorenzo C, Dell'Agli M, Badea M, Dima L, Colombo E, Sangiovanni E, Restani P, Bosisio E. Plant food supplements with anti-inflammatory properties: a systematic review (II). *Crit Rev Food Sci Nutr* 2013; 53: 507–516
- [147] Ernst E. Frankincense: systematic review. *BMJ* 2008; 337: 1–4
- [148] Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J* 2013; 15: 195–218
- [149] Schiborr C, Kocher A, Behnam D, Jandasek J, Toelstede S, Frank J. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Mol Nutr Food Res* 2014; 58: 516–527
- [150] European Food Safety Authority. “General function” health claims under Article 13. Available at <http://www.efsa.europa.eu/en/ndaclaims/ndaclaims13.htm>. Accessed August 16, 2017
- [151] Kuszak AJ, Hopp DC, Williamson JS, Betz JM, Sorkin BC. Approaches by the US National Institutes of Health to support rigorous scientific research on dietary supplements and natural products. *Drug Test Anal* 2016; 8: 413–417
- [152] Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An Internet based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore)* 2005; 84: 197–207
- [153] U.S. Food Drug Administration. Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims-Final. Washington, D.C.: U.S. Food Drug Administration; 2009. Available at <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm>. Accessed August 18, 2017
- [154] Finley JW, Finley JW, Ellwood K, Hoadley J. Launching a new product or dietary supplement in the United States: industrial, regulatory, and nutritional considerations. *Annu Rev Nutr* 2014; 34: 421–447
- [155] Costello RB, Coates P. In the midst of confusion lies opportunity: fostering quality science in dietary supplement research. *J Am Coll Nutr* 2001; 20: 21–25
- [156] Wilson T, Bauer BA. Advising consumers about dietary supplements: lessons from cranberry products. *J Diet Suppl* 2009; 6: 377–384