ADVERSE EFFECTS OF PLANT FOOD SUPPLEMENTS AND BOTANICAL PREPARATIONS: A SYSTEMATIC REVIEW WITH CRITICAL EVALUATION OF CAUSALITY

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SUMMARY

Aims: The object of this review was to collect available data on 1) adverse effects observed in humans from the intake of plant food supplements (PFS) or botanical preparations; 2) the misidentification of poisonous plants; 3) interactions between PFS/botanicals and conventional drugs or nutrients.

Methods: PubMed/MEDLINE and Embase were searched from database inception to June 2014, using the terms "adverse effect/s", "poisoning/s", "plant food supplement/s", "misidentification/s", and "interaction/s" in combination with the relevant plant name. All papers were critically evaluated according to the WHO Guidelines for causality assessment.

Results: Data were obtained for 66 plants that are common ingredients of PFS; of the 488 papers selected, 398 (81.6%) dealt with adverse effects directly associated with the botanical and 89 (18.2%) concerned interactions with conventional drugs. Only 1 case was associated with misidentification. Adverse effects were reported for 39 out of the 66 botanical substances searched. Of the total references, 86.5% were associated with 14 plants, including *Glycine max*/soybean (19.3%), *Glycyrrhiza glabra*/liquorice (12.5%), *Ginkgo biloba*/ginkgo and *Camellia sinensis*/green tea (both 8.6%).

Conclusions: Considering the length of time examined and the number of plants included in the review, it is remarkable that: 1) the adverse effects due to botanical ingredients were relatively infrequent, if assessed for causality; 2) the number of severe clinical reactions was very limited, but some fatal cases have been described.

Data presented in this review were assessed for quality in order to make the results maximally useful for clinicians in identifying or excluding deleterious effects of botanicals.

INTRODUCTION

The use of food supplements is growing in both Europe and USA [1]. Food supplements can contain vitamins, minerals, botanicals, amino acids, enzymes and many other ingredients, and are marketed in a variety of forms: tablets, capsules and powders, as well as drops, beverages and energy bars.

Food supplements are products intended to complement the normal diet; as they are foods and not drugs, they must not be claimed to be diagnostic, preventative or therapeutic. The wide diffusion of food supplements containing botanicals (plant food supplements, PFS) has far exceeded the availability of scientific information on their benefits, adverse effects and drug interactions. The information on benefits may be partially covered by the "tradition of use", but it is more difficult to evaluate possible adverse clinical effects due to plant properties, plant misidentification or interaction with pharmaceutical drugs or nutrients.

The first difficulty in this assessment is related to the discrimination of plant food supplements from traditional herbal products, because the same ingredient/product could be sold in different countries in one or the other category, and the relevant international legislation is not harmonised. Even in the European Union there are some differences in regulatory approaches [2].

Several papers have considered the adverse effects associated with botanicals, and in some cases reviewed data in a specific clinical area. A 5-year toxicological study published by Shaw et al. (1997) showed that among 1297 symptomatic enquiries associated with botanicals (both food supplements and traditional remedies), there was a possible or confirmed association in 785 cases [3]. Some cases reported hepatotoxicity following the use of Chinese herbal medicine for skin disorders, allergic reactions to royal jelly and propolis and heavy metal poisoning caused by remedies from the Indian subcontinent. The conclusion by Shaw et al. was that although the overall risk to public health appeared to be low, certain groups of traditional remedies/food supplements could be associated with a number of potentially serious adverse effects.

Valli and Giardina in 2002 [4] reviewed the adverse cardiovascular events due to herbal preparations, while Pitter et al. in 2005 [5] considered food supplements aimed at body weight reduction, and reported adverse events including hepatic injury and death after the use of some herbal food supplements. For herbal *Ephedra* and ephedrine-containing food supplements (now banned in most countries, including European Union and USA) an increased risk of psychiatric, autonomic or gastrointestinal adverse events and heart palpitations have been reported.

A retrospective study performed by the Poison Center Surveillance Project evaluating dietary supplement-related calls to the centre in 2006 showed that: 1) most supplement-related adverse events were minor; 2) of 275

calls, two-thirds were rated as probably or possibly related to supplement use; 3) sympathomimetic toxicity was most common, with caffeine-containing products accounting for 47%, and products containing *Yohimbe* spp. accounting for 18% of supplement-related symptomatic cases; 4) drug–herb interaction was suspected in some cases [6].

The European Project PlantLIBRA (Plant Food Supplements: Levels of Intake, Benefit and Risk Assessment, Project n. 245199 – www.plantlibra.eu) aims to foster the safe use of food supplements containing plants or botanical preparations by increasing science-based decision-making by regulators, researchers and food chain operators. The aim of this systematic review was to summarise, and critically assess for causality, the published data on: 1) adverse effects related to PFS/botanical ingredients, 2) the misidentification of poisonous plants, and 3) the interactions of PFS/botanicals with pharmaceutical drugs or nutrients.

MATERIALS AND METHODS

Botanical ingredients

The plants included in this review were derived from a consensus among partners reached after numerous meetings in the framework of the PlantLIBRA EU project and mainly represent those most commonly used in PFS. The 66 plants included in the search are listed in **Table 1**.

Literature Search

Two of the most important scientific databases of references and abstracts on life sciences and biomedical topics, PubMed/MEDLINE and Embase, were systematically searched to create the present work. The following search strategy and selection criteria were used: data were collected from database inception to June 2014, with the terms “adverse effect/s”, “poisoning/s”, “plant food supplement/s”, “misidentification/s”, and “interaction/s” in combination with the relevant plant name.

Causality assessment

The assessment of reports on adverse reactions to PFS and/or their botanical ingredients was performed according to the WHO Causality Assessment Criteria as described in **Table 2** [7].

Online Supplementary Data

The number of papers collected during the project is very high, so that we cite only 150 papers but we offer the whole list of papers classified according to the WHO Causality Assessment Criteria as Online Supplementary Data.

RESULTS AND DISCUSSION

The summary of data collected from the literature and assessed according to the WHO criteria of causality is reported in **Table 3**. Reports of adverse effects were found for 39 out of 66 botanical ingredients searched, representing 59% of all the plants included in the database search. Of the 492 papers collected, 402 (81.7%) described cases due to adverse effects directly associated with the botanical and 89 (18.1%) to interactions with conventional drugs. Only 1 case was associated with a misidentification of the ingredient *Passiflora incarnata* [8].

Most events (426, or 86.6%) were associated with 14 botanical ingredients; the number of papers for each of them ranged between 13 and 95.

Adverse effects due to the botanical as such or as an ingredient of PFS

The distribution of adverse effects was different in relation to the plant considered; **Table 4** lists the number of papers regarding specific adverse effects associated with the botanicals searched and the relative causality according to the WHO classification. Since the use of a rechallenge is rare or even ethically unacceptable, the class "Certain" and "Probable/likely" are considered together as "Certain/probable association".

For the 14 most documented plants, the total number of papers was 343, but during the evaluation the causality was considered uncertain/unclassifiable in 61of them; 41.4% of all the papers were associated with only two botanicals: *Glycine max* (91) and *Glycyrrhiza glabra* (51).

Adverse effects due to interaction with nutrients or conventional drugs

Table 5 illustrates the papers regarding the interaction of PFS/botanicals with food, beverages or conventional drugs; assessment of causality is also reported. Of the 83 papers, 38.6% was associated with *Citrus aurantium* (18) and *Ginkgo biloba* (14).

Form responsible for adverse effects

Table 6 lists the part of plant used and the commercial form (botanical as such, PFS, food) associated with the adverse effects described. In some cases, the description of product was limited and was carefully considered in causality assessment.

Case reports and side effects associated with PFS and botanical ingredients: a review of the top 14

As reported above, even though 39 plants (among those searched) were associated with adverse effects, only those reported as causal in at least 10 papers (total number in Table 3) were considered in this review. As a consequence, details will be reported for only 14 plants, listed according to the alphabetical order of the Latin name.

Camellia sinensis (L.) Kuntze (green tea)

Numerous papers (34) have been collected on adverse effects related to *C. sinensis* (L.) Kuntze; 29 of them were considered sufficiently documented for causality assessment. Side effects were associated with derivatives from green tea leaves and involved mainly acute hepatotoxicity. Patients showed clinical symptoms with different severity, ranging from a mild increase of serum aminotransferase levels to fulminant hepatitis requiring liver transplantation [9-12].

The types of preparation responsible for the adverse effects, with different degrees of relationship, were plant food supplements based on green tea extracts; among them:

- hydroalcoholic extract [13-15];
- ethanolic extract [10,12,16];
- aqueous extract of green tea, consumed as tea or in capsules [9, 11, 17].

Supplements were used principally for body weight control and in one case for reducing hair loss. For tea infusion, the daily intake was from 2/3 cups up to some litres. Generally, the time of onset of the reactions ranged from 5 days to 2 years of daily consumption. Most cases were classified as "certain/probable" or "possible" when other factors could contribute to the adverse effect such as age, concomitant pathological

conditions, several ingredients present in the preparation. Moreover, since the substance involved in the adverse effect was not always identified, an adulteration or contamination could not be excluded. For example, in two papers, the hepatotoxicity due to two Chinese herbal supplements containing tea was attributed to the presence of N-nitroso phenfluoramine [18-19].

Adverse effects of *C. sinensis* seem to be modulated by various factors, and in particular by the chemical composition and the type of herbal preparations. In fact, all preparations differ in their chemical composition: 1) powdered leaves contain all the tea active components; 2) infusions and aqueous extracts contain mostly hydrophilic compounds; and 3) hydroalcoholic extracts contain both hydrophilic and lipophilic components. The components most frequently indicated as responsible for hepatotoxicity are catechins and their gallic esters. In particular, the role of EGCG (EpiGalloCatechin-3-Gallate) seems predominant, as shown also in experimental *in vitro* and *in vivo* assays (20); this conclusion could also be supported by its high concentration in green tea extracts [21]. The association seems further confirmed by the lack of known adverse effects to fermented tea (black tea), where the content of EGCG is significantly reduced.

Interaction between green tea and conventional drugs was recognised in 9 papers; 3 of them with certain/probable and 6 with possible causality. Most interactions were with statins, where an increase in plasma concentration and a worsening of the related side effects, such as rhabdomyolysis, were observed [21-22]. Green tea was also responsible for interfering with a certain number of drugs such as warfarin, with inhibition of activity due to the presence of vitamin K in tea [23], or acetaminophen, with exacerbation of the hepatotoxicity [24], and other natural compounds such as lutein [21], usnic acid and guggulsterones [25] or *Cassia angustifolia* extract [26]. In the papers reporting interaction, aqueous and hydroalcoholic extract were the most usual forms involved.

***Cimicifuga racemosa* (L.) Nutt (black cohosh)**

Papers related to *C. racemosa* described mainly specific adverse effects (19/23) and among them 14 were classified as "certain/probable" and 5 "possible".

The cases described included:

1) hepatotoxicity [27-28], with cases of autoimmune hepatitis [29]
2) myopathy with severe asthenia and rhabdomyolysis [30];
3) reversible complete heart block with bradycardia [31];
4) cutaneous vasculitis [32] and cutaneous pseudolymphoma [33].

Adverse reactions were due to the chronic ingestion of *C. racemosa* extracts, as such or as an ingredient of PFS (**Table 6**). In the case of hepatotoxicity, the event was quickly reversible after discontinuation, except in two cases where liver transplant became necessary [27, 34], and in the case described by Lynch et al [27], the event was fatal.

The possible interaction with conventional drugs is mainly based on *in vitro* tests, where the inhibition of CYP3A4 activity was observed [35].

Cinnamomum verum J. Prest (cinnamon)

Adverse effects collected in the scientific literature for *C. verum* were mainly classified as events with certain/probable causality (17/23 or 73.9%). Adverse effects were mainly localised in the oral cavity and were due to the use of cinnamon-flavoured beverages, candies and chewing-gum. The most important adverse effects were:

1) stomatitis with swelling and burning of lip, tongue and cheeks with a case of ulceration [36-37];
2) hyperkeratotic plaques covering most of the dorsal and lateral tongue and involving the buccal mucosa [38];
3) allergic leukoplakia of oral mucosa [39], and contact allergy [40];
4) squamous cell carcinoma of the tongue [41].

Some contact dermatitis was experienced after consumption of cinnamon-flavoured food or solutions [42] or PFS containing *C. verum* oil [43]. One case of intoxication was observed in a child [44]. No case of interaction with nutrients or conventional drug was found.

Citrus aurantium L. (bitter orange)

Specific adverse effects (7) and interaction with conventional drugs (18) have been reported.

The most usual adverse reactions were in the cardiovascular system, including hypertension, tachycardia, and ventricular extrasystoles [45].

Ischaemic colitis [46], allergic bronchospasm [47] and hepatitis with massive necrosis [45] were also reported.

Attempted weight loss was the most common reason for using PFS containing *C. aurantium*. In one case, the subject used a decoction of leaves to treat a common cold [48]. An extract of ripe or unripe fruit (usually

unspecified) was the most usual form taken by consumers. The presence of stimulant amines, such as synephrine and octopamine, in *C. aurantium* explains the numerous adverse cardiovascular effects. The chemical structure of synephrine resembles that of the neurotransmitter adrenalin and of the alkaloid ephedrin, so that it acts as a sympathomimetic substance [49].

When *C. aurantium* was used in combination with caffeine, ephedrine, yohimbine and phenylethylamine, but also thyroxine, enhancement of the adverse effects was reported: stimulant cardiovascular effects, such as tachycardia and hypertension [50], ventricular fibrillation [51], angina [52], acute myocardial infarction [53], ischaemic stroke [54] and exercise-induced syncope [55].

Less frequently described were rhabdomyolysis [45], ischaemic colitis [56] and psychosis [57].

Cases of adverse effects to *C. aurantium* were mainly classified as "possible" due to the frequent presence of accompanying conditions such as obesity, hypothyroidism, asthma, diabetes, hypertension, hyperlipidaemia, alcoholism, drug abuse, depression, anxiety, nicotine use, and dehydration.

Echinacea purpurea (L.) **Moench (Eastern purple coneflower)**

The review selected a total of 20 papers reporting adverse effects due to ***E. purpurea***. They were mainly associated with ethanolic extracts of root and herb, but side reactions to aqueous extracts were also reported. Causality was often (10/18) defined as "unclassifiable" because of the lack of clear information on the botanical preparation, description of the adverse event, patient's anamnesis or insufficient evidence of exposure. The lack of data could be partially explained by the fact that many adverse effects were found in papers from regulatory bodies (WHO, ADRAC, BfArM, FDA), where details on the specific *E. purpurea* preparation were not included.

Adverse reactions were associated with both allergy and hepatic or gastrointestinal effects. Allergic reactions were mainly due to IgE-mediated hypersensitivity [58] and could be due to the known immuno-stimulating properties of *E. purpurea*. *Echinacea* derivatives stimulate macrophage and enhance cytokine production, which could be responsible for adverse consequences in humans [59]. Hepatotoxicity was described as an acute event with features of cholestatic autoimmune hepatitis [60], and as a case of fatal liver necrosis [61]. Other clinical manifestations probably associated with *E. purpurea* were: a case of erythema nodosum [62], diarrhoea, vomiting, headache and drowsiness [63].

The possible interaction of *E. purpurea* with pharmaceutical drugs was considered by some authors. Gorski et al. (2004) [64] considered that the observed induction of CYP3A4 activity explained the interaction of unspecified root extracts with various medications, such as tolbutamide, midazolam (oral or intravenous administration),

dextromethorphan. Other interactions with albuterol, allopurinol, beclomethasone, dihydrocodeine, roxithromycin were evaluated as unclassifiable because of the lack of clinical details [58].

In contrast, Gurley et al. (2004) [65] found there to be no significant effect of *E. purpurea* on cytochromes CYP3A4, CYP1A2, CYP2E1 or CYP2D6 activity. The incongruence with the results of Gorski et al. (2004) [64] is probably due to the different type of extracts used: Gorski et al. (2004) used the root extract (containing more than 1% phenols as cichoric acid, chlorogenic acid and echinacoside), while Gurley et al. (2004) [65] used the whole plant extract, containing principally cichoric acid.

***Ginkgo biloba* L. (ginkgo)**

The review of adverse effects associated with *Ginkgo biloba* produced 42 papers, 28 related to adverse effect to the plant derivative as such and 14 reporting interaction with conventional drugs. Most of them (33) were classified as events with certain/probable and possible causality. Leaves and seeds are the parts most usually consumed, both as such (roasted or cooked seeds) and as extracts. The type of extract is normally undefined apart from the study by Yagmur et al (2005) [66], where the product is specifically indicated (EGb761).

Adverse reactions are usually associated with haemorrhagic complications [67-68], with one case of a subdural haematoma [69]. The activity is probably due to the antiplatelet activity of ginkgosides, and the Ginkgolide B seems to be the main terpenoid responsible for such effects [69-70].

In some papers, other symptoms were identified: acute generalised exanthematous pustulosis [71], toxic epidermal necrolysis [72], and ventricular arrhythmia [73] or convulsions [74].

An increased risk of bleeding complications was observed when *G. biloba* was taken concomitantly with other conventional drugs acting on coagulation, such as acetyl salicylic acid [75-76], ibuprofen [77], and warfarin [78].

A subtherapeutic level of anticonvulsants (phenytoin and valproic acid), due to an induction of the cytochrome CYP2C19 by ginkgo active compounds, was also observed in a case of fatal breakthrough seizure [79].

***Glycine max* (L.) Merr (soybean)**

The review produced 95 papers reporting adverse effects associated with the consumption of *Glycine max*; among these, only a few (4) documented an interaction with nutrients or drugs. In particular, a decreased absorption of levothyroxine was attributed to the use of a food supplement containing soybean proteins [80], while soy milk and seaweed ingestion was associated with serious thyroid dysfunction [81]. Moreover, foods containing soybean and its isoflavones were responsible for bleeding when combined with oestradiol [82].

During a clinical trial studying the effect of soy isoflavones and melatonin in relieving menopausal symptoms, one patient experienced tachycardia, weight gain, insomnia, drowsiness and headache [82].

The adverse effects due to *Glycine max* are mainly associated with the well-known allergenic potential of this legume (30/91), which is used as an ingredient in several foods and preparations such as soy milk, paediatric formulas, lecithin, etc [83-84]. Soybean is included in the list of major allergens requiring specific labelling, and the proteins responsible for the allergic reactions have been widely studied (IUIS Allergen Nomenclature Sub-Committee - http://www.allergen.org/search.php?allergensource=Glycine+max) and identified [84].

The second most important group of side effects due to soybean derivatives is associated with the isoflavone fraction [85-86]. *G. max* isoflavones are frequently contained in food supplements aimed at reducing menopause-related symptoms and diseases. Side effects due to their pseudo-hormonal activity have been observed both in females and males. In particular: precocious thelarche [87], uterine fibroids [88], ureteral mullerian carcinosarcoma associated with endometriosis [89], gynaecomastia [90], hypogonadism and erectile dysfunction [91], testicular cancer and reproductive disorders [85, 87].

Other case reports associated with *Glycine max,* with satisfactory demonstration of causality, follow:

1. gastro-intestinal adverse effects, including enterocolitis, vomiting, abdominal pain and diarrhoea, gastric cancer and hepatitis [92-95];
2. thyroid dysfunction caused by the assumption of soybean "milk" containing high levels of iodine [96];
3. bladder cancer [97];
4. cases with different symptoms, such as hypophosphatemia in very-low-birth-weight infants, fatal hypernatremia, migraine, hypochloremic alkalosis, transient methemoglobinemia [98-101].

***Glycyrrhiza glabra L.* (liquorice)**

The review selected 60 papers reporting adverse reactions (specific reactions and interactions) after the consumption of liquorice. Most of them were classified as certain/probable (44), and only three were deemed "unlikely". The root is the plant part utilised; sweets, chewing gum, drinks and PFS are the most usual forms consumed but data on the preparation is not always included in papers. Most adverse events had the same symptomatic pattern, which is attributable to the biological activity of glycyrrhetic acid. Hypokalemia and hypertension are the most frequent adverse events [102-103], which can be worsened by the concomitant use of

conventional drugs, such as bendrofluazide [104], hydrochlorothiazide [105], or other diuretics [106]. Interaction with oral contraceptives, with a similar clinical pattern (hypokalemia and water retention), has also been reported [107]. In some cases, the clinical evolution was particularly severe with rhabdomyolysis [108], hypokalemic paralysis [109], hypokalemic encephalopathy [110], and cardiac arrest [111].

The adverse effects are mainly due to the liquorice's active compound, glycyrrhetic acid, which inhibits the 11-β hydroxysteroid dehydrogenase-type 2 (11β-HSDH-2) enzyme that is present in the principal cells of the cortical collecting duct. Since cortisol and aldosterone are similar steroid hormones, the enzyme is needed to inactivate cortisol before it binds the aldosterone receptor inside principal cells. When 11b-HSDH-2 is inhibited, an aldosterone-like effect is promoted, which suppresses the renin-angiotensin-aldosterone axis and causes volume expansion, hypertension, hypokalemia and metabolic alkalosis [112].

Harpagophytum procumbens (Burch) DC (Devil's claw)

Case reports associated with this botanical mainly referred to the treatment of low back pain or arthrosis of hip and knee. All studies were classified as probable/likely and were associated with derivatives of the tuber or the whole plant (extracts or PFS, see Table 6). Acting as a COX-2 inhibitor, adverse effects associated with *H. procumbens* preparations, which were predictable and dose-dependent, included mainly gastrointestinal disorders [113]. Throbbing frontal headache, tinnitus, anorexia and loss of taste for food were described in one patient by Grahame and Robinson in 1981 [114].

Hypericum perforatum L. (St John's wort)

Among the 10 papers describing adverse effects associated with *H. perforatum*, 4 (40%) were classified as certain/probable and 6 as possible. The best described cases reported convulsions and confusion [115], manic attack [116] and hypertension with [117] or without delirium [118]. Other authors described sexual dysfunction [119], serotonin-syndrome-like symptoms with anxiety, hypertension, tachycardia and nausea [120] and finally, a 5-fold increase of transaminases [121].

Several authors reported clinical cases of patients suffering from adverse effects due to an interaction between H. perforatum and drugs. The events were considered certain/probable in 6 out of the 9 cases and possible in the other 3. It has been shown that there may be clinically significant drug-drug interactions between *H. perforatum* and substances metabolized through the CYP3A4 isozyme. Specifically, reductions in therapeutic efficacy at standard doses of important CYP3A4 substrates may be observed [122].

When *H. perforatum* was used in combination with drugs, reduced bioavailability was shown for the following: verapamil [123], glicazide, nifedipine, omeprazole, voriconazole, anticoagulant drugs such as phenprocoumon and warfarin, statins such as atorvastatin and simvastatin [124], talinolol [125], digoxin [124, 126], nevirapine [127], contraceptive drugs, cyclosporine, tacrolimus and theophylline [124, 126], loperamide together with *Valeriana officinalis* [128]. Other authors described an interaction with selective serotonin re-uptake inhibitors to give serotonin-syndrome [126]. In addition, long-term use of *H.perforatum* was considered responsible for adrenergic desensitisation and decreased responsiveness to vasopressors, leading to a cardiovascular collapse in a patient during anaesthesia [129]. Further interactions producing a decrease of bioavailability were suggested by Hu et al. [126] with amitriptyline, alprazolam, midazolam, fexofenadine, imatinib, irinotecan, methadone, indinavir, quazepam.

Panax ginseng **C.A. Meyer (ginseng)**

The adverse effects collected in the scientific literature for ginseng can be classified as specific effects in 11 cases and as an interaction with conventional drugs in 5.

Among the 11, one was classified as certain/probable and 6 as possible; the remaining 4 papers were not sufficiently documented. The part of the plant utilised is the root and little information is normally included about the method of preparation. The adverse reactions described were: stimulant effects, such as nervousness and tremor, a maniacal episode in a patient with recurrent depressive illness [130], metrorrhagia [131], and allergic reactions including generalised urticarial rash and difficulty in breathing [132].

Clinical events associated with co-administration of *P. ginseng* with conventional drugs included interaction with: the anticoagulant drug warfarin [133], the antidepressant drugs phenelzine, [134] and clomipramine [135] inducing manic symptoms, and the tyrosine-kinase inhibitor imatinib responsible for liver damage via an interaction with the cytochrome CYP3A4 [136].

Valeriana officinalis **L. (valerian)**

Cases were classified as specific adverse effects in 6 out of 14 papers or interaction with nutrient and conventional drugs in the remaining 8. Causality of the adverse effects was rarely documented, likewise the kind of product used by the patient. The case classified as certain/probable reported hepatotoxicity [137], including a fulminant hepatic failure [138].

Among the cases of interaction with conventional drugs, nutrients or food/beverages, only 4 cases were considered sufficiently documented, they reported cases of:

1) hypotension due to an interaction with *Matricaria chamomilla* and *Melissa officinalis* [139];
2) hand tremor, dizziness and muscular fatigue due to co-administration with *Passiflora incarnata* and lorazepam [140];
3) change of mental status due to a consumption together with alcohol and *Ginkgo biloba* [141];
4) hepatitis due to interaction with *Scutellaria lateriflor*, containing alkylating agents, glycoside and volatile oils [142].

***Vitex agnus castus* L. (vitex or 'chaste tree')**

Nineteen papers described adverse effects to *V. agnus castus*. Some of them were observed during clinical studies performed during postmarketing surveillance. This is because in several European Countries *V. agnus castus* is included among botanical ingredients used in traditional medicine (mainly Germany and Austria), requiring marketing authorisation. All these products contain ethanolic extracts of the fruit of *V. agnus castus*, and are used for premenstrual syndrome. Adverse effects reported vary widely; the most frequent and documented clinical events are:

1) inter-menstrual bleeding or disorders [143-145];
2) gastrointestinal disorders with diarrhoea, persistent gastroenteritis and nausea [143, 145-146];
3) acneform facial inflammation [146];
4) headache [145];
5) weight gain 143, 145-146];
6) dizziness [143, 146];
7) allergic reactions with pruritus, erythema and gastrointestinal symptoms [144].

Other less frequent adverse effects were: arteriospasm and hepatitis [147].

Causality between plant intake and adverse effects was considered certain/probable in most cases (13/18), because the adverse effects were registered during well controlled clinical studies, and the plant was often the only "treatment" used.

***Vitis vinifera L.* (grape)**

All papers collected for effects of this botanical (14) were classified as "certain/probable". Most of them can be

considered as allergic reactions, including: oral syndrome, urticaria, angioedema, hypotension and respiratory distress, anaphylaxis and finally exercise-induced anaphylaxis [148-150]. The most important allergens from grapevine are endochitinase A and B, a lipid transfer protein (LTP), and a thaumatin-like protein [149]. No interaction with nutrients or conventional drugs has been described.

4. CONCLUSIONS

At the first step in searching databases for adverse effects to the 66 botanical ingredients considered (Table 1), some thousands of papers were considered. With the application of WHO assessment criteria (Table 2), the number of papers with sufficient evidence of a causal relationship was reduced to 492 for 39 plants (see Table 3). No paper describing significant adverse effects was found for the remaining 27 plants. Fourteen plants were the most frequently cited, and among them two were responsible for 32% of the adverse effects reported:

1. *Glycine max* (soybean) was considered in 95 papers, where its role in allergic reactions and hormonal-like activity was demonstrated. Both effects are well known; in fact soybean is included in the list of major food allergens and the hormonal activity of phytoestrogens is the reason that it is used in menopause.
2. *Glycyrrhiza glabra* (liquorice) was usually responsible for hypokalemia and hypertension due to its content of glycyrrhetic acid. The hypertensive potential of liquorice and its interaction with conventional drugs are also quite well known in clinical practice.

Generally speaking, we could conclude that:

1. cases of adverse effects to botanicals are numerous, in term of citations by scientific literature or phytovigilance centres, but an assessment according to the WHO criteria indicates that the number of those with adequate evidence for a causal relationship is significantly less,
2. given the long period of time considered and the number of plants included in the review, the occurrence of adverse effects of botanical ingredients is relatively low,
3. the number of severe clinical reactions is very limited, but some fatal cases have been described,
4. it is important to recognise that an underestimation is also possible, for different reasons: a) the consumer usually considers botanicals as safe products and does not report their use if they are admitted to hospital or emergency service, b) since they use PFS at their own discretion, consumers

could avoid informing the family doctor, fearing a reprimand, c) data collected by poison centres are published only in a relatively few cases.

Despite these apparently reassuring findings, we still consider it important to direct the attention of clinicians to the possibility of rare but severe adverse effects from botanical preparations or ingredients of food supplements or traditional medicines. For example, the severe hepatotoxicity of *Camellia sinensis* (green tea) was unknown before the product Hexolise, containing a hydroalcoholic extract was marketed and which was found to be responsible for a number of cases of acute hepatitis in France and Belgium [13, 17]. Although very rare (considering the large number of green tea consumers in the world), the severity of these reactions needs information and vigilance.

Similarly *Citrus aurantium,* which contains adrenergic amines, must be considered a potential risk both for athletes and the general population, taking into consideration the possible abuse as a substitute for the products containing *Ephedra*, now banned.

Data presented in this review were assessed for quality, in order to be of maximum value for clinicians and the clinical management of affected patients.

DECLARATION OF INTEREST

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Table 1 - Plants included in the review

Abies alba Mill.	*Cynara scolymus* L.	*Ocinum basilicum* L.
Aesculus hippocastanum L.	*Echinacea pallida* Nutt.	*Olea europaea* L.
Aloe ferox Mill.	*Echinacea purpurea* (L.) Moench	*Panax ginseng* C.A. Meyer
Artemisia abrotanum L.	*Epimedium brevicornum* Maxim/*sagittatum*	*Passiflora incarnata* L.
Artemisia dracunculus L.	*Eschscholzia californica* Cham.	*Pelargonium sidoides* DC
Borago officinalis L.	*Foeniculum vulgare* Mill.	*Peumus boldus* Molina
Boswellia serrata Roxb. ex Colebr.	*Ginkgo biloba* L.	*Pimpinella anisum* L.
Calendula officinalis L.	*Glycine max* (L.) Merr.	*Plantago lanceolata* L.
Camellia sinensis (L.) Kuntze	*Glycyrrhiza glabra* L.	*Plantago ovata* Forssk
Carica papaya L.	*Grindelia robusta* Nutt.	*Pseudowintera colorata* (Raoul) Dandy
Carum carvi L.	*Harpagophytum procumbens* (Burch.) DC	*Rhamnus purshiana* DC
Cassia angustifolia Vahl/ *Cassia senna* L.	*Helichrysum italicum* (Roth) Don	*Salvia hispanica/columariae* L.
Cassia obtusifolia L./*Cassia tora* L	*Heliotropium* spp.	*Serenoa repens* (W Baltram) Small.
Chrysanthemum balsamita (L) Baill	*Hibiscus sabdariffa* L.	*Serenoa serrulata* Hook f.
Cichorium intybus L.	*Hippophae rhamnoides* L.	*Silybum marianum* (L.) Gaertn.
Cimicifuga racemosa (L.) Nutt.	*Humulus lupulus* L.	*Taraxacum officinale* Wiggers
Cinnamomum verum J. Presl (*Cinnamomum zeylanicum*)	*Hypericum perforatum* L.	*Thymus serpyllum* L.
Citrus aurantium L.	*Lavandula angustifolia* Mill.	*Trifolium pratense* L.
Citrus limon (L) Burm.	*Lycium barbarum* L.	*Vaccinium myrtillus* L.
Citrus sinensis L.	*Matricaria recutita* L.	*Valeriana officinalis* L.
Crataegus monogyna Jacq.	*Melissa officinalis* L.	*Vitex agnus castus* L.
Cuminum cyminum L.	*Myrtus communis* L.	*Vitis vinifera* L.

Table 2 - Causality categories according to WHO [7]

Causality classification	**Details**
Certain	a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drugs (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary
Probably/Likely	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition
Possible	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
Unlikely	a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
Conditional/ Unclassified	a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination
Unassessable/ unclassifiable	a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

Table 3 - Number of scientific papers describing adverse effects to botanicals/PFSs, including misidentification and interaction with nutrient or conventional drugs

Plant by scientific name **(common name)**	**Number of references to adverse effects as such**	**Number of references to misidentification**	**Number of references to interactions**	**Total references**
Glycine max (L.) Merr (soybean)	91	0	4	95
Glycyrrhiza glabra L. (licorice)	51	0	9	60
Camellia sinensis (L.) Kuntze (tea)	34	0	9	43
Ginkgo biloba L. (ginkgo/Maideinhair tree))	28	0	14	42
Citrus aurantium L. (bitter orange)	7	0	18	25
Cinnamomum verum J.Prest *(C. zeylanicum)* (cinnamon)	23	0	0	23
Cimicifuga racemosa (L.) Nutt (black cohosh)	19	0	4	23
Echinacea purpurea (L.) Moench (Eastern purple coneflower)	18	0	2	20
Vitex agnus castus L. (vitex/chaste tree)	18	0	1	19
Hypericum perforatum L. (St John's wort)	10	0	9	19
Panax ginseng C.A. Meyer (ginseng)	11	0	5	16
Valeriana officinalis L. (valerian)	6	0	8	14
Vitis vinifera L. (grape)	14	0	0	14
Harpagophytum procumbens (Burch) DC (Devil's claw)	13	0	0	13
Boswellia serrata Roxb (Indian frankincense)	9	0	0	9
Serenoa repens (W Baltram) Small (saw palmetto)	6	0	0	6
Citrus sinensis (L.) Osbeck (sweet orange)	5	0	0	5
Taraxacum officinale Weber (dandelion)	5	0	0	5
Aesculus hippocastanum L. (horse chestnut)	2	0	2	4
Cassia angustifolia Mill/*Cassia senna* L. (senna)	4	0	0	4

Aloe ferox Mill. (bitter aloe)	3	0	0	3
Melissa officinalis L. (lemon balm)	3	0	0	3
Passiflora incarnata L. (Passion flower)	1	1	1	3
Peumus boldus Molina (boldo)	1	0	2	3
Cassia obtusifolia L./Cassia tora L. (sickle senna/Java bean)	2	0	0	2
Foeniculum vulgare Mill (fennel)	2	0	0	2
Matricaria recutita L. (chamomile)	1	0	1	2
Ocimun basilicum L. (sweet basil)	2	0	0	2
Olea europea L. (olive)	2	0	0	2
Silybum marianum (L.) Gaertn (milk thistle)	2	0	0	2
Borago officinalis L. (Borage)	1	0	0	1
Crataegus monogyna Jacq. (hawthom)	1	0	0	1
Cynara scolymus L. (globe artichoke)	1	0	0	1
Echinacea pallida Nutt (pale purple coneflower)	1	0	0	1
Pelargonium sidoides DC (Umckaloab)	1	0	0	1
Pimpinella anisum L. (anise)	1	0	0	1
Plantago lanceolata L. (ribwort plantain)	1	0	0	1
Rhamnus purshiana DC (cascara sagrada)	1	0	0	1
Trifolium pratense L. (red clover)	1	0	0	1
TOTAL	**402**	**1**	**89**	**492**

Table 4 - Number of papers describing specific adverse effects to the botanicals considered and their ranking by causality*

Plant by scientific name **(common name)**	**Total number of papers describing side effects**	**Papers reporting certain/probable association**	**Papers reporting possible association**	**Papers showing unlikely/unassessable association**
Glycine max (L.) Merr (soybean)	91	58	11	22
Glycyrrhiza glabra L. (licorice)	51	38	11	2
Camellia sinensis (L.) Kuntze (tea)	34	15	14	5
Ginkgo biloba L. (ginkgo/Maideinhair tree)	28	19	4	5
Cinnamomum verum J Presl *(zeylanicum)* (cinnamon)	23	17	2	4
Vitex agnus castus L. (vitex/chaste tree)	18	13	1	4
Echinacea purpurea (L.) Moench (Eastern purple coneflower)	18	8	0	10
Cimicifuga racemosa (L.) Nutt (black cohosh)	19	14	5	0
Vitis vinifera L. (grape)	14	14	0	0
Harpagophytum procumbens DC (Devil's claw)	13	13	0	0
Hypericum perforatum L. (St John's wort)	10	4	6	0
Panax ginseng C.A. Meyer (ginseng)	11	1	6	4
Citrus aurantium L. (bitter orange)	7	5	0	2
Valeriana officinalis L. (valerian)	6	1	2	3
TOTAL	**343**	**220**	**62**	**61**

*Because of the high number of citations, the whole list of papers is organized for plant and causality in the Online Supplementary Data

Table 5 - Number of papers reporting interactions between the botanicals considered and nutrients, food or conventional drugs with ranking by causality*

Plant by scientific name **(common name)**	**Total number of papers describing interactions**	**Papers reporting certain/probable association**	**Papers reporting possible association**	**Papers showing unlikely/unassessable association**
Citrus aurantium L. (bitter orange)	18	6	11	1
Ginkgo biloba L. (ginkgo/Maideinhair tree)	14	7	3	4
Glycyrrhiza glabra L. (licorice)	9	6	2	1
Camellia sinensis (L.) Kuntze (tea)	9	3	6	0
Hypericum perforatum L. (St John's wort)	9	6	3	0
Valeriana officinalis L. (valerian)	8	0	4	4
Glycine max (L.) Merr (soybean)	4	1	2	1
Cimicifuga racemosa (L.) Nutt (black cohosh)	4	0	4	0
Panax ginseng C.A. Meyer (ginseng)	5	1	4	0
Echinacea purpurea (L.) Moench (Eastern purple coneflower)	2	1	1	0
Vitex agnus castus L. (vitex/chaste tree)	1	0	0	1
TOTAL	**83**	**31**	**40**	**12**

*Because of the high number of citations, the whole list of papers is organized for plant and causality in the Online Supplementary Data

Table 6 - Form used by consumers experiencing adverse effects

Plant by scientific name **(common name)**	**Botanical part used (when specified)**	**Food and beverages (functional, flavoured etc.)**	**PFS (type)**	**Other**
Camellia sinensis (L.) Kuntze (tea)	Leaves	Tea (high quantity)	Capsules containing micronized leaf powder or different extracts	Acqueous, ethanolic, hydroalcoholic extracts
Cimicifuga racemosa (L.) Nutt (black cohosh)	Rizhoma	-	Capsules containing 6 plants including *C.racemosa*	Standardized unspecified extract
Cinnamomum verum J Presl *(zeylanicum)* (cinnamon)	Bark	Flavoured candies and foods; sweet vermouth and coffee	PFS (containing oil)	Oil, chewing-gum, toothpaste, mounthrinse
Citrus aurantium L. (bitter orange)	Ripe and unripe fruit Fruit rind	-	-	Unspecified extracts, decoction
Echinacea purpurea (L.) Moench (Eastern purple coneflower)	Root or coneflower	Juice	Juice combined with other ingredients	Hydroalcoholic, acquous or unspecified extracts
Ginkgo biloba L. (ginkgo/Maideinhair tree)	Leaves, seeds	Roasted ginkgo seeds, microwave cooked seeds	PFS containing extracts	Extracts, ginkgolide mixtures
Glycine max (L.) Merr (soybean)	Seeds	Soybean protein based formula, soybean "milk", Miso (fermented soybean), Tofu, Baloney (sausage)	Supplements containing soybean isoflavones	Lecithins, soybean protein concentrates, soybean granules, soybean flour
Glycyrrhiza glabra L. (licorice)	Root	Licorice rope and candies, juices, drinks, Pontefract cake	PFS tablets, "herbal tonic"	Chewing-gum, decoction, concentrated juice
Harpagophytum procumbens DC (Devil's claw)	Tuber, root tuber, secondary tuber, whole plant	-	Capsules containing extract from whole plant	Acqueous extract, ethanol extract, powder from root or secondary tubers

Hypericum perforatum L. (St John's wort)	Flowering herb	-	Tablets, unspecified preparations, including an extract enriched in hyperforin	Unspecified extracts
Panax ginseng C.A. Meyer (ginseng)	Root	Candies and teas	Ginseng syrup	Dry root, extracts (from standardized to unspecified), chewing-gum
Valeriana officinalis L. (valerian)	Root	-	Infusions	Raw root material
Vitex agnus castus L. (vitex/chaste tree)	Fruit	-	-	Ethanolic/acquous extracts
Vitis vinifera L. (grape)	Fruit and leaves	Fresh and dry fruit, Juices	-	Acquous extract, hydroalcoholic extract; unspecified skin extract