NPC Natural Product Communications

2015
Vol. 10
No. 1
125 - 131

Herbal Medicinal Products *versus* Botanical-Food Supplements in the European market: State of Art and Perspectives

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Received: August 4th, 2014; Accepted: October 2nd, 2014

Botanical products marketed in Europe are diverse, classified as herbal medicinal products, dietary supplements, cosmetics, foods and beverages depending on the relevant applicable legislation. Many factors are taken into account in the classification of a botanical product (e.g. intended use, labeling, preparations and dosages) according to how it is placed on the market. Herbal medicinal products (HMPs) can only be sold in pharmacies, under the supervision of a pharmacist, and are marketed after full or simplified registration procedures according to their classification, i.e. as over-the-counter drugs (OTC) available without special restrictions and prescription only medicine (POM), which must be prescribed by a licensed medical practitioner. The dietary supplement segment is also sold in the market in dose form (such as capsules, tablets, ampoules of liquids, drops etc) and represents 15-20% of the botanical market at the European level with high variability among each country (i.e. in Italy it reaches up to 80%). In many cases the distinction between medicinal products and food supplements has generated borderline botanical-sourced products, which generally produce confusion and mislead the consumers. As a consequence, there is an urgent need of consumer education and in addition to collect comprehensive data and make this database systematically available to herbalists, nutritionists and medical specialists for a proper classification and harmonization of the use of botanical ingredients, and, as consequence, a correct use of these products.

Keywords: European Union (EU) legislation, Herbal Medicinal Products (HMPs), Traditional HMPs (THMPs), Foodstuff and Food Supplement regulations, Harmonized use of botanical ingredients.

A large number of botanical materials (e.g. whole, fragmented, cut plants or parts of plants, algae, fungi, lichens) defined according to the European Pharmacopoeia as herbal drugs (HDs) [1], and botanical preparations obtained from these materials by various processes (e.g. extraction, distillation, purification, concentration and fermentation) defined according to the European Pharmacopoeia as herbal drug preparations (HDPs) [2], represent the ingredients of the overall botanical world market. Botanical substances are defined by the botanical name of the plant according to the binomial system (genus, species, variety and author) and the part used (e.g. leaf, root, fruit). The world markets offer numerous botanical products with considerable differences in their classification, namely foodstuff, herbal medicinal products (HMPs), cosmetics and medical devices. Foodstuffs include food supplements, food ingredients, functional and fortified foods, novel foods and foods for particular nutritional use. A huge part of the market is represented by the registered HMPs with some important differences between the different countries, but a common legislation: sold in pharmacies and marketed after full or simplified registration procedures according to the traditional or well established use status, in the form of over-the-counter drugs (OTC) available without special restrictions or prescription only medicine (POM), which must be prescribed by a licensed medical practitioner. Among the different segments of the botanical market, the category of dietary supplements is also sold in dosage form and represents ca. 15-20% of the European herbal market, even if with high variability among the different countries (in Italy it reaches ca. 80% of the botanical products sold in dosage form). Under the restrictions in the reimbursement situation, both dietary supplements and the self-medicated OTC drugs have recently started to grow, while the group of prescribed botanical products is decreasing. Actually, in several European countries, botanical products have always been part of mainstream medicine and therefore have already found their way into the regulations of each country from the beginning.

This paper aims to focus on the legislation governing HMPs and food supplements of the European Union (EU) and arguing the issues of the borderline between them. Specifically, the regulatory status of these different categories in the diversified, complex and ever-changing European regulatory environment is examined and some remarkable cases are reported.

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European Union law (commonly referred to as Union Law, historically called "European Community law") represents the body of treaties and legislation, such as Regulations and Directives, which have eithr direct or indirect effect on the laws of European Union Member States. As a consequence, an overview of all the directives, regulations, notes, etc…, of HMPs and food supplements, as reported in the Official Journal of the European Union, is given.

Herbal medicinal products

HMPs are medicinal products and consequently fall within the scope of Directive 2001/83/EC [3] of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, formerly 65/65/ECC [4], as amended by Directive 2004/27/EC [5]. This foresees that their marketing requires an ad hoc authorization to be granted on the basis of results of tests and experimentations concerning quality, safety and efficacy. Commission Directive 2003/94/EC [6] of 8 October 2003 lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, while the Regulation (EC) No 726/2004 [7] of the European Parliament and of the Council of 31 March 2004 lays down the Community procedures for the authorization and supervision of medicinal products for human and veterinary use, creating the European Medicines Agency (EMA). Commission Regulation (EC) No 1084/2003 [8] of 3 June 2003 concerns the examination of variations to the terms of a marketing authorization for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State. The definition of medicinal products by the Directive 2001/83/EC is BY FUNCTION "Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" or BY PRESENTATION "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings".

As a consequence, HMPs are defined as "any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations".

Three categories of medicinal products can be ascribed as Herbal Medicinal Products, based on the evaluation of available scientific data (well-established use) or on the historic use of that product in the European Community (traditional use), or those products following the regular registration procedures for the market authorization. For those medicinal products that are, according to adequate published data (recognised efficacy and level of safety), of well-established use in the meaning of art. 10, paragraph 1, letter (a), point (ii) of the above-mentioned Directive 2001/83/EC and as specified in Part 3 of Annex 1 of the same Directive, there is no need to provide safety and efficacy data. However, for a large number of the herbal products already in use for a long time there are no adequate published data to show well established medical use; therefore, they are not eligible for an authorisation. Although new tests and experimentations could be carried on such products to make it possible to authorise them under the above-mentioned regulations, apart from the considerable associated costs, it would be very difficult to justify animal tests and human clinical trials on products for which a longstanding tradition of use makes it possible to evaluate safety and efficacy. For this category of HMPs a simplified registration procedure was introduced in 2004 by Directive 2004/24/EC [9] of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. The simplified procedure allows the registration of herbal medicinal products without requiring particulars and documents on tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the Community. With regard to the manufacturing of these products and their quality, applications for registration of traditional herbal medicinal products have to fulfil the same requirements as applications for a marketing authorization. In view of the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products (HMPC) was established in September 2004 at the European Medicines Agency, replacing the CPMP Working Party on Herbal Medicinal Products. A major task for the HMPC, in accordance with Directive 2001/83/EC as amended, is to establish Community monographs for traditional herbal medicinal products, and, with the objective of further facilitating the registration and harmonization in the field of traditional herbal medicinal products, prepare a list of herbal substances which have been in medicinal use for a sufficiently long time, and hence are considered not to be harmful under normal conditions of use. As regards the safety and efficacy of a traditional herbal medicinal product, applicants can refer to the list. However, they would still need to demonstrate the quality of the medicinal products they seek to register. The first 'list of herbal substances, preparations and combinations thereof for use in traditional medicinal products' was published by Commission Decision 2008/911/EC [10] of 21 November 2008 and included the monographs of the following herbal drugs:

Table 1: First "Community list" published in 2004.

Plant part	*Scientific name*
Anisi fructus	*Pimpinella anisum* L. (aniseed)
Calendulae flos	*Calendula officinalis* L. (calendula flower)
Echinaceae purpureae herba	*Echinacea purpurea* (L.) Moench (purple coneflower herb)
Eleutherococci radix	*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (eleutherococcus root)
Foeniculi amari fructus	*Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare* (bitter-fennel fruit)
Foeniculi dulcis fructus	*Foeniculum vulgare* Miller subsp. *vulgare* var. *dulce* (Miller) Thellung. (sweet-fennel fruit)
Linum, semen	*Linum usitatissimum* L. (linseed)
Menthae piperitae aetheroleum	*Mentha x piperita* L. (peppermint oil)
Valerianae radix	*Valeriana officinalis* L.(valerian root)

In April 2012, the European Medicines Agency approved the 100th herbal Community monograph since the Committee began work in 2004 [11]. This was a significant achievement for the Committee and a key step in supporting the harmonization of procedures and provisions for herbal medicinal products within the European regulatory framework. The information contained in a herbal Community monograph is used by Member States to support the evaluation of marketing applications from companies for medicines containing a herbal substance, a herbal preparation or a combination of one or more of both herbal substances and herbal preparations. The HMPC evaluates scientifically all available information, including non-clinical and clinical data, but also documented long-standing use and experience in the Community, and, as a consequence, the community herbal monograph comprises the HMPC's scientific opinion on the herbal medicine based on its evaluation of available scientific data (well-established use) or on the historic use of that product in the European Community (traditional use) and includes:

- what the herbal product is used for;
- who the herbal product is intended for (e.g. adults only or children as well, in pregnant and lactating women, etc.);
- safety information such as information regarding undesirable effects and interaction with other medicines.

Monographs are published together with other documents, including an assessment report containing reviews of all available data relevant for the medicinal use of the herbal substance or preparations.
Community monographs are divided into two columns:

- well-established use (marketing authorization): demonstrated with sufficient safety and efficacy data;
- traditional use (simplified registration): accepted on the basis of sufficient safety data and plausible efficacy.

Table 2: Partial list (page 1) of published "Herbal Community Monographs".

Latin name of the genus	Latin name of herbal substance	Botanical name of plant	English common name of herbal substance	Status
Achillea	Millefolii herba	*Achillea millefolium* L.	Yarrow	F
Achillea	Millefolii flos	*Achillea millefolium* L.	Yarrow flower	F
Adhatoda	Adhatodae vasicae folium	*Adhatoda vasica* Nees	Malabar-nut leaf	F
Aesculus	Hippocastani semen	*Aesculus hippocastanum* L.	Horse-chestnut seed	F
Aesculus	Hippocastani cortex	*Aesculus hippocastanum* L.	Horse-chestnut bark	F
Agrimonia	Agrimoniae herba	*Agrimonia eupatoria* L.	Agrimony	P
Agropyron	Agropyri repentis rhizoma	*Agropyron repens* (L.) P. Beauv.	Couch grass rhizome	F
Allium	Allii sativi bulbus	*Allium sativum* L.	Garlic	D
Allium	Allii cepae bulbus	*Allium cepa* L.	Onion	F
Aloe	Aloe bardadensis / Aloe capensis	*Aloe barbadensis* Miller / *Aloe ferox* Miller	Aloes	F
Althaea	Althaeae radix	*Althaea officinalis* L.	Marshmallow root	F
Andrographis	Andrographidis paniculatae folium	*Andrographis paniculata* Nees, folium	Kalmegh	F
Angelica	Angelicae sinensis radix	*Angelica sinensis* (Oliv.) Diels	Winter cherry root	F
Arctium	Arctii radix	*Arctium lappa* L.	Burdock root	F
Arctostaphylos	Uvae ursi folium	*Arctostaphylos uva-ursi* (L.) Spreng.	Bearberry leaf	F
Arnica	Arnicae flos	*Arnica montana* L.	Arnica flower	P
Artemisia	Absinthii herba	*Artemisia absinthium* L.	Wormwood	F
Avena	Avenae herba	*Avena sativa* L.	Oat herb	F
Avena	Avenae fructus	*Avena sativa* L.	Oat fruit	F
Betula	Betulae folium	*Betula pendula* Roth / *Betula pubescens* Ehrh.	Birch leaf	F
Calendula	Calendulae flos	*Calendula officinalis* L.	Calendula flower	F
Calendula	Calendulae herba	*Calendula officinalis* L.	Marigold	C
Camellia	Camelliae non fermentatum folium	*Camellia sinensis* (L.) Kuntze, non fermentatum folium	Green tea	F
Capsella	Bursae pastoris herba	*Capsella bursa-pastoris* (L.) Medikus	Shepherds purse	F
Capsicum	Capsici fructus	*Capsicum annuum* L. var. *minimum* (Miller) Heiser	Capsicum	R

Each herbal preparation is assessed individually as information available may vary from one preparation to another. As a result, some preparations will appear in the well-established use section of the monograph and others will be in the traditional use section, as in the case of St. John's wort. Some preparations might not be included if data are insufficient.

In July 2014 the herbal Community monographs are 180 [12], tabulated as reported in Table 2, including Latin name of the genus, Latin name of herbal substance, botanical name of plant, English common name of herbal substance and the status type, i.e
R: Rapporteur assigned
C: Ongoing call for scientific data
D: Draft under discussion
P: Draft published
PF: Assessment close to finalization (pre-final)
F: Final opinion adopted

Food Supplements
Food supplements are defined in Article 2 of Directive 2002/46/EC [13] as "Food stuffs 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, drops dispensing bottles and other similar forms of liquids and powders designated to be taken in measures of small unit quantities". This Directive shall not apply to medicinal products as defined by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. The Directive reports in Article 3 that Member States shall ensure that food supplements may be marketed within the Community only if they comply with the rules laid down in this Directive. There is a wide range of nutrients and other substances used as ingredients that might be present in food supplements including, but not limited to:
– Vitamins
– Minerals
– Amino acids
– Essential fatty acids
– Fiber
– Various herbal extracts
– Miscellaneous of natural bioactive substances (i.e. Lycopene, Lutein, Spirulin, Soy isoflavones etc..)
Food supplements are only allowed to be sold in pre-packaged forms under the name 'Food Supplement' with specific labelling requirements for food supplements as outlined below.
The label should declare according to Articles 6, 7, 8 & 9 of Directive 2002/46/EC:

- The category names of nutrients or substances that characterize the product or an indication of the nature of those nutrients or substances, e.g. multi-vitamins, probiotics, herbal substances, fish oils etc.
- The portion of the product recommended for daily consumption.
- The amount of the nutrients or substances with a nutritional or physiological effect that is provided by the daily recommended portion. This information shall be provided in numerical form. The units for vitamins and minerals are specified in Schedule 1 of S.I. No. 506 of 2007 [14]. Information on the amounts of vitamins and minerals should also be expressed as a percentage of the RDA as specified in Directive 90/496/EEC [15], as amended. This information may also be given in graphical form.
- A warning not to exceed the recommended daily dose.
- A statement indicating that the product shall not be used as a substitute for a varied diet.
- A statement indicating that the products should be stored out of reach of young children.

Table 3: Partial list of the Italian positive list of botanicals that can be used in food supplements (Annex 1 of Ministerial Decree on 9 July 2012).

NOME BOTANICO	PARTE UTILIZZATA	NOTE	EFFETTI FISIOLOGICI
Abarema cochliocarpos (Gomes) Barneby & J. W. Grimes	oleum		Oleum: Naturali difese dell'organismo
Abelmoschus esculentus (L.) Moench	fructus		Fructus: Funzionalità delle mucose dell'apparato resiratorio. Benessere della gola. Azione emolliente e lenitiva (sistema digerente, vie urinarie)
Abelmoschus moschatus Med.	semen		semen: Funzione digestiva. Eliminazione dei gas intestinali. Contrasto di stati di tensione localizzati.
Abies alba Mill.	conus, cortex, folium, gemma, aetheroleum, resina		gemma: Effetto balsamico. Drenaggio liquidi corporei e funzionalità delle vie urinarie. folium: Funzionalità articolare
Abies balsamea Mill.	balsamum		balsamum: Fluidità delle secrezioni bronchiali. Drenaggio dei liquidi corporei. Funzionalità delle vie urinarie
Abies fraseri Lindl.	balsamum		balsamum: Drenaggio dei liquidi corporei. Fluidità delle secrezioni bronchiali. Effetto balsamico.

Conversely, there is no harmonization at European level concerning botanicals to be used in food supplements. Some Member States have adopted national laws and as general food safety requirement applies, with a general statement: food shall not be placed on the market if it is unsafe (Art. 14 Reg. (EC) No 1924/2006) [16].
National legislations may foresee:
• Positive lists of botanicals which may be used.
• Negative lists of botanicals which may not be used.
• Restrictions / modalities for their use (maximum limits; labeling requirements, i.e. No specific rules at EU level warnings)

This is the case in Italy and Belgium, but there are huge differences between the various national legislations at European level contributing to create barriers in trade according to Principle of mutual recognition (Art 34/36 of TFUE) [17].

The 1997 Belgian Royal Decree of 29 August 1997 [18] has an appendix with 3 lists:
1. Negative list: plants and compounds which are not allowed for use in or as foodstuffs.
2. List of eatable mushrooms.
3. Positive list: list of plants which are allowed in food supplements.

Italy has a similar legislation. The Ministerial Decree of 9 July 2012 [19] established the "Rules on the use of substances and botanicals in food supplements", with a positive list of botanicals and their products that may be used in the manufacture of food supplements.

In Annex 1, all botanicals and preparations allowed in food supplements are alphabetically listed, together with the plant parts, under the terms set out therein, as reported in Table 3. All the botanicals must be indicated in the ingredients list on the label of the food supplement with the common name of the plant, followed by the scientific name of the plant (binominal system). The list contains the botanical name of the HD including the author, part(s) of the used HD (including indications), and the notes and restrictions. The last updated list is dated back to January 2013, at the website of the Health Minister [20]. Besides the list of admitted botanicals (positive list) there is a list of botanicals banned from food (negative list) (Table 5). It contains the botanical name and part(s) of the plant material [21]. The positive list contains ca. 60 tables for a total of about 1,200 plants, while the negative list consists of 8 tables for a total of ca. 400 banned plants.

In the positive list, restrictions in dosage, age of patients, contraindications, and interactions are also reported. Typical plants with restrictions are *Cimicifuga racemosa* (Note of the Health Ministry n. 600.12/I.5.i.h./4160, 1 February 2007), *Citrus aurantium* ssp. *amara* (Note of the Health Ministry n. 600.12/AG45.1/2688, 20 October 1999), *Ginkgo biloba* (Note of the Health Ministry n. 600/AG45.1/9113 21 November 2001) and *Hypericum perforatum* (Note of the Health Ministry n. 600/12/AG45.1/2688 etc…)

Table 5: Partial list of botanicals banned from food (negative list)
Ministero della Salute
ESTRATTI VEGETALI NON AMMESSI NEGLI INTEGRATORI ALIMENTARI

NOME	PARTE
Abrus precatorius L.	seme
Acokanthera oubaio Cath.	legno, seme
Acokanthera schimperi Benth et Hook	frutto, legno
Aconitum anthora L.	fiore, pianta erbacea, radice
Aconitum chasmanthum Stap.	radice
Aconitum ferox Wall.	radice
Aconitum heterophyllum Wall.	pianta erbacea, radice
Aconitum napellus L.	foglia, pianta erbacea, radice, tubero
Aconitum variegatum L.	radice

Cimicifuga racemosa Nutt. (rhizome) is indicated for menopausal and menstrual disturbances, functionality of bone skeleton. Contraindications are hepatic diseases and there are restrictions in the dosages.

Citrus aurantium ssp. *amara* is reported as fructus, pericarpium, oleum, oleum ex floribus, flos, within different indications, according to the used part plant. Dosage of sinefrin is required in the label with a maximum dose of 30 mg/day, corresponding to about 800 mg of *Citrus aurantium* containing 4% sinefrin. Restrictions of use are pregnancy, breast-feeding and age less than 12. *Ginkgo biloba* L. has restrictions due to the concomitant use of anticoagulants or blood platelet antiaggregants, pregnancy and breast-feeding. For *Glycine max* (L.) Merr., a maximum intake of 80 mg/day isoflavones is admitted. *Hypericum perforatum* L. is reported to normalize the humor, to relax and for mental wellness. The daily dose of hypericin is not more than 0.7 mg and the ratio hyperforins/hypericin not more than 7. Restrictions are represented by the age of consumers and the possibility of metabolic interaction.

Italian regulation concerning botanicals that can be used in food supplements has been recently updated (D.M. 27th March, 2014) [22] by the Italian Health Ministry and, in addition to the positive list published of January 2013, the BEL.FR.IT. list is also reported (Annex 1.bis), including ca. 1,000 plants (Table 6) and fungi (Table 7), 120 of them not previously included in the Italian positive list [23]. The list includes for each plant the botanical name, family, synonym, part traditionally used/specific preparations, and notes. No data on indications are reported. BEL.FR.IT. is a cooperative project between Belgium, France, and Italy, with the scope of reaching a common discipline on the use of plants and derivatives in food supplements and the adoption of a common list of botanicals derived from the comparison of the national lists. Belgium and France have also recently adopted the BELFRIT list.

Other counties have only a negative list. Denmark has a list concerning toxicological evaluation of plants in food supplements; the list contains plants considered as unacceptable, plants with a restriction on daily use (max. level), and plants that are evaluated at a daily dose ("Drogelisten" (2000) and later update March 2011)

Table 6: First page of BEL.FR.IT list of plants (Annex 1bis of the D.M. 27th March, 2014).

BOTANICAL NAME	FAMILY	SYNONYM	PART TRADITIONALLY USED/SPECIFIC PREPARATIONS
Abelmoschus esculentus (L.) Moench	Malvaceae		fruit
Abelmoschus moschatus Medik.	Malvaceae		seed
Abies alba Mill.	Pinaceae		bark, branch, needle, seed, resin
Abies balsamea (L.) Mill.	Pinaceae		bark, needle, resin, twig; essential oil
Abies nordmanniana subsp. *equitrojani* (Asch. & Sint. ex Boiss.) Coode & Cullen	Pinaceae	*Abies pectinata* DC. var. *equitrojani* Asch. & Sint. ex Boiss	bark, branch, needle
Abies sibirica Ledeb.	Pinaceae		bark, branch, needle, seed, resin
Abroma augusta L.f.	Malvaceae		root bark
Acacia catechu (L.f.) Willd.	Fabaceae		flower, wood, gum
Acacia decurrens Willd.	Fabaceae		flower, wood, gum
Acacia farnesiana (L.) Willd.	Fabaceae		flower, pod, wood
Acacia nilotica (L.) Delile	Fabaceae	*Acacia arabica* (Lam.) Willd.	bark, fruit, gum
Acacia senegal (L.) Willd.	Fabaceae		bark, gum
Acalypha indica L.	Euphorbiaceae		leaf, root

Table 7: BEL.FR.IT list of fungi (Annex 1bis of the D.M. 27th March, 2014).

BOTANICAL NAME	FAMILY	SYNONYM	PART TRADITIONALLY USED/SPECIFIC PREPARATIONS
Bovista plumbea Pers.	Agaricaceae		fruiting body
Cordyceps sinensis (Berk.) Sacc.	Ophiocordycipitaceae	*Paecilomyces hepiali* Q.T. Chen & R.Q. Dai	fungus
Ganoderma lucidum (Curtis) P. Karst.	Ganodermataceae		fungus
Grifola frondosa (Dicks.) Gray	Meripilaceae		fruiting body
Grifola umbellata (Pers.) Pilat	Meripilaceae		fruiting body
Lasiosphaera gigantea Batch ex Pers.	Lasiosphaeriaceae		fruiting body
Lentinula edodes (Berk.) Pegler	Marasmiaceae		fungus
Monascus purpureus	Monascaceae		microfungi
Pleurotus ostreatus (Jacq.: Fr.) P. Kumm	Pleurotaceae		fungus
Polyporus umbellatus (Pers.) Fr.	Polyporaceae	*Grifola umbellata* (Pers.) Pilát	fungus
Wolfiporia extensa (Peck) Ginns	Polyporaceae	*Poria cocos* F. A. Wolf	*sclerotium*

[24]. Spain has a Regulation (Ministerio de Sanidad y Consumo Orden SCO/ 190/2004) concerning plants for which public sale is forbidden or limited because of toxicity [25].

On June 2004 EFSA's Scientific Committee [26] published a discussion paper on botanicals and botanical preparations widely used in food supplements and related products expressing concerns about quality and safety issues, and which highlights the need for a better characterisation of the range of products on the market and for harmonising risk assessment and consumer information approaches.

Accordingly, in September 2009 EFSA published a toolkit [27] to help assess the safety of botanicals and derived preparations which are intended for use in food supplements. This work was undertaken under EFSA's own initiative; it represents a guidance document identifying the data needed to assess the safety of botanicals and suggesting a science-based approach for the safety assessment. It also provides a set of criteria to prioritise botanicals for safety assessment and is a report with a number of examples illustrating how to apply the proposed scientific approach, and a Compendium of botanicals that have been reported to contain substances that may be of health concern when used in food or food supplements. The last updated version was published in 2012 [28].

The Compendium contains specific information organised in 6 columns (Table 8); the first contains the scientific name (synonyms are in brackets), the second the family name, and the third the plant parts in which the compounds of concern were reported to be present. The fourth column lists the main compounds of concern and the chemical class to which they belong. The fifth deals with information concerning adverse health effect(s) found in the literature, but that cannot be associated with the compound(s) of concern listed in the fourth column. The last column contains selected reference(s) retrieved from literature searches for the data given, and/or standard reference text books providing monographs or more general scientific information for the botanicals considered.

Table 8: Partial list of EFSA compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements.

BOTANICAL NAME	FAMILY	PARTS OF PLANTS OF POSSIBLE CONCERN	CHEMICAL OF CONCERN	REMARKS ON TOXIC/ADVERSE EFFECT(S) NOT KNOWN TO BE RELATED TO THE IDENTIFIED CHEMICAL(S) OF CONCERN	SPECIFIC REFERENCES
Abrus precatorius L.	Fabaceae (Leguminosae)	Seed	Glycoproteins (lectins): e.g. abrin		Frohne D, Pfänder, HJ, Anton R. (**2009**). Plantes à risques. Ed. Tec et Doc-Lavoisier, ISBN: 978-2-7430-0907-1
Acacia spp.	Fabaceae (Leguminosae)	Bark, leaf and seed	Genus in which species may contain dimethyltryptamine derivatives and cyanogenic glycosides (e.g. prunasin, sambunigrin, acacipetalin)		Seigler DS, Ebinger JE. (**1987**). Cyanogenic glycosides in ant-acacias of Mexico and Central America. Southwest. Nat. 32, 499-503.
Achillea abrotanoides Vis.	Asteraceae (Compositae)	Aerial part	Essential oil: bicyclic monoterpenes: beta-thujone (16.8%), pinocarvone (15,6%), camphor (14%), and monoterpene etheroxide: 1,8-cineole (11,3%)		Bicchi C. *et al*. 1988. On the composition of *Achillea abrotanoides* (Vis.) Vis. essential oil. Flavour Frag. J. 3, 101-104
Achillea fragrantissima Sch.Bip.	Asteraceae (Compositae)	Aerial part	Essential oil: bicyclic monoterpenes: thujones		Elgamal MHA. et al. (**1991**). Constituents of *Achillea fragrantissima.* Fitoterapia. 62, 362

The compendium also covers fungi and the Index Fungorum (www.indexfungorum.org) was used as the main source of information for scientific names and families.

Concluding remarks

Botanicals and derived preparations made from plants, algae, fungi and lichens have become widely available on the EU market mainly as HMPs and food supplements. Examples include ginkgo, garlic, St. John's Wort and ginseng. Botanical food supplement category has to be distinguished from HMPs by carefully interpreting the data on physiological *versus* pharmacological and health *versus* disease conditions on dose/concentration basis, taking into consideration the Directive 2002/46/EC on Food Supplements and Directives 2004/27/EC and 2004/24/EC on medicinal products and traditional herbal medicinal products, respectively. Classification is based on the *presented claim*(*s*) *and the intended use*(*s*) will be the first decision points. The posology/dosage and possible *pharmacological actions* should be considered on the basis of original or bibliographic data as a second decision point: a) if the posology is *equal or above* the pharmacologically active dosage demonstrated by the studies or by bibliography related to medicinal use, the product is likely to be classified as *medicine*. If the posology is *lower* or if such data do not exist, the product may be classified as a *food supplement*, if the conditions as set out by Directive 2002/46/EC (e.g. safety, listing) and other relevant legislation related to food (e.g. evidence for claims) are met.

The complex panorama of botanical products is complicated by the fact that for some herbs the national requirements are very different, such as in the classification of *Ginkgo biloba*, which can be sold as a food supplement in the United Kingdom, Italy and Netherlands, as a registered OTC medicine in Germany and France, but as a 'prescription only' medicine (POM) in Ireland.

To confuse further the situation there was also no agreement between the EU countries in terms of indications and efficacy. For example, garlic (*Allium sativum* L.) is used for colds and coughs in the United Kingdom, whereas in Germany it is sold for the prevention of arteriosclerosis. In Germany the law prevents garlic being sold in unit dose form as supplements, while in the UK there are some garlic products licensed as medicines, whilst in the same market there are a number of garlic products being sold as supplements under food law. In Italy garlic is only marketed as a food supplement. In many cases there are available on the market borderline botanical-sourced products whose claims are not substantiated and clearly distinguished from a medicine and in many cases consumers prefer to buy a food supplement, rather than an HMP because of a general perception that botanical foods could be safer than HMPs whose adverse effects have been growing in the last decade and reported by the media.

Attempts to have a real harmonization include the publication of community herbal monographs by EMA, an important objective of further facilitating the registration of HMPs, based on all available information including non-clinical and clinical data, but also documented long-standing use and experience in the Community**.** However, the Member States are not obliged to follow the monographs and could not accept the content of a monograph as adopted by the HMPC. This is the case of St. John's wort, which is not admitted in Italy as a traditional HMP, but is present on the market as a POM for mild depression, because the Italian Health System refuses the traditional indications due to "safety concerns". By contrast, St. John's wort is on the market as a food supplement with the following claims: "to normalize the humor, to relax and mental wellness". These preparations, according to the Italian positive list of botanicals, can be used in food supplements (Annex 1 of Ministerial Decree on 9 July 2012), but the dose of hypericin should not be more than 0.7 mg and the ratio of hyperforins/hypericin not more than 7. No restrictions are reported on the label. As a consequence, the consumer can find on the market two kinds of St. John's wort products: a POM with a series of advertisements and contraindications and a food supplement having no restrictions. Which product should he prefer, a medicine or a foodstuff?

As a consequence, one of the most important issues of botanical products is regarding harmonization on safety and quality aspects of botanicals used as ingredients of food supplements. In 2012 EFSA updated a harmonized common list of plants reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements. In 2014 BELFRIT cooperation has produced a list of plants considered safe on the basis of the traditional use and of the whole complex of available scientific evidence, and that can be used because of their "physiological effects". Both lists represent important tools to expand and promote the botanical food supplement safety approach under EU food laws, but other aspects are not yet regulated at European level, first of all the claims and quality of extracts of botanicals used as ingredients, principally the definition of DER and markers to be evaluated.

In conclusion, the lack of an authorization procedure centralized at EU level for the use of botanicals and derived preparations in food, together with the mentioned troubles actually slow down the free circulation of both HMPs and food supplements within the Member States. Moreover, the most urgent feature is to provide an easy and safe access for consumers to a wide variety of affordable and well regulated food supplements containing botanicals which can be bought over the counter in pharmacies, supermarkets, specialist shops and via the Internet, and it is a very urgent matter to collect comprehensive data and make this database systematically available to doctors, pharmacists, herbalists, nutritionists and health professionals who can inform patients and consumers. Finally, it is true that phytovigilance maintains surveillance of HMPs by requiring prompt reports from manufacturers of all adverse effects brought to their attention and by reports from physicians and patients, but this supervision is not possible with food supplements because pre-marketing safety testing is not required, and there is no mandatory requirement for manufacturers of supplements to record and investigate adverse effects they might receive. The distribution and widespread sale of adulterated products [29-30], and the marked increase in misleading promotional claims on the Internet demand prompt action to protect the public health. For this reason, vigorous and concerted action is needed to educate the public about the critical need for new regulatory safeguards and for government funding to implement them.

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