Research Article

Adverse Effects of Plant Food Supplements Self-Reported by Consumers in the PlantLIBRA Survey Involving Six European Countries

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Abstract

Background

The use of food supplements containing botanicals is increasing in European markets. Although intended to maintain the health status, several cases of adverse effects to Plant Food Supplements (PFS) have been described.

Objectives

To describe the self-reported adverse effects collected during the European PlantLIBRA PFS Consumer Survey 2011–2012, with a critical evaluation of the plausibility of the symptomatology reported using data from the literature and from the PlantLIBRA Poisons Centers’ survey.

Subjects/Setting

From the total sample of 2359 consumers involved in the consumers’ survey, 82 subjects reported adverse effects due to a total of 87 PFS.

Results

Cases were self-reported, therefore causality was not classified on the basis of clinical evidence, but by using the frequency/strength of adverse effects described in scientific papers:
52 out of 87 cases were defined as possible (59.8%) and 4 as probable (4.6%). Considering the most frequently cited botanicals, eight cases were due to Valeriana officinalis (garden valerian); seven to Camellia sinensis (tea); six to Ginkgo biloba (Maidenhair tree) and Paullinia cupana (guarana). Most adverse events related to the gastrointestinal tract, nervous and cardiovascular systems.

Conclusions
Comparing the data from this study with those published in scientific papers and obtained by the PlantLIBRA Poisons Centers’ survey, some important conclusions can be drawn: severe adverse effects to PFS are quite rare, although mild or moderate adverse symptoms can be present. Data reported in this paper can help health professionals (and in particular family doctors) to become aware of possible new problems associated with the increasing use of food supplements containing botanicals.

Introduction
The European Union (EU) Directive on Food Supplements (2002/46/EC) defines food supplements (which include PFS): “… foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles and other similar forms of liquids and powders designed to be taken in measured small quantities”. Their market is growing significantly both in Europe and the USA [1]. Although there exists some overlap/confusion with traditional herbal medicinal products [2], plant food supplements cannot be sold as having any diagnostic, preventative or therapeutic properties; their role is only complementary to the diet.

The consumption of Plant Food Supplements (PFS) is usually estimated on the basis of market data, and mainly from import/export of raw ingredients, but since botanicals are used in both food and medicinal areas, the extrapolation to PFS is quite difficult [3]. Data on the use of dietary supplements reported by consumers are very limited and normally include only those products containing vitamins and minerals [4]; other available data come from studies relating to complementary/traditional medicine [5].

To provide new data on PFS usage patterns, a survey was performed with consumers of PFS in the framework of the European Project PlantLIBRA (n. 249159); it involved 2359 adults from Finland, Germany, Italy, Romania, Spain and UK. The main results of the PlantLIBRA PFS Consumer Survey (2011–2012) were published in 2014 [6]; the present paper deals with the adverse effects self-reported by the consumers participating in the survey.

Adverse effects to PFS have been reported by several authors; most of the studies were: a) case reports describing a specific acute event, or b) reviews of cases in a specific clinical area (cardiovascular, gastrointestinal, etc.) [7–8]. A critical limitation of the information reported to date in the scientific literature is a lack of assessment of causality; in other words, the strict association between the intake of a specific plant and the clinical event is rarely demonstrated by measuring biomarkers or by the de-challenge/re-challenge approach. On this basis, a systematic review of the data on adverse effects due to PFS/botanical ingredients, including misidentification and interactions of PFS/botanicals with pharmaceutical drugs or nutrients was undertaken [9]. Data were collected for 66 botanicals, which are common ingredients of PFS;
all papers were classified for causality according to the WHO guidelines [10] and grouped as "certain, probable, possible and uncertain/unclassifiable events". Among the 492 papers selected, 402 (81.7%) dealt with adverse effects due to the botanical as such or in a PFS, and 89 (18.1%) described interactions with conventional drugs. Misidentification was confirmed in one case [9].

The aims of this paper are: 1) to identify the adverse effects reported by the European participants in the PlantLIBRA PFS Consumer Survey, and 2) to critically evaluate the plausibility of the symptomatology reported as being related to PFS.

**Materials and Methods**

The survey was conducted in 6 European countries (Finland, Germany, Italy, Romania, Spain and the United Kingdom), and recruitment of participants occurred in 4 cities in each country. In this study, "Botanical" means raw material and derived preparations made from plants, algae, fungi or lichens (http://www.efsa.europa.eu/en/topics/topic/botanicals). The botanicals to be included in the survey were clearly defined at the outset; PFS were defined as the "food-stuffs the purpose of which is to supplement the normal diet and which are concentrated sources of botanical preparations that have nutritional or physiological effect, alone or in combination with vitamins, minerals and other substances which are not plant-based". Herbal remedies, other medicinal products based on botanicals, herbal teas or juices were excluded [6].

In order to obtain a sample of 400 consumers/each country, approximately 2000 individuals were screened per country (total number close to 2400) [6]. Eligible consumers completed a detailed questionnaire on PFS usage, providing product/plant names, dosage forms, frequency of use, reasons for use, adverse effects, places and patterns of purchase and information sources on products. Data on a maximum of five different PFS for each consumer was recorded; when PFS were more than 5, the inclusion was based on the frequency of use. Responders’ sociodemographic data, including age, gender, level of education and employment status, as well as height, weight and health-related lifestyle information, were also collected. Further details on the survey have been reported previously [6]. The composition of each PFS was obtained from the label, if at disposal, or by searching the PFS ingredients in the website of producers.

Regarding the collection of data on adverse effects, the following two questions were included for each product:

1. Have you experienced any adverse effects while taking this product?
2. If yes, which one? (list of symptoms provided, with "other" as an option).

**Ethical aspects**

Approval of the survey protocols was obtained from four ethics committees: the Bioethics Commission of the University of Barcelona, Spain; the Ethics Committee of the Università degli Studi di Milano, Italy; the Ethical Committee of the Faculty of Medicine—Transilvania University of Brasov, Romania; and the Coordinating Ethics Committee, Hospital District of Helsinki and Uusimaa, Finland.

Approval of the survey by these four ethics Committees required submitting all survey material to their members for evaluation. No ethical approval for the survey was needed in Germany and the United Kingdom. Furthermore, the ethical aspects were considered in the European Commission Consolidated Review Report dated 30th September 2013 and evaluated as “ethical issues regarding the surveys have been handled appropriately”.

In all countries, informed consent was obtained from survey participants verbally after reading the survey information sheet. The data were collected anonymously on paper
questionnaires and then transferred to an electronic database; all responders were assigned an ID number prior to data analyses.

**Statistical analysis**

All data were entered into the statistical package SPSS for Windows v. 18 (IBM Corporation, Somers, NY, USA), which was used for analysis.

**Results and Discussion**

A total of 11783 consumers (5799 males and 6004 females) were screened during the PlantLIBRA survey, of which 2359 were considered eligible and included in the study. The number of consumers per country and the percentage self-reporting adverse effects are listed in Table 1.

Considering the entire survey, the percentage of consumers, who reported adverse effects was approximately 3.5%. Differences were observed between countries; the number of consumers reporting adverse effects ranged between 5 and 6% of the total interviewed in three countries (Finland, Germany and Spain), while they were less numerous in Romania (2%), Italy (1%) and the United Kingdom (0.3%).

There were no significant differences based on sex or age groups (Table 1 and Table 2).

The data collected on adverse effects are presented in Table 3. Details of each of the 82 cases are recorded including:

- ID of the 82 consumers reporting adverse effects. ID 1–23 were from Finland, ID 24–45 from Germany, ID 46–69 from Spain, ID 70–74 from Italy, ID 75–81 from Romania, ID 82 from the United Kingdom. When a consumer reported adverse effects for two PFS, letters A and B follow the ID;

### Table 1. Consumers included in the PlantLIBRA PFS Consumer Survey and self-reporting adverse effects.

| Country      | Number of consumers in the survey | Number of consumers reporting adverse effects | Percentage |
|--------------|-----------------------------------|-----------------------------------------------|-------------|
| Finland      | Total number 401                  | 23                                            | 5.7         |
|              | Males 193                         | 10                                            | 5.2         |
|              | Females 208                       | 13                                            | 6.3         |
| Germany      | Total number 398                  | 22                                            | 5.5         |
|              | Males 197                         | 13                                            | 6.6         |
|              | Females 201                       | 9                                             | 4.5         |
| Italy        | Total number 378                  | 5                                             | 1.3         |
|              | Males 187                         | 2                                             | 1.1         |
|              | Females 191                       | 3                                             | 1.6         |
| Romania      | Total number 400                  | 7                                             | 1.8         |
|              | Males 199                         | 4                                             | 2.0         |
|              | Females 201                       | 3                                             | 1.5         |
| Spain        | Total number 402                  | 24                                            | 6.0         |
|              | Males 174                         | 9                                             | 5.2         |
|              | Females 228                       | 15                                            | 6.6         |
| United Kingdom| Total number 380                 | 1                                             | 0.3         |
|              | Males 191                         | 1                                             | 0.5         |
|              | Females 189                       | 0                                             | -           |
| Total        | Total number 2359                 | 82                                            | 3.5         |
|              | Males 1141                        | 39                                            | 3.4         |
|              | Females 1218                      | 43                                            | 3.5         |

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Adverse Effects Reported in the PlantLIBRA Survey
• Age and gender;
• The botanical/s contained in the PFS associated with the reported adverse effect. For a more precise identification, Latin names have been used but the corresponding common names are reported in Table 4 (see table note for scientific sources);
• The daily dose and the period of intake;
• The reason for use reported by the consumer, i.e. the physiological effect expected by the consumer;
• An assessment of the suitability of the botanical ingredient(s) present in the consumed PFS for the condition used, based on what the literature says about these ingredients. The main literature sources were the list of physiological effects published by the Italian Ministry of Health [11] and the EMA website [12]. In specific cases, other scientific papers were cited;
• The general health status of the consumer. These data allow a better assessment of adverse effect causality;
• Any reported simultaneous intake of conventional medicines and other food supplements; these data allow the assessment of possible interactions;
• The adverse effects reported by the consumers;
• A judgement as to the likelihood of causality, according to previous scientific citations and taking into consideration all available data.

Considering the suitability of the botanical product used in relation to the physiological effect expected by the consumers, the choice was considered appropriate in 88% of cases. One case (ID 4) was considered non pertinent and nine (ID 8, 11, 12, 18, 23, 33, 44, 57, 74) judged as unlikely or with limited evidence. One consumer (ID 08) used a product containing 12 herbal ingredients, but only *Citrus aurantium* could claim to have tonic properties due to the presence of active amines. None of the herbal ingredients present have any reported immune activity [11–12].

Since all cases were self-reported, it was not possible to establish causality of adverse effects on the basis of clinical evidence. The scientific literature was used to assess the likelihood of the

| Country          | Consumers in the whole survey (m ±SD) | Consumers reporting adverse effects (m ±SD) |
|------------------|---------------------------------------|-------------------------------------------|
| Finland          | 48.3±15.7                             | 48.7±13.8                                 |
| Germany          | 47.0±15.8                             | 48.3±16.4                                 |
| Italy            | 44.0±16.2                             | 40.6±15.2                                 |
| Romania          | 42.9±16.7                             | 43.1±17.9                                 |
| Spain            | 47.1±13.9                             | 50.6±11.4                                 |
| United Kingdom   | 48.9±14.2                             | 35.0*                                     |
| **Total**        | **46.4±15.6**                         | **48.0±14.2**                             |

m±SD = mean±Standard Deviation

* no SD since only one consumer reported adverse effects

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Table 3. Adverse effects reported by PlantLIBRA PFS Consumer Survey participants.

| ID | Age/Gender | Botanical/s* | Dose and period | Reasons for use | “Suitability” | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|----|------------|--------------|-----------------|-----------------|---------------|----------------------------------------|------------------------|----------------|-----------|
| 01 | 55/F       | Camellia sinensis, Panax ginseng | 1/d x 2w | Tonic | Yes [11] | Migraine | Antihistaminics, Corticosteroids, Ibuprofen, Roxithromycin + FO, PO, VM | Gastric problems | Possible worsening of gastric side effects of anti-inflammatory drugs |
| 02 | 31/M       | Echinacea angustifolia, E. purpurea | 2/d x 2w | Immunity | Yes [11–12] | None | No drug + AA, VM | Gastric problems | Possible [43–44] |
| 03 | 55/F       | Glycine max | 1/d x 6m | Menopause | Yes [11] | Allergy | Antiallergic drugs + Vitamin D | Gastric problems | Possible [45–46] |
| 04 | 36/F       | Gossypium spp., Zingiber officinale | 2/d x 3m | Neuralgia | No | Allergy/asthma, joint/bone pain | Budesonide, Formoterol, Salbutamol + FO, VM | Gastric problems | Possible [14; 47] |
| 05 | 54/F       | Zingiber officinale | 1/d x 24d | Joints/bones | Yes [11] | HCHO | Simvastatin + PO, VM | Gastric problems | Possible [14; 47] |
| 06 | 72/F       | Echinacea angustifolia, E. purpurea | 3/d x 4d | Immunity | Yes [11–12] | HCHO | No drug + Vitamin D | Gastric problems | Possible [43–44] |
| 07 | 57/F       | Echinacea angustifolia, E. purpurea | 3/d x 3d | Immunity | Yes [11–12] | Cancer | No drug + FO, V | Tachycardia | Unlikely |
| 08 | 44/F       | Achillea millefolium, Citrus aurantium, Crataegus spp., Daucus carota, Equisetum arvense, Foeniculum vulgare, Fucus vesiculosus [alga], Hibiscus rosa-sinensis, Ribes nigrum, Spinacia oleracea, Triticum spp., Urtica dioica | 2/w x 1m | Immunity, tonic | Unlikely | Migraine | No drug + VM | Gastric problems | Unassessable due to the presence of several ingredients |
| 09 | 53/F       | Arctium lappa, Betula spp., Cichorium intybus, Cynara scolymus, Filipendula ulmaria, Foeniculum vulgare | 2/d x 1m | Detoxification | Yes [12] | None | No drug + AA, E, FO, PO, PE, VM | Increased diuresis | Possible due to the presence of diuretic ingredients [Betula spp., Arctium lappa] [48–49] |
| 10 | 61/M       | Equisetum arvense | 3/d x 12m | Hair/skin | Yes [11] | None | No drug + FO, V | Hair loss/fragile nail | Possible due to decreased level of thiamine [50] |

(Continued)
### Table 3. (Continued)

| ID | Age/Gender | Botanical/s* | Dose and period | Reasons for use | "Suitability" | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|----|------------|--------------|-----------------|-----------------|---------------|--------------------------------------|-------------------------|----------------|-----------|
| 11 | 31/F       | Calendula officinalis, Citrus sinensis, Dunaliella salina [alga], Glycine max, Picea spp. | 1/d x 6m | Antioxidant | Limited evidence [19] | None | No drug + PO, VM | Gastric problems | Unassessable due to the presence of several ingredients |
| 12 | 42/M       | Zingiber officinalis | 1/d x 1m | Bodybuilding, tonic | Unlikely [14] | None | No drug + AA | Gastric problems | Possible [14; 47] |
| 13 | 35/M       | Camellia sinensis | 2/d x 2m | Immunity, body weight, tonic, HCHO | Yes [11] | HCHO | No drug + Vitamin D, AA, FO | Insomnia and nausea | Possible for the content in caffeine [51] |
| 14 | 39/M       | Olea europaea (olive oil) | 1/d x 9m | Immunity, hair/skin, tonic, mood, joints/bones, blood circulation | Yes [11] | Psoriasis | No drug + FO, PE, VM | Diarrhoea and nausea | Possible—high intake of olive oil could produce laxative effect [22] |
| 15 | 72/F       | Oryza sativa + Monascus purpureus [fungus] | 1/d x 12m | HCHO | Yes [15–19] | Asthma, hypertension, cancer, depression, joint/bone pain | Acetylsalicylic acid, Amilodipine, Lisinopril, Pantoprazole + VM | Gastric problems | Possible [51–52] Possible worsening of gastric side effects of anti-inflammatory drugs |
| 16 | 46/M       | Oryza sativa + Monascus purpureus [fungus] | 1/d x 12m | HCHO | Yes [15–19] | HCHO, hypertension | Drugs for hypertension + FO, PO, VM | Increased liver enzymes | Possible [52–53] |
| 17A | 70/M       | Oryza sativa + Monascus purpureus [fungus] | 1/d x 11m | HCHO | Yes [15–19] | HCHO, diabetes, hearth disease, allergy, depression | Acetylsalicylic acid, Enapril, Loratadine, Metoprolol, Mometasone + E, FO, PO, VM | Dry skin | Unlikely [52–53] |
| 17B | 39/F       | Plantago psyllium, Prunus africana | 1/d x 2m | Urinary tract | Yes [20] | Gastric problems | Glucosamine + VM | Possible [54] Possible worsening of gastric side effects of anti-inflammatory drugs |
| 18 | 49/M       | Gossypium spp., Zingiber officinalis | 1/d x 2m | Sleeping, joints/bones | Unlikely | Muscle, joint/bone pain | Bisoprolol, Olanzapine, Thyroxin, Zopiclon + VM | Gastric problems | Possible [14, 47] |
| 19 | 68/F       | Oryza sativa + Monascus purpureus [fungus] | 1/d x 12m | HCHO | Yes [15–19] | HCHO, hypertension, depression | Biscoprol, Olanzapine, Thyroxin, Zopiclon + VM | Difficulty in swallowing | Possible [55] |
| 20 | 39/F       | Oryza sativa + Monascus purpureus [fungus] | 1/d x 6m | HCHO | Yes [21–22] | HCHO, hypertension, diabetes | Metformin, Telmisartan + FO, PO, VM | Increased liver enzymes | Possible [52–53] |

(Continued)
| ID | Age/Gender | Botanical/s\(^*\) | Dose and period | Reasons for use | “Suitability” | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|----|------------|-------------------|-----------------|----------------|--------------|-------------------------------------|------------------------|----------------|----------|
| 22 | 24/M       | *Camellia sinensis* | 1/d x 2m        | Immunity, body weight, tonic, antioxidant | Yes [11–12] | None | No drug + E, FO, PO, VM | Nausea | Possible [57] |
| 23 | 40/F       | *Urtica dioica*    | 3/d x 2m        | Body weight, immunity | Limited evidence [23–24] | None | No drug + AA, FO, PO, VM | “Easy” sweating | Possible [58] |
| 24 | 48/F       | *Arthrospira platensis* [alga] | 1/d x 5m | Antioxidant, immunity | Yes [25–26] | Migraine | Analgesics + V | Insomnia | Uncertain |
| 25 | 47/M       | *Auricularia auricula-judae* [fungus], *Coffea arabica*, *Fallopia japonica*, *Polygonum cuspidatum*, *Ginkgo biloba*, *Panicum miliaceum*, *Polyporus umbellatus* [fungus], *Saccharomyces cerevisiae* [yeast], *Serenoa repens*, *Trigonella foenum-graecum*, *Ziziphus jujuba* | 2/d x 12m | Hair/skin, energy | Yes [11, 27–28] | HCHO | None | Discomfort | Unassessable due to the presence of several ingredients |
| 26 | 57/M       | *Cucurbita maxima*, *Vaccinium macrocarpon* | 2/d x 2m | Urinary tract | Yes [11] | HCHO, hypertension | Benazepril | Discomfort | Unassessable |
| 27 | 45/M       | *Saccharomyces cerevisiae* [yeast] | 3/d x 3m | Hair/skin | Yes [29–30] | None | None | Skin problems | Unlikely [Allergy?] |
| 28 | 42/M       | *Asparagus officinalis*, *Cynara scolymus*, *Cichorium intybus* (inulin), *Plantago psyllium* | 1/d x 2w | Constipation | Yes [11] | None | No drug + M | Diarrhoea | Possible [59] |
| 29 | 64/F       | *Nigella sativa*   | 1/d x 1m        | Immunity, HCHO | Yes [31–32] | None | No drug + M | Mild flatulence | Unlikely |
| 30 | 42/F       | *Cynara scolymus*  | 1/d x 6m        | Digestion, HCHO | Yes [11–12] | HCHO | No drug + VM | Nausea | Possible [59] |
| 31 | 62/F       | *Glycine max*      | 3/d x 3m        | Menopause | Yes [11] | Allergy | No drug + FO, M | Gastric problems | Possible [45–46] |
| 32 | 31/M       | *Matricaria recutita, Melissa officinalis, Valeriana officinalis* | 3/d x 6m | Sleeping and mood problems | Yes [11–12] | Migraine, peptic ulcer, sleep disorders | None | Dizziness | Possible [60] |
### Table 3. (Continued)

| ID | Age/ Gender | Botanical/s^* | Dose and period | Reasons for use | “Suitability” | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|----|-------------|---------------|-----------------|-----------------|---------------|-------------------------------------|-------------------------|----------------|-----------|
| 33 | 56/M        | Brassica oleracea | 2/d x 2m       | Body weight    | Unlikely      | Hypertension, sleeping disorders, chronic bronchitis | None                    | Gastric problems | Unlikely  |
| 34 | 29/M        | Saccharomyces cerevisiae [yeast] | 2/d x 3m    | Hair/skin      | Yes [29–30]  | None                                | None                    | Gastric problems, diarrhoea | Unlikely  |
| 35A| 64/F        | Cynara scolymus | 1/d x 5d       | Body weight, HCHO, digestion | Yes [12] | Hypertension, asthma, diabetes, joint/ bone pain | Beclometason [spray], Formoterol [spray], Metformin, Thyroxin + VM, E (lactase) | Diarrhoea | Possible [22] |
| 35B|             | Camellia sinensis, Crataegus spp., Olea europaea (olive oil), Viscum album | Unknown |                  |               |                                                     |                         | Possible (olive oil) |           |
| 36 | 27/F        | Olea europaea (olive oil) | 1/d x 5w | HCHO, body weight, digestion, blood circulation | Yes [11–12] | HCHO | No drug + FO, VM | Diarrhoea | Possible [22] |
| 37 | 65/M        | Ginkgo biloba | 4/w x 12m      | Memory         | Yes [11–12]  | HCHO | Iron supplementation, V | Insomnia | Possible [61] |
| 38 | 66/F        | Ginkgo biloba | 5/w x 6m       | Memory         | Yes [11–12]  | None | None | Constipation | Possible [62] |
| 39 | 23/M        | Paullinia cupana | 1/d x 2m | Energy | Yes [11–12] | None | None | Diarrhoea | Unlikely |
| 40 | 19/M        | Paullinia cupana | 2/w x 3w | Energy, urinary tract | Yes [11–12] | None | None | Constipation | Unlikely |
| 41 | 71/M        | Cynara scolymus | 2/w x 4w | Antioxidant, immunity, digestion | Yes [11–12] | HCHO, hypertension | Metopolol, Ramipril | Gastric problems | Possible [59] |
| 42A| 31/M        | Peumus boldus | 2/w x 1w       | Digestion      | Yes [11–12]  | None | None | Constipation | Unlikely |
| 42B|             | Linum usitatissimum | 2/w x 3w | Digestion      | Yes [11–12]  | None | None | Constipation | Unlikely |
| 43 | 66/F        | Panax ginseng | 1/w x 6w       | HCHO, relaxing, hair/ skin | Yes [33–34] | HCHO, cataract | None | Constipation | Possible [63] |
| 44 | 66/M        | Olea europaea | 5/w x 2w       | Hair/skin      | Unlikely      | None | None | Gastric problems | Unlikely |
| 45 | 41/F        | Oenothera biennis | 2/d X 3m     | Immunity, hair/skin | Yes [11–12] | Hypertension, allergy | Antihypertensive drugs, Thyroxin | Mild eruption | Possible [64] |
| 46 | 57/F        | Camellia sinensis, Paullinia cupana | 2/d x 2m | Body weight, digestion, energy/tonic | Yes [11–12, 35] | None | No drug | Insomnia | Probable due to the content in caffeine [35] |
| 47 | 43/F        | Cassia angustifolia, Illicium verum, Raphanus sativus var. niger, Rhamnus purshiana | 1/d x 4w | Body weight, digestion | Yes [11] | Hypertension, migraine | No drug | Diarrhoea | Possible [65–66] |

(Continued)
### Table 3. (Continued)

| ID  | Age/Gender | Botanical/s* | Dose and period | Reasons for use | “Suitability” Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|-----|------------|--------------|----------------|----------------|---------------------------------------------------------|--------------------------|----------------|-----------|
| 48  | 47/F       | Rhamnus purshiana | 1/d x 9m | Digestion | Yes [11] | Chronic neutropenia, glaucoma, vascular problems | Bimatoprost, Timolol | Gastric problems | Possible [66] |
| 49  | 36M        | Valeriana officinalis | 4/w x 5m | Sleeping, relaxing, mood | Yes [11–12] | None | None | Insomnia | Unlikely but described [67] |
| 50  | 61/M       | Punica granatum | 2/d x 12m | Prostate | Yes [36] | Cancer | None | Diarrhoea | Possible for high intake or previous intestinal disorders [68] |
| 51  | 46/F       | Cassia angustifolia, Raphanus sativus var. niger | 1/d x 2m | Digestion | Yes [11] | None | None | Flatulence | Possible [65] |
| 52  | 69/F       | Pimpinella anisum | 2/d x 12m | Digestion | Yes [11–12] | Hypertension, osteoporosis | Amlodipine | Diarrhoea | Uncertain (associated with allergic reaction) |
| 53  | 61/F       | Valeriana officinalis | 2/d x 12m | Sleeping, relaxing, mood | Yes [11–12] | HCHO, heart disease, muscles, joint/bone pain, cataract | Alprazolam, Simvastatin | Constipation | Possible—abdominal cramps have been described [69] |
| 54  | 72/F       | Valeriana officinalis | 1/d x 8m | Sleeping, memory, relaxing | Yes [11–12] | Cancer, joint/bone pain | None | Migraine | Possible [67] |
| 55  | 36/F       | Panax ginseng, Paullinia cupana | 1/d x 3m | Energy/tonic | Yes [11–12] | None | Birth-control pill | Tachycardia | Probable [70] |
| 56  | 39/M       | Passiflora incarnata | 1/d x 10m | Sleeping, relaxing | Yes [11–12] | Fatigue; insomnia | None | Insomnia | Unlikely |
| 57  | 63/M       | Malus domestica, Citrus limon | 2/d x 4m | Constipation | Unlikely | HCHO, heart disease, hypertension | Quinapril/ Hydrochlorothiazide, Diosmin/Esperidin (flavonoids) | Gastric problems | Unlikely |
| 58  | 50/F       | Paulinia cupana | 1/d x 2w | Energy/tonic | Yes [11–12] | Hypertension, anxiety, depression | Fluoxetine | Tachycardia | Probable [70] |
| 59  | 49/F       | Valeriana officinalis | 1/d x 3m | Relaxing | Yes [11–12] | HCHO; hypertension, migraine, allergy, anxiety | No drug + Si, VM | Flutamide | Possible—abdominal cramps have been described [69] |
| 60  | 64/F       | Oenothera biennis | 3/d x 9m | Breast nodule | Yes [12] | Hypertension, allergy | Valsartan + AA, V, SI | Cystitis | Unlikely |
| 61  | 60/F       | Harpagophytum procumbens | 3/d x 1m | Joints/bones | Yes [11–12] | Bone/joint pain, low back pain | None | Gastric problems | Possible [71] |
| 62  | 42/M       | Allium sativum | 3/d x 2m | Immunity | Yes [37] | Asthma, renal problems | Amoxicillin/ clavulanic acid | Allergic symptoms | Possible (quite rare) |

(Continued)
| ID  | Age/Gender | Botanical/s^* | Dose and period | Reasons for use | “Suitability” | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|-----|------------|----------------|-----------------|----------------|---------------|--------------------------------------|------------------------|----------------|-----------|
| 63  | 49/M       | Taraxacum officinale | 3/d x 8m        | Digestion, diuretic | Yes [11–12]  | Liver disease | None | Diarrhoea | Unlikely |
| 64  | 42/M       | Valeriana officinalis | 2/d x 4m        | Sleeping, relaxing | Yes [11–12]  | Liver disease, gallbladder inflammation | None | Insomnia | Unlikely but described [67] |
| 65A | 38/F       | Equisetum arvense | 2/d x 4m        | Hair/skin, urinary tract | Yes [11–12]  | Muscle and bone pain, migraine, ulcer, anxiety and depression, urinary problems | Trimethoprim, Sulfamethoxazol, Ibuprofen | Constipation | Possible—gastrointestinal complaints have been reported [72] |
| 65B | Taraxacum officinale | 1/d x 4m | Urinary tract | Yes [11–12]  | None | Dizziness | Unlikely even though described for interaction with acetylsalicylic acid |
| 66  | 46/F       | Lepidium meyenii | 2/d x 3m       | Urinary tract [kidney stones] | Yes [38]  | Allergy, kidney stones | Ibuprofen, Metamizole, Potassium citrate | Diarrhoea | Unlikely |
| 67  | 54/M       | Echinacea angustifolia | 3/d x 1m      | Flu cold | Yes [12]  | HCHO, hypertension | Metformin, Olmesartan/Medoxomil | Increased glycaemia | Unlikely |
| 68  | 61/M       | Echinacea spp | 1/d x 2m        | Sinusitis | Yes (cold) [12]  | HCHO, anxiety and depression | Atorvastatin, Enalapril | Gastric problems | Possible [73] |
| 69A | 30/M       | Allium sativum | 1/d x 3m        | Immunity, flu cold | Yes [37]  | Allergy | None | Gastric problems | Possible [74] |
| 69B | Valeriana officinalis | 2/d x 12m | Sleeping | Yes [11–12]  | Allergy | None | Migraine | Possible [67] |
| 70  | 29/F       | Foeniculum vulgare | 3/d x 2m        | Body weight, urinary tract | Yes [12]  | Asthma, allergy | Beclometasone, Drosiprenone/Ethyl estradiol, Salbutamol | Difficult swallowing reported in cases of allergy |
| 71  | 35/M       | Paullinia cupana | 1d x 5m         | Energy/tonic, mood | Yes [11–12]  | Heart disease | None | Dizziness | Possible [75] |
| 72  | 52/M       | Aloe barbadensis, Harpagophyllum procumbens | 2 x 4w | Joints/bones | Yes [11–12]  | Muscle, bone/joint pain | None | Unspecified | Unassessable |
| 73  | 26/F       | Panax ginseng | 1d x 2w         | Energy/tonic | Yes [11–12]  | None | No drug + Inositol, folic acid | Tachycardia | Possible [76] |
| 74  | 61/F       | Cyamopsis tetragonoloba | 20/m x ? | Body weight, energy/tonic | Unlikely [39–40]  | Diabetes | None | Nausea | Possible [40] |
| 75  | 69/M       | Ginkgo biloba | 2/d x ?         | Joints/bones, blood circulation | Yes [11]  | Diabetes, heart disease, hypertension, liver disease, stroke, gallbladder inflammation/stones | Acenocumarole, Captopril, Trimetazidine | Insomnia | Possible [77] |
adverse effects being associated with the botanical used and 56 out of 87 (64%) cases were defined as possible (52) or probable (4) according to 1) the daily dose and period of intake, and 2) the frequency and strength of scientific evidence. The most significant references are reported in Table 3. The association was not confirmed for 28 cases. The interaction with conventional drugs was considered possible in three cases (ID 01, 15 and 17B). It is important to underline that comparing the list of conventional drugs used with the column "Present or past main health problems", there are several incongruences; this is due to the self-reported nature of information collected.

The frequency of self-reported adverse effects in relation to each botanical is reported in Table 4; the total number of botanical ingredients contained in PFS with reported adverse effects was 72 and the total counts were 144. In most cases (46%), the PFS involved contained one ingredient. Forty botanicals (55.6% of the total) were associated with a single adverse event and 80% of them were included in PFS containing two or more ingredients. Considering the

Table 3. (Continued)

| ID | Age/ Gender | Botanical/s | Dose and period | Reasons for use | "Suitability" | Present or past main health problems | Conventional drugs + FS | Adverse effects | Causality |
|----|-------------|-------------|-----------------|-----------------|---------------|--------------------------------------|-------------------------|----------------|----------|
| 76 | 21/F        | Ginkgo biloba | 1/d x ?         | Memory          | Yes [11]      | None                                 | No drug + Polyphenols  | Dizziness      | Possible [78] |
| 77 | 19/M        | Ginkgo biloba | 2/d x 14d       | Memory          | Yes [11]      | Hypertension                          | Captopril              | Insomnia       | Possible [77] |
| 78 | 41/F        | Arthospira platensis [alga], Hippophae rhamnoides | 1/d x ? | Immunity, energy/tonic | Yes [11] | Anemia, arrhythmia                   | None                    | Gastric problems, nausea | Unlikely |
| 79 | 50/M        | Camellia sinensis | 1/d x 2w | Immunity         | Yes [41]     | HCHO, diabetes, migraine             | None                    | Diarrhoea, gastric problems (nausea) | Unlikely |
| 80 | 49/M        | Camellia sinensis | 1/d x 2w | Immunity         | Yes [41]     | Migraine, ulcer                      | None                    | Diarrhoea, gastric problems (nausea) | Unlikely |
| 81 | 53/F        | Betula spp., Equisetum arvense, Juniperus communis, Pimpinella anisum, Vaccinium vitis-idea | 3/d x 20d | Urinary tract    | Yes [11]     | HCHO, asthma, diabetes, heart disease, hypertension, liver disease, chronic bronchitis, cataract, osteoporosis, allergy, cancer, Basedow disease | Enalapril, Metformin, Nicergoline, Simvastatin | Gastric problems | Unassessable due to the presence of several ingredients |
| 82 | 35/M        | Aloe vera     | 3/w x 12m       | Joints/bones    | Yes [42]     | None                                 | None                    | Diarrhoea       | Probable [laxative effect] |

^ according to: for plants US Department of Agriculture (plants.usda.gov); for algae www.algaebase.org; for fungi www.indexfungorum.org  
? unknown  
AA= Supplement containing amino acids; FO= Fish Oil; E= Enzymes; HCHO= Hypercholesterolemia; M= Supplement containing minerals; PE= Prebiotics; PO= Probiotics; SI= Soy isoflavones; V= Supplement containing vitamins; VM= Supplement containing vitamins and minerals; d= day; m= month; w= week  
doi:10.1371/journal.pone.0150089.t003
| Latin name                      | Common name            | Total for country | Number of counts | Adverse Effects Reported in the PlantLIBRA Survey |
|--------------------------------|------------------------|-------------------|------------------|--------------------------------------------------|
| Valeriana officinalis          | Garden valerian        | 1                 | 7                | 8 7 1                                            |
| Camellia sinensis              | Tea                    | 3 1 2 1           | 7 4 2 1          |                                                  |
| Ginkgo biloba                  | Maidenhair tree        | 3 3              | 6 5              | 1                                               |
| Paulinia cupana                | Guarana                | 2 1 3            | 6 4 2            |                                                  |
| Cynara scolymus                | Globe artichoke        | 1 4              | 5 3              | 2                                               |
| Echinacea angustifolia/purpurea | Black Samson Echinacea/Eastern purple coneflower | 3 2 5 5 | |                                                 |
| Olea europaea                  | Olive                  | 2 3              | 5 3 1 1          |                                                  |
| Oryza sativa + Monascus purpureus | Red rice            | 5                | 5                | 5                                               |
| Panax ginseng                  | Chinese ginseng        | 2 1 1            | 1 5 2 3          |                                                  |
| Equisetum arvense              | Field horsetail        | 2 1 1            | 4 2              | 2                                               |
| Allium sativum                 | Cultivated garlic      | 3                | 3                |                                                  |
| Foeniculum vulgare             | Sweet fennel           | 2 1              | 3 1              | 2                                               |
| Glycine max                    | Soybean                | 2 1              | 3 2              | 1                                               |
| Saccharomyces cerevisiae        | Yeast                  | 3                | 3 2              | 1                                               |
| Aloe barbadensis/vera           | Barbados aloe          | 1 1              | 2 1              | 1                                               |
| Arthrospira platensis          | Spirulina              | 1 1              | 2 1              | 1                                               |
| Betula spp.                    | Birch                  | 1 1              | 2                | 2                                               |
| Cassia angustifolia            | Alexandrian senna      | 2 2              | 1 1              |                                                  |
| Citrus aurantium               | Sour orange            | 2                | 2                | 2                                               |
| Crataegus spp.                 | Hawthorn               | 1 1              | 2                | 2                                               |
| Cichorium intybus              | Chicory                | 1 1              | 2                | 2                                               |
| Gossypium spp.                 | Cotton                 | 2                | 2                | 2                                               |
| Harpagophytum procumbens       | Devil's claw           | 1 1              | 2 1              | 1                                               |
| Melissa officinalis            | Common balm            | 1 1              | 2                | 2                                               |
| Oenothera biennis              | Common evening primrose| 1 1              | 2 2              |                                                  |
| Pimpinella anisum              | Anise burnet saxifrage | 1 1              | 2 1              | 1                                               |
| Plantago psyllium              | Psyllium               | 1 1              | 2                | 1 1                                             |
| Raphanus sativus var. niger    | Spanish black radish   | 2                | 2                | 1                                               |
| Rhamnus purshiana              | Cascara buckthorn      | 2 2              | 1 1              |                                                  |
| Taraxacum officinale           | Common dandelion       | 2 2              | 2                |                                                  |
| Urtica dioica                  | Stinging nettle        | 2                | 2 1              | 1                                               |
| Zingiber officinale            | Garden ginger          | 2                | 2 1              | 1                                               |
| Achillea millefolium           | Common yarrow          | 1                | 1                | 1                                               |
| Arctium lappa                  | Greater burdock        | 1                | 1                | 1                                               |
| Asparagus officinalis          | Garden asparagus       | 1 1              | 1 1              |                                                  |
| Auricularia auricula-judae     | Jew's ear              | 1                | 1 1              |                                                  |
| Brassica oleracea              | Cabbage                | 1                | 1                | 1                                               |
| Calendula officinalis          | Pot marigold           | 1                | 1                | 1                                               |
| Citrus limon                   | Lemon                  | 1                | 1 1              |                                                  |
| Coffea arabica                 | Arabian coffee         | 1 1              | 1 1              |                                                  |
| Cucurbita maxima               | Winter squash          | 1                | 1 1              |                                                  |
| Cyamopsis tetragonoloba        | Guar                   | 1                | 1                | 1                                               |

(Continued)
most prevalent botanicals associated with adverse effects, 14 were associated with 68 reported adverse effects, representing the 47.2% of the total counts. In particular, eight were due to *Valeriana officinalis* (seven of them in Spain), seven to *Camellia sinensis*, six to *Ginkgo biloba* and six to *Paullinia cupana*.

The association of adverse effects with different organ systems is listed in Table 5.
Approximately 60% of adverse events were related to the gastrointestinal tract, distributed between gastric problems (where nausea was the most reported symptom) and intestinal effects (mainly diarrhoea).

The nervous system was the second most affected area with nine cases of insomnia, four of dizziness and two of migraine; the cardiovascular system was reported in four cases of tachycardia. The stimulating effects of botanicals containing caffeine can explain the insomnia and tachycardia reported by consumers 13, 46, 55, and 58, but in other cases, the effects were unexpected. An example is the case of insomnia due to *Valeriana officinalis* (ID 49 and ID 64), which is the opposite of the usual physiological effect, associated with this botanical [11–12]. *Ginkgo biloba* was involved in three cases of insomnia and one of dizziness.

Hair and skin were affected in three cases. A case of hair loss was reported by consumer 10, taking *Equisetum arvense* 3 units/day for 12 months. This adverse effect could be associated with the reported effect of *E. arvense* in reducing the bioavailability of thiamine after chronic consumption [50]. On the other hand, the role of thiamine deficiency in hair loss has been hypothesised but insufficiently documented [79]. Hepatotoxicity, defined as an increased level of liver enzymes, was reported by two consumers using red rice (*Oryza sativa* fermented by the fungus *Monascus purpureus*). Red rice is widely used in mild hypercholesterolemia, as a “natural” alternative to statins. Several side effects have been described in consumers using this ingredient, such as headache, dizziness, heartburn, gas and digestive tract discomfort, and it should be used cautiously by people suffering from liver disease and those at risk of it [52–53]. Allergies to *Allium sativum* and to a PFS containing *Melissa officinalis* and *Olea europaea* were reported by two consumers (ID 62 and ID 21, respectively).

A difficulty in swallowing was reported by a consumer (ID 19), using red rice to reduce blood cholesterol. Even though this effect has not been previously associated with red rice, there are some reports concerning the statins (having similar biological activity) for which the impaired swallowing was considered among possible symptoms of muscle degeneration [55].

Table 5 compares the plants most prevalently involved in adverse effects as reported by the PlantLIBRA project, in relation to: 1) data from the literature [9], 2) reports from Poisons Centers [80]; and finally from this study.

It is important to underline that the review from the literature did not separate cases due to botanicals used as food supplements or traditional medicines as was the case in the other two data reviews. Moreover, due to the very high number of botanicals in PFS, the review on the scientific literature included "only" 66 among the most frequently consumed botanicals. The
lists of plants most reported by Poisons Centers and by the consumers’ survey are similar, sharing five out 13 botanicals; among them *Valeriana officinalis* (garden valerian) and *Camellia sinensis* (tea) were in the first two positions. Moreover, a similar position in the ranking was occupied by *Paullinia cupana* (guarana), *Cynara scolymus* (globe artichoke), and *Panax ginseng* (chinese ginseng).

**Conclusions**

The cases of adverse effects described here were self-reported and thus without any supporting clinical evidence; the agreement with data published in scientific papers and in particular with the survey performed by the PlantLIBRA project among Poisons Centers allows the following conclusions:

1. As reported previously, severe adverse effects related to PFS are quite rare [80];
2. Mild or moderate adverse symptoms can be present but most of them do not require clinical support;
3. Data reported in this paper confirm that some plants are more frequently involved in adverse effects than others and can help family doctors, among other health professionals, to become aware about the possible consequences of the increasing use of food supplements containing botanicals;
4. This information could also be used to educate the public as to the possibility of adverse effects associated with the consumption of these food supplements.

**Author Contributions**

Conceived and designed the experiments: LSM LRB AGA BE LD FMM MMR MB. Analyzed the data: PR CDL RMV LRB AGA. Wrote the paper: PR CDL. Responsible for the survey: LSM. Coordination of the survey: AGA. Material elaboration: AGA BE LD FMM LRB MMR
MB. Data reviewing/handling/cleaning: AGA BE LD FMM LRB MB FB MS AM LU. Data analysis strategy: LRB LSM AGA RMV BE MMR LD FMM MB AM LU PR CDL AC SL. Drafts reviews: AC SL AGA LRB LD FMM BE MMR MB AM LU LSM. Manuscript coordination: PR.

References
1. NBJ’s Supplement Business Report. An analysis of markets, trends, competition and strategy in the U. S. dietary supplement industry. Nutrition Business Journal 2012. Available: http://newhope360.com/site-files/newhope360.com/files/uploads/2013/04/TOC_SUMM120928.supp%20report%20FINAL%20standard.pdf. Accessed 8 January 2016.
2. Silano V, Coppens P, Larrañaga-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. doi: 10.1039/c1fo10105f PMID: 21997496
3. European Advisory Services (EAS). The use of substances with nutritional or physiological effect other than vitamins and minerals in food supplements. Study undertaken for DG SANCO, European Commission. Service contract nRSANCO/2006/E4/018, 2007. Available: http://ec.europa.eu/food/safety/docs/labelling_nutrition-supplements-2007_a540169_study_other_substances_en.pdf. Accessed 8 January 2016.
4. Skeie G, Braaten T, Hjartåker A, Lentjes M, Amiano P, Jakobsen P, et al. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. Eur J Clin Nutr. 2009; 63: S226–S238. doi: 10.1038/ejcn.2009.83 PMID: 19888276
5. Vargas-Murga L, Garcia-Alvarez A, Roman-Viras B, Ngo J, Ribas-Barba L, van den Berg SJ, et al. Plant food supplement (PFS) market structure in EC Member States, methods and techniques for the assessment of individual PFS intake. Food Funct. 2011; 2: 731–739. doi: 10.1039/c1fo10075k PMID: 21879100
6. Garcia-Alvarez A, Egan B, de Klein S, Dima L, Maggi FM, Isoniemi M, et al. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014; 9: e92265. doi: 10.1371/journal.pone.0092265 PMID: 24842692
7. Valli G, Giardina E.G. Benefits, adverse effects and drug interactions of herbal therapies with cardiovascular effects. J Am Coll Cardiol. 2002; 39: 1083–1095. PMID: 11923030
8. Pittler MH, Schmidt K, Ernst E. Adverse events of herbal food supplements for body weight reduction: systematic review. Obes Rev. 2005; 6: 93–111. PMID: 15836459
9. Di Lorenzo C, Ceschi A, Kupferschmidt H, Lüde S, De Souza Nascimento E, Dos Santos A, et al. 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. doi: 10.1111/bcp.12519 PMID: 25251944
10. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. World Health Organization, Geneva, 2004.
11. Decreto of the Italian Ministry of Health n 169 dated 21.07.2012 on “Disciplina dell’impiego negli integratori alimentari di sostanze e preparati vegetali—Allegato 1 Riferimento per gli effetti fisiologici” [Guidelines for the use of botanicals and derivatives in food supplements - Annex 1 —Physiological effects]. Available: http://www.salute.gov.it/imgs/C_17_pagineAree_1268_listaFile.ItemName_2_file.pdf. Accessed 8 January 2016.
12. European Medicines Agency (EMA). Herbal medicine for human use. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp&mid=WC0b01ac058001fa1d. Accessed 8 January 2016.
13. Pau I, Carlsen MH, Halvorsen BL, Blomhoff R. Antioxidants in herbs and spices: roles in oxidative stress and redox signaling. In: Benzie IFF, Wachtel-Galor S, editors. Herbal medicine: Biomolecular and clinical aspects. 2nd edition. Boca Raton (FL): CRC Press; 2011. Chapter 2. Available: http://www.ncbi.nlm.nih.gov/books/NBK92763.
14. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. Food Chem Toxicol. 2008; 46: 409–420. PMID: 17950516
15. Erdogrul O, Azirak S. Review of the studies on the red yeast rice (Monascus purpureus). Turkish Electronic J Biotech. 2004; 2: 37–49.
16. Lin CC, Li TC, Lai MM. Efficacy and safety of Monascus purpureus. Went rice in subjects with hyperlipidemia. Eur J Endocrinol. 2005; 153: 679–686. PMID: 16260426
17. Liu J, Zhang J, Shi Y, Grimsdgaard S, Alraek T, Fennebe V. Chinese red yeast rice (Monascus purpureus) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. Chin Med. 2006; 1: 4. PMID: 17302963
18. Klimek M, Wang S, Ogunkanmi A. Safety and efficacy of red yeast rice (Monascus purpureus) as an alternative therapy for hyperlipidemia. P T. 2009; 34: 313–327. PMID: 19572049
19. DFG—Permanent Senate Commission on Food Safety SKLM. Toxicological evaluation of red mould rice: An update. Deutsche Forschungsgemeinschaft, 2013. Available: http://www.dfg.de/download/pdf/dfg_improfil/reden_stellungnahmen/2013/131206_sklm_red_mould_rice_update.pdf
20. Cheetham PJ. Role of complimentary therapy for male LUTS. Curr Urol Rep. 2013; 14: 606–613. doi: 10.1007/s11934-013-0372-3 PMID: 24026362
21. Drozd J, Anuszewska E. The effect of the Melissa officinalis extract on immune response in mice. Acta Pol Pharm. 2003; 60: 467–470. PMID: 15080594
22. Ghanbari R, Anwar F, Alkharfy KM, Gilani AH, Saari N. Valuable nutrients and functional bioactives in different parts of olive (Olea europaea L.)-a review. Int J Mol Sci. 2012; 13: 3291–3340. doi: 10.3390/ijms13033291 PMID: 22489153
23. Akbay P, Basaran AA, Undeger U, Basaran N. In vitro immunomodulatory activity of flavonoid glycosides from Urtica dioica L. Phytother Res. 2003; 17: 34–37. PMID: 12557244
24. Borsuk OS, Masnaya NV, Sherstoboev EY, Isaykina NV, Kalinkina GI, Reihart DV. Effects of drugs of plant origin on the development of the immune response. Bull Exp Biol Med. 2011; 195: 149–196. PMID: 22238748
25. UMM—University of Maryland Medical Center. Spirulina. 2013 c. Available: http://umm.edu/health/medical/altmed/supplement/spirulina. Accessed 8 January 2016.
26. Karkos PD, Leong SC, Karkos CD, Sivaji N, Assimakopoulos DA. Spirulina in clinical practice: evidence-based human applications. Evid Based Complement Alternat Med. 2011; 2011: 531053. doi:10.1093/ecam/nen058 PMID: 18955364
27. Reuter J, Merfort I, Schempp CM. Botanicals in dermatology: an evidence-based review. Am J Clin Dermatol. 2010; 11: 247–267. doi: 10.2165/11533220-000000000-00000 PMID: 20509719
28. Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. J Altern Complement Med. 2002; 8: 143–152. PMID:12006122
29. Shenefelt PD. Herbal treatment for dermatological disorders. In: Benzie IFF; Wachtel-Galor S, eds. Herbal medicine: biomolecular and clinical aspects, 2nd edition. Boca Raton (FL), CRC Press. 2011, Cap 18.
30. Fleming T. Medical Economics Co; PDR for herbal medicines. Montvale (NJ), 2nd ed. 2000.
31. Salem ML. Immunomodulatory and therapeutic properties of the Nigella sativa L. seed. Int Immunopharmacol. 2005; 5: 1749–1770. PMID: 16275613
32. Kaatabi H, Bamosa AO, Lebda FM, Al Elq AH, Al-Sultan AI. Favorable impact of Nigella sativa seeds on lipid profile in type 2 diabetic patients. J Family Community Med. 2012; 19: 155–161. doi: 10.4103/2230-8229.102311 PMID: 23203380
33. Oh GN, Son SW. Efficacy of korean red ginseng in the treatment of alopecia areata. J Ginseng Res. 2012; 36: 391–395. doi: 10.5142/jgr.2012.36.4.391 PMID: 23717141
34. Kim SH, Park KS. Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol Res. 2003; 48: 511–513. PMID: 12967598
35. Bailey RL, Saldanha LG, Dwyer JT. Estimating caffeine intake from energy drinks and dietary supplements in the United States. Nutr Rev. 2014; 72 Suppl 1: 9–13. doi:10.1111/nure.12138 PMID: 25293539
36. Arun N, Singh DP. Punica granatum: a review on pharmacological and therapeutic properties. Int J Pharmaceutical Sci Res. 2012; 3: 1240–1245.
37. Harris JC, Cottrell SL, Plummer S, Lloyd D. Antimicrobial properties of Allium sativum (garlic). Appl Microbiol Biotechnol. 2001; 57: 282–286. PMID: 11759674
38. Wright CI, Van-Buren L, Kroner CI, Koning MM. Herbal medicines as diuretics: a review of the scientific evidence. J Ethnopharmacol. 2007; 114: 1–31. PMID: 17804183
39. EFSA—Scientific opinion on the substantiation of health claims related to Cyamopsis tetragonoloba (L.) Taubert and maintenance or achievement of a normal body weight (ID 2428) and long-term maintenance of normal blood glucose concentrations (ID 2429) pursuant to Article 13 (1) of Regulation (EC) No 1924/2006. EFSA J. 2009; 7: 1287.
40. Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. Am J Med. 2001; 110: 724–730. PMID: 11403757
41. Chacko SM, Thambi PT, Kuttan R, Nishigaki I. Beneficial effects of green tea: a literature review. Chin Med. 2010; 5: 13. doi: 10.1186/1749-8546-5-13 PMID: 20370896
42. Davis RH, Stewart GJ, Bregman PJ. Aloe vera and the inflamed synovial pouch model. J Am Podiatr Med Assoc. 1992; 82: 140–148. PMID: 1578350
43. Barrett MJ. Medicinal properties of Echinacea: a critical review. Phytomedicine. 2003; 10: 66–86. PMID: 12622467
44. Pamham MJ. Benefit-risk assessment of the squeezed sap of the purple coneflower (Echinacea purpurea) for long-term oral immunostimulation. Phytomedicine 1996; 3: 95–102 doi: 10.1016/S0944-7113(96)80020-1 PMID: 23194871
45. Chaaibane M, Bidat E, Chevallier B. A new case of food protein-induced enterocolitis syndrome. Arch Pediatr. 2010; 17: 502–506. doi: 10.1016/j.arcped.2010.02.011 PMID: 20346636
46. Minami T, Fukutomi Y, Saito A, Sekiya K, Tsuburai T, Taniguchi M, Akiyama K. Frequent episodes of adult soybean allergy during and following the pollen season. J Allergy Clin Immunol: In Practice 2015; 3: 441–442.e1.
47. EMA (European Medicines Agency). Community herbal monograph on Zingiber officinale Roscoe, rhizoma. Last version March 2012. 2012 (b). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2012/06/WC500128142.pdf. Accessed 8 January 2016.
48. EMA (European Medicines Agency). Community herbal monograph on Arctium lappa L., radix. Last version September 2010. 2010 c. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2011/01/WC500100388.pdf. Accessed 8 January 2016.
49. EMA (European Medicines Agency). European Union herbal monograph on Betula pendula Roth and/or Betula pubescens Ehrh. as well as hybrids of both species, folium. Last version November 2014 (a). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2016/03/WC500148282.pdf. Accessed 8 January 2016.
50. Henderson JA, Evans EV, McIntosh RA. The antithiamine action of Equisetum. J Am Vet Med Assoc. 1952; 120: 375–378. PMID: 14927511
51. EMA (European Medicines Agency). Community herbal monograph on Camellia sinensis (L.) Kuntze, non fermentatum folium. Last version November 2013 (a). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2014/04/WC500165888.pdf. Accessed 8 January 2016.
52. UMM—University of Maryland Medical Center. Red Yeast Rice. 2013 a. Available: http://umm.edu/health/medical/altmed/supplement/red-yeast-rice. Accessed 8 January 2016.
53. Bumham TH, Siweain SL, Short RM eds, Monascus In: The review of Natural Products, St Louis, MO, Facts and Comparisons, 1997.
54. Cunningham AB, Mbenkum FT eds. Sustainability of harvesting Prunus africana bark in Cameroon. A medicinal plant in international trade. People and plants working paper. The United Nations Educational, Scientific and Cultural Organization, Paris, UNESCO Press, 1993.
55. NIAMS—National Institute of Arthritis and Musculoskeletal and Skin Diseases. Research Finds Link Between Statin Use and Progressive Muscle Disease. 2011, Available:http://www.niams.nih.gov/news_and_events/spotlight_on_research/2011/statin_use.asp. Accessed 8 January 2016.
56. Unsel M, Ardeniz O, Mete N, Ersoy R, Sin AZ, Gulbahar O, Kokuludad A. Food allergy due to olive. J Investig Allergol Clin Immunol 2009; 19: 497–9. PMID: 20128426
57. NCCIH—National Center for Complementary and Integrative Health—NIH. 2012. Green tea. Available at: https://nccih.nih.gov/health/greentea
58. McIntyre A. Urtica dioica/urens. In: Herbal treatment of children: western and ayurvedic perspectives. Elsevier Health Science, 2005, pp 59–60.
59. EMA (European Medicines Agency). Assessment report on Cynara scolymus L., folium. Last version November 2011 (a). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/12/WC500119940.pdf. Accessed 8 January 2016.
60. Mayo Clinic. Valerian: A safe and effective herbal sleep aid? 2010. http://www.mayoclinic.com/health/valerian/AN02046http://www.mayoclinic.com/health/valerian/AN02046. Accessed 8 January 2016.
61. Salehi B, Imani R, Mohammadi MR, Fallah J, Mohammadi M, Ghanizadeh A, et al. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34: 76–80. doi: 10.1016/j.pnpbp.2009.09.026 PMID: 19815048
62. Mayo Clinic. Ginkgo (Ginkgo biloba). 2013. http://www.mayoclinic.org/drugs-supplements/ginkgo/safety/hrb-20059541. Accessed 8 January 2016.
63. EMA (European Medicines Agency). Community herbal monograph on Panax ginseng C.A. Meyer, radix. Last version July 2013 (b). Available: http://www.ema.europa.eu/docs/en_GB/document_library/
64. EMA (European Medicines Agency). Assessment report on *Oenothera biennis* L., *Oenothera lamarckiana* L., oleum. Last version December 2011. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/04/WC500124922.pdf. Accessed 8 January 2016.

65. EMA (European Medicines Agency). Community herbal monograph on *Cassia senna* L., fructus and *Cassia angustifolia* Vahl, fructus. Last version September 2006. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2009/12/WC500018202.pdf. Accessed 8 January 2016.

66. EMA (European Medicines Agency). Community herbal monograph on *Rhamnus purshianus* D.C., cortex. Last version September 2007. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2009/12/WC500018424.pdf. Accessed 8 January 2016.

67. Bauer BA. I read that the herbal supplement valerian can help you fall asleep if you have insomnia. Is valerian safe, and does it actually work? Mayo Clinic website. Available: http://www.mayoclinic.org/diseases-conditions/insomnia/expert-answers/valerian/faq-20057875. Accessed 8 January 2016.

68. PennState Hershey, Milton S. Hershey Medical Center. Pomegranate. Available: http://pennstatehershey.adam.com/content.aspx?productId=107&pid=33&gid=002881. Accessed 8 January 2016.

69. EMA (European Medicines Agency). Community herbal monograph on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos. Last version May 2010 (b). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2010/09/WC500096128.pdf. Accessed 8 January 2016.

70. EMA (European Medicines Agency). Assessment report on *Paullinia cupana* Kunth ex H.B.K., var. *sorbilis* (Mart.) Ducke, semen. Last version May 2012. 2012 (c). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/06/WC500129149.pdf. Accessed 8 January 2016.

71. EMA (European Medicines Agency). Community herbal monograph on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne, radix. Last version November 2008. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2010/01/WC500059018.pdf. Accessed 8 January 2016.

72. EMA (European Medicines Agency). European Union herbal monograph on *Equisetum arvense* L., herba. Discussion in MLWP May 2015b. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Herbal_monograph/2009/12/WC500018411.pdf. Accessed 8 January 2016.

73. UMM—University of Maryland Medical Center. Echinacea. 2014. Available: http://umm.edu/health/medical/altmed/herb/echinacea. Accessed 8 January 2016.

74. UMM—University of Maryland Medical Center. Garlic. 2013 b. Available: http://umm.edu/health/medical/altmed/herb/garlic. Accessed 8 January 2016.

75. Smith N, Atroch AL. Guaraná’s Journey from Regional Tonic to Aphrodisiac and Global Energy Drink. Evid Based Complement Alternat Med. 2010; 7: 279–282. doi:10.1093/ecam/nem162 PMID: 18955289

76. Kabalak AA, Soyal OB, Urfalioglu A, Saracoglu F, Gogus N. Menometrorrhagia and tachyarrhythmia after using oral and topical ginseng. J Womens Health (Larchmt). 2004; 13: 830–833.

77. eHealthMe—Review: could Ginkgo biloba cause Insomnia? Available at: http://www.ehealthme.com/ds/ginkgo+biloba/insomnia. Accessed 8 January 2016.

78. EMA (European Medicines Agency). Community herbal monograph on *Ginkgo biloba* L. folium. Last version January 2014 (b). Available: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2014/02/WC500161210.pdf. Accessed 8 January 2016.

79. Lonsdale D. Thiamin deficiency and alopecia. Journal of Advancement in Medicine 1998; 11: 209–212.

80. Lüde S, Vecchio S, Sinno-Tellier S, Dopter A, Mustonen H, Vucinic S, Jonsson B, Müller D, Fruchten- garten L, Hruby K, De Souza Nascimento E, Restani P, Kupferschmidt H, Ceschi A. Retrospective Poisons Centers-based study on adverse effects due to plant food supplements. Clin Toxicology 2013; 51: 267–268.