Traditional herbal medicinal products and botanical food supplements: Which regulations and scientific criteria are applicable in the EU for efficacy and safety?

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Disclaimer

- This presentation does not necessarily reflects the viewpoints of EFSA, but only those of the Author.
Part of this presentation has been recently published in an article entitled «Regulations applicable to plant food supplements and related products in the European Union» by V.Silano, P. Coppens, A. Larranaga-Guetaria, Paola Minghetti and R. Roth-Ehrang, appeared in Food Funct. 2011, 2, 710-718.
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PART I - GENERAL CONSIDERATIONS
Botanicals and botanical preparations contain many different biologically-active substances

- Many substances with largely different therapeutic activities (e.g. amino acids, alkaloids, cardiac glycosides, mono-, di-, tri- and sesquiterpenes, phenolic compounds, coumarins and enzymes) have been, during recent decades, identified in a large number of common botanical species and parts to whom human beings have been exposed in different geographical areas for long periods of time.

- As much as 40% of current mono-molecular medicines derive directly or indirectly from botanicals species and their preparations.
Botanicals and botanical preparations contain many different biologically-active substances

- A number of other substances are known to be present in botanicals and botanical preparations (e.g. vitamins, minerals, other nutrients and many other less known substances with physiological effects), helping the human body in maintaining its homeostasis.
- Moreover, it cannot be excluded that also some recognized therapeutic substances may, at low concentrations, exert a homeostatic effect rather then a therapeutic effect.
Botanicals and botanical preparations contain many different biologically-active substances.

- Therefore, it is not surprising that highly heterogeneous preparations obtained from many different botanical species and parts have been used for long time and are currently used with the objective of:
  - correcting altered physiological processes in case of diseases or preventing their occurrence (traditional herbal medicinal products- THMP);
  - helping the human body in maintaining its homeostasis, i.e. normal functioning of physiological processes (traditional plant food supplements- TPFs).
Traditions of use of botanical products are very different in different countries

- Due to the heterogeneity of botanical preparations being used as THMP or TPFS, it is quite rare to be able to identify the nature of the components relieving symptoms of a disease or exerting homeostatic effects.

- Moreover, for long time herbal products have been used, becoming traditional, in the current European Member countries under no regulation, mainly depending on the country’s availability of botanicals, on prevalent medical and nutritional practices, as well as cultural, technological and social factors.
Traditions of use in different countries of botanical products are very different in different countries.

- It is not surprising, therefore, that the development of national regulations on these botanical products in the 20th century was in all countries based on the long term tradition of use, but quite different in different countries for the already explained reasons.

- The European Institutions have started their action for harmonizing applicable regulations and scientific criteria to botanical products only recently and with a limited success.
Recent initiatives of the EU institutions to harmonize regulations on botanicals

- In 2002, a framework legislation (Directive 2002/46/EC) was adopted on food supplements, including the botanical ones, whereas the nutritional and health indications were only regulated in 2006 (Reg. (CE) 1924).

PART II- TRADITIONAL HERBAL MEDICINAL PRODUCTS (THMP)
Botanical products intended to modify, to correct or to restore organic human functions should fall under the regulation on medicinal products (THMP).

- When, on 1st July 2003, the Council Pharmaceutical W.G. started its work on the draft proposal on THMP, everybody knew that no traditional medicinal product could have never been authorized under any of the European Directives and Regulations existing at that time, mainly due to limitations of available data on efficacy.

- For this reason, under Directive EC/24/04, to register a THMP, it has only to be demonstrated that the product is “non toxic under the specific conditions of use and the pharmacological effects and efficacy are plausible on the basis of long term use and of available experience”.
Registration of traditional herbal medicinal products

- A “facilitated authorization”, including *ad hoc* indications and contra-indications (so called “THMP registration”), can be released, at national level, for oral, external or inhalation administration of products already present on the market for 30 years, of which 15 in an European Union Member State. This requirement is satisfied even if the product has been marketed without a specific authorization and even if the number and amount of active substances has been reduced over time. Vitamins and minerals can be present as long as their action is ancillary.
Registration of traditional herbal medicinal products

- The registration as THMP is considerably simplified in case the product is included in the Community List of substances, preparations and their combinations for the use in THMP, prepared and systematically updated by the EMA Committee competent for THMP, or an *ad hoc* monograph has been produced by this Committee.
The report, recently published by EMA, shows that:

- In total, since the implementation of Directive 2004/24/EC, 1790 applications for THMP were received in the EU Member States: of these, 751 were granted (375 in 2011 and 225 in 2010), 107 refused, 72 withdrawn, and 852 are under assessment;
- The top 3 therapeutical areas are: cough and cold; gastro-intestinal disorders and mental stress and mood disorders.
- The countries with most registrations are: Poland (164), UK (150), Germany (107) and Austria (92).
PART III- TRADITIONAL PLANT FOOD SUPPLEMENTS (TPFS)

- It is clear that the Directive 2004/24/EC on traditional herbal medicines has not been extensively implemented. In fact, after about 9 years from the adoption, this Directive has been generally used at a limited extent in most EU Member States and even almost not used in some EU countries.

- This situation depends on the fact that, in some countries, traditional botanical products (already on the market before 15 May 1997) are marketed mainly as traditional botanical food supplements.
Annual sales (+) of traditional botanical products being marketed in selected countries as food supplements and medicinal products

<table>
<thead>
<tr>
<th>Country</th>
<th>Botanical Food Supplements</th>
<th>Total (i.e. Botanical Food Supplements plus Botanical Medicinal Products)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>1454</td>
<td>1500</td>
</tr>
<tr>
<td>Germany</td>
<td>841</td>
<td>2400</td>
</tr>
<tr>
<td>France</td>
<td>532</td>
<td>1500</td>
</tr>
</tbody>
</table>

(+ )Millions of euros
Directive 2002/46/EC on Food Supplements

- Food supplements, including the botanical ones, are concentrated sources of nutrients or of other substances with a nutritional or physiological effect;

- Traditional botanical food supplements are regulated by the Directive 2002/46/CE that harmonizes, at an European level, general definitions, labelling, publicity and vitamins and minerals used, but not the marketing procedures;
Decisions concerning safety and efficacy of food supplements, including the botanical ones, have depended for long time mainly on manufacturers, whereas EU Member States competent Authorities have supervised the market according to their own criteria which are not harmonised.
The current Regulation on marketing of Food Supplements in Italy

- Only substances and botanical preparation listed in an *ad hoc* Annex can be used in food supplements;
- Labels of new food supplements must be notified to the Ministry of Health before marketing according to D.Legs.21 maggio 2004, n.169 (implementation in Italy of Directiva 2002/46/EC);
- The principle of mutual recognition is applied to food supplements in compliance with regulations in other Member States;
- No nutritional or health claims are foreseen as they have to be approved, according to Reg. EC 1924/2006, at an European level.
Table 1. Examples of different national approaches for the use of selected botanicals in food supplements in the Member States of the EU

- **1. *Alium sativum*** (AU, BE and IT-Permitted as food supplement; BL and CY-an authorization is needed for each product; Czech Rep., DE and IR-Permitte with specific prescriptions; FR-Not permitted, but it could authorized; SP e SW- It is considered a medicinal product).

- **2. *Ginkgo biloba*** (IT,NL and PL- Permitted as food supplement;DE,GR,IR, SL, SP and SW- Not permitted as it is considered a medicinal product; BE, Czech Rep. and HON- Permitted, but only within maximum levels.)
Conclusions on safety of botanical food supplements at national level in the EU are contradictory and conflicting.

According to documents officially published, out of about 1900 herbal species (AESGP, 2007), several hundreds botanical species are:

- prohibited from use in some M.S. and not regulated in other;
- allowed for use in some M.S., prohibited in other M.S. and not regulated in other M.S.; or
- allowed for use in some M.S. and not regulated in other M.S.
A harmonized procedure for safety assessment has been produced by EFSA

- On request of the EFSA Advisory Forum, a guidance document to assess safety of botanical food supplements, together with a Compendium on substances of concern in each species, has been recently produced by EFSA.
- The Compendium (version II) lists a very large number of botanical genus, species and varieties reported to naturally contain toxic, addictive, psychotropic, or other substances of possible concern and identify them and the plant parts where they occur.
More EFSA work on TPFS is coming

- EFSA has requested the Scientific Committee to update the Compendium of botanicals reported to contain inherent substances of possible concern for human health that is available on the EFSA website. The resulting version N°3 of the Compendium will:
  - (i) Be expanded with botanicals used in the non-European countries or marketed in the European Union but that have not been considered in the previous versions of the Compendium;
  - (ii) Provide information on target organs, mode of action and toxic/adverse effects in a systematic manner;
  - (iii) Be built in a database format, searchable on the EFSA website and compatible with the EFSA chemical hazard database.
More EFSA work on TPFS is coming

- For this purpose, the Scientific Committee will consider making use of available data collection framework to outsource the data collection for:
  - Listing non-European botanicals that should be considered for possible inclusion in the Compendium;
  - Performing a systematic literature review / data search for:
    - The above-mentioned non-European plants;
    - The botanical species already listed in the Compendium, starting from those species that have not been updated in the second version of the Compendium.
More EFSA work on TPFS is coming

- To develop the guidance for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, which foresees that botanicals or botanical preparations for which an adequate body of knowledge exists could benefit from a “presumption of safety” without any need for further testing.
However, it is currently difficult to know whether and at what extent the EFSA’s guidance is being used by companies and Member States at national level to systematically review botanical food supplements available on their market.
Another critical issue for botanical food supplements is related to voluntary nutritional and health claims that have to comply with Regulation 1924/2006, i.e. they have to be authorized case by case, based on EFSA’s evaluation of “generally accepted scientific data”.

Moreover, according to such a Regulation, generic claims, which are quite important to inform consumers on the benefit of food supplements have to be well understood by the average consumer.

However, as all the claims on botanical food supplements evaluated so far by EFSA have been refused, the European Commission has requested EFSA to suspend the evaluation.
Regulation EC 1924/2006 on nutrition and health claims

- Although the lack of claims does not prevent botanical food supplements from being marketed, it remains a major problem for the consumer to understand, in the absence of claims, the benefits, if any, associated with the consumption of the product.

- The pending question here is why the more tolerant regulatory approach adopted by Directive 2004/24/EC for traditional medicinal products to take into account specificities of botanical products has not been followed also for botanical food supplements?
PART IV - LACK OF DISTINCTION OF THE BOTANICAL SPECIES USED AS TRADITIONAL FOOD SUPPLEMENTS AND MEDICINAL PRODUCTS
The distinction and separation of the botanical species used as traditional food supplements and medicinal products in EU Member States is highly problematic. In fact, a number of botanical species used under a specific regulatory domain (e.g. food supplements) are also used in the other domain (e.g. traditional medicinal products) with a very broad overlap.

- A study on 171 botanical species carried out in 2010.
Double traditional uses of individual botanical species as food medicinal products and food supplements

<table>
<thead>
<tr>
<th>Botanical species</th>
<th>Community List of traditional medicinal products</th>
<th>AESGP Food Supp. use catalogue (No. of countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendula officinalis</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Echinacea purpurea</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Eleutherococcus senticosus</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Foeniculum vulgare var. dulce</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Foeniculum vulgare var. bitter</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Linum usitatissimum</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Pimpinella anisum L.</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Mentha piperita</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Valeriana officinalis</td>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>
Double traditional uses of individual botanical species as food medicinal products and food supplements

<table>
<thead>
<tr>
<th>Plant(s) –mono</th>
<th>No of products registered</th>
<th>Known food supplement use (AEGSP inventory)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pelargonium sidoides</em></td>
<td>21</td>
<td>in 5 countries</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>17</td>
<td>in 7 “limit.”</td>
</tr>
<tr>
<td><em>Harpagophytum procubens</em></td>
<td>12</td>
<td>in 7 “limit.”</td>
</tr>
<tr>
<td><em>Valeriana officinalis</em></td>
<td>11</td>
<td>in 8 “limit”</td>
</tr>
<tr>
<td><em>Hypericum perforatum</em></td>
<td>9</td>
<td>in 7 “limit.”</td>
</tr>
<tr>
<td><em>Passiflora incarnata</em></td>
<td>7</td>
<td>in 11 “limit.”</td>
</tr>
<tr>
<td><em>Arnica montana</em></td>
<td>5</td>
<td>in 3 “limit.”</td>
</tr>
<tr>
<td><em>Rhodiola roseae</em></td>
<td>4</td>
<td>in 6 “limit.”</td>
</tr>
<tr>
<td><em>Salvia officinalis</em></td>
<td>3</td>
<td>in 8 “limit.”</td>
</tr>
<tr>
<td><em>Tanacetum parthenium</em></td>
<td>3</td>
<td>in 5 “limit.”</td>
</tr>
<tr>
<td><em>Aesculus hippocastanum</em></td>
<td>2</td>
<td>in 4 “limit.”</td>
</tr>
</tbody>
</table>
Food supplement use in different countries of traditional botanical species with an EMEA Monograph concerning medicinal use

- Echinacea pallida (4);  - Sambucus nigra (9);
- Equisetum arvense (7);   - Solidago spp (3);
- Melilotus officinalis (4);   - Betula spp (6)
- Plantago ovata (7);   - Centaure cyanus (7)
- Primula spp (5);   - Harpagophitum procumbens (2);
- Frangula purshiana (2);   - Polypodium vulgare (3)
- Salix alba (4);   - Ruscus aculeatus (4);
- Urtica spp (4);   - Thymus spp (3);
- Aloe vera (7);   - Verbascum spp. (6)
- Althea officinalis (6);   - Melissa officinalis (8)
- Avena sativa (8);   - Passiflora spp (3)

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In parenthesis the number of countries in which the botanical species is used as food supplements
Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- **AU**: Passiflora incarnata—uneasiness, stress, sleeping disorders and agitation (4); Pelargonium sidoides—cold (5); Arnica—muscles and joints; Capsicum—muscles and joints (3); Rhodiola rosea—stress (4); Harpagophytum procumbens—rheumatic pain (7).
- **FI**: Gingo biloba—cold hands and feet due to mild bloodflow disruption in peripheral vessels (2).
- **DE**: Melissa officinalis—nervousness, tension, anxiety and headaches (8); Crataegus spp—circulatory functions; Levisticum officinale (8) plus Centaurium erythraea (8) and Rosmarinus officinalis (8)—inflammatory diseases of the lower urinary tract and decrease of kidney stones (8); Graminis—Valeriana—stress and sleep (2).
- **GR**: Harpagophytum procumbens—minor articular pain (7); Eleutherococcus senticosus—asthenia due to fatigue and weakness (5).

In parenthesis the number of countries in which the botanical species is used as food supplements.
Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- **NL:** *Pelargonium sidoides* - cold (5);
- **SR:** *Crataegus* spp. (8) plus *Melissa officinalis* (8) and *Valeriana* (2) - support of cardiovascular system under stress and convalescence;
- **SL:** *Crataegus* spp. (8) - support of cardiac and circulatory functions; *Crataegus* spp. (8) plus *Passiflora* spp. (4) - support of cardiac and circulatory functions and mild nervous heart complaints; *Primula* spp (5) plus *Thymus* (3) - cold; *Plantago* spp (6) plus *Malva sylvestris* (6) - cold; *Valeriana* (2) plus *Melissa* spp (8), *Mentha piperita* (7) and *Lupulus* - mental stress and aid sleep;

In parenthesis the number of countries in which the botanical species is used as food supplements.
Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications that are also as food supplements in other EU countries)

- **SP**: Arnica montana - muscular aches, pains and stiffness, sprains, bruises and swelling after contusions;
- **SW**: Rhodiola rosea (3) - fatigue and sensation of weakness; Pinus mugo (4) plus Citrus limon (5), Illicium verum (6), Foeniculum vulgare (7); Eucalyptus globulus (6), Mentha piperita (6), Thymus vulgaris (5), Tilia cordata (5), Pimpinella anisum (8), Carum carvi (8), Polygonum aviculare (4) - cold symptoms and occasional cough.

In parenthesis the number of countries in which the botanical species is used as food supplements
Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- **UK:** Arnica montana – see SP; Harpagophytum procumbens-minor articular pain(7); Tanacetum parthenium (5)-migraine headaches; Cimicifuga racemosa (2)-symptoms of the menopause; Serenoa repens (6)-benign prostatic hypertrophy; Vitex agnus castus-sleep disturbances; Valeriana officinalis (2)-sleep disturbances; Aesculus hippocastanum-low mood and mild anxiety; Pelargonium sidoides (5)-cold; Echinacea purpurea (7)-common cold and influenza type infections; Rhodiolae rosa-stress (4); Hypericum perforatum (2)-low mood and slight anxiety.

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- In parenthesis the number of countries in which the botanical species is used as food supplements
On 31 December 2011, 751 THMPs were registered in the different EU Member States.

The 10 most registered plants (used in mono-component products -246 over 375 registrations in 2011) are: *Hyperici herba*, *Pelargonii radix*, *Harpagophyti radix*, *Valeriana radix*, *Crataegi flium cum flore*, *Echinaceae purpureae radix*, *Hippocastanum semen*, *Passiflorae herba*, *Salvia officinalis folium* and *Melissae folium*.

Clearly these botanical species find very large use also as food supplements.
Just before the last summer break (in July 2012), the European Commission distributed among all Member States a reflection paper summarizing her perception of the current situation and asked for an opinion on what to do next, offering the two following options:

- Ask EFSA to resume its assessment of health claims on botanicals with no changes to the approach; or
- Recognise the peculiarity of the botanical case and address it through a review of the legislation on claims or on botanicals.
PART V- OVERALL CONCLUSIONS
CONCLUSION 1

- The nature of the commercial botanical products made available to consumers as traditional medicinal products or food supplements, depends, more than on the intrinsic properties of the botanical products and their constituent, mainly on the country under consideration as a consequence of how competent National Authorities and manufacturing companies interpret and apply current regulations rather than on
## Conclusion N.2

<table>
<thead>
<tr>
<th>Safety</th>
<th>Traditional Botanical Food Supplement</th>
<th>Traditional Botanical Medicinal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncertainty on how it is assessed.</td>
<td>Supported by EMEA Monographs or by ad hoc assessment case by case.</td>
</tr>
<tr>
<td></td>
<td>Comparability in different countries unknown.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy with Claims</th>
<th>Generally accepted scientific data (generally unavailable)</th>
<th>Plausibility based on traditional use data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy without Claims/Indic.</td>
<td>Unclear</td>
<td>Impossible</td>
</tr>
</tbody>
</table>

- A number of traditional botanical products used indifferently as food supplements and traditional medicinal products.
Conclusion n.3

- It would be advisable, in my opinion, that the European Commission and Member States, with the collaboration of EFSA and EMEA, undertake an *ad hoc* collaborative effort to improve the current regulatory framework by developing:

- a practical approach to better identify/characterize botanical species and preparations more suited for use as food supplements or medicinal products;

- a balanced approach to safety and efficacy assessment of both typologies of products, preferably based on traditional use, to be used throughout the EU in a substantially coherent manner.
FINAL CONCLUSIONS

1. Botanical food supplements are intended to complement the normal diet, whereas medicinal products should be mainly intended for treating or preventing specific symptoms of disease;

2. Botanical food supplements could be for lifetime exposure, whereas this is not generally the case for medicinal products;

3. Even for products based on the same botanical species and parts of the plant, dietetic long-term use levels should likely to be lower that those applicable to medicinal products;

4. Indications of use for food supplements and medicinal products should be clearly different; EFSA and EMA should collaborate to help the European Commission to clearly establish such differences.