

Plants and parts of plants used in food supplements: an approach to their safety assessment

Brunella Carratù^(a), Elena Federici^(b), Francesca R. Gallo^(b), Andrea Geraci^(b), Marco Guidotti^(a), Giuseppina Multari^(b), Giovanna Palazzino^(b) and Elisabetta Sanzini^(a)

^(a)Dipartimento di Sanità Pubblica Veterinaria e Sicurezza Alimentare;

^(b)Dipartimento del Farmaco, Istituto Superiore di Sanità, Rome, Italy

Summary. In Italy most herbal products are sold as food supplements and are subject only to food law. A list of about 1200 plants authorised for use in food supplements has been compiled by the Italian Ministry of Health. In order to review and possibly improve the Ministry's list an *ad hoc* working group of Istituto Superiore di Sanità was requested to provide a technical and scientific opinion on plant safety. The listed plants were evaluated on the basis of their use in food, therapeutic activity, human toxicity and in no-alimentary fields. Toxicity was also assessed and plant limitations to use in food supplements were defined.

Key words: food supplements, botanicals, herbal products, safety assessment.

Riassunto (*Piante o parti di piante usate negli integratori alimentari: un approccio per la valutazione della loro sicurezza d'uso*). In Italia i prodotti a base di piante utilizzati a scopo salutistico sono integratori alimentari e pertanto devono essere commercializzati secondo le normative degli alimenti. Le piante che possono essere impiegate sono raccolte in una "lista di piante ammesse" stabilita dal Ministero della Salute. Allo scopo di rivedere ed eventualmente incrementare tale lista, un gruppo di lavoro dell'Istituto Superiore di Sanità è stato chiamato ad esprimere un parere tecnico-scientifico sulla sicurezza d'uso delle piante elencate. Le piante sono state valutate sulla base del loro uso a scopo alimentare o terapeutico o in campi diversi. In funzione delle eventuali sostanze potenzialmente tossiche contenute in tali piante sono state individuate delle limitazioni per il loro uso negli integratori alimentari.

Parole chiave: integratori alimentari, ingredienti vegetali, prodotti salutistici, sicurezza d'uso.

INTRODUCTION

Botanicals and botanical preparations are widely available to consumers through several distribution channels in the EU and elsewhere. They are sold over the counter in pharmacies and can also be bought in supermarkets, herbalists and other shops, or via the Internet. Their ready availability and widespread use are such that they have almost become part of the common diet, thus generating a significant level of human exposure from a public health point of view. This heterogeneous group of preparations includes both unprocessed and processed plant parts (bark, leaves, flowers, fruits, root and stem) in the form of extracts and/or essential oils. These products are available in a variety of forms, including infusions, powders, tablets, capsules and elixirs, and may be marketed as single substances or in combination with other materials such as vitamins, minerals, amino acids or non-nutrient ingredients. According to their intended use and claims, these products fall under different Community regulatory frameworks, and for some types of products no legal provisions

for preliminary risk assessment are yet in place. The main regulations that are relevant in this field are Directive 2002/46/EC on food supplements and Directive 2004/24/EC on traditional herbal medicinal products for human use [1, 2].

Food supplements are foodstuffs whose purpose 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. Legally, food supplements have to be considered unambiguously as food, although they possess some unique characteristics and specific legislation is devoted to this category of products.

A medicinal product is defined as any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

At present botanicals and botanical preparations are partially harmonised at EU level; nevertheless there is still considerable discretion at the national level, and Member States may classify a product as a food supplement or as a drug. It is not surprising, therefore, that difficulties arise and tensions exist because of the differences among EU Member States in their approaches, particularly to the classification of some herbal products as food supplements or as traditional or well established or as other types of medicinal products.

In Italy the majority of herbal products are sold as food supplements and are subject only to generic food law, in particular to Italian Legislative Decree n. 169/2004 [3] incorporating EU Directive 2002/46/EC [1]. In Italy 41 000 products had been notified to the Ministry of Health up to March 2009, only 24 000 of which were included in the Register of food supplements; 10 000 of these contain plants and herbal extracts, 2000 include nutrients and plants. The Ministry of Health has compiled a list of plants which may be added to food supplements, and recently the competent department decided to review and possibly improve it. For this reason, the Istituto Superiore di Sanità (ISS) was requested to provide a technical and scientific opinion on the list of approximately 1200 plants and/or plant parts for use in food supplements. The aim of this report was to describe the methodology adopted by an ISS working group to evaluate the safety of these listed plants.

METHODOLOGY

For several years the Italian Ministry of Health has maintained a list of plants in herbal food supplements which have to be used for salutistic aims. This list is continually updated with data generated by scientific research, so that some plants may be excluded and others added.

In July 2008 the Italian Ministry of Health asked ISS to review an updated list of plants whose presence in herbal food supplements is authorised. To this end a working group of eight researchers (ISS working group) was formed. The members of the group were drawn from two ISS departments: Department of Veterinary Public Health and Food Safety and Department of Therapeutic Research and Medicines Evaluation. The working group discussed various aspects that should be considered in order to determine the safe use of these types of ingredients.

The safety evaluation of food constituents such as additives and/or pesticides is based on data derived from internationally accepted standard approaches (e.g. admissible dietary intake, ADI) which incorporate the use of large uncertainty factors and provide a wide margin of safety. For plant materials this approach may not always be appropriate, as the margin between the desired beneficial effect and adverse effects may be narrower.

No harmonised approach is currently in place to assess the risks associated with plants or plant

parts authorised for use in food supplements, so the working group decided to start from the reports developed by the Scientific Committee and Advisory Forum Unit of the European Food Safety Authority (EFSA) regarding the safety assessment of botanical ingredients based on contributions from industry, food supplement manufacturing organisations and similar bodies.

In this work the two compendia drawn up in 2008 by a working group of the EFSA's Scientific Committee on Botanicals, were taken into account: the first is a Draft compendium of botanicals that have been considered for a food and/or food supplement use and that have been reported to contain toxic, addictive or psychotropic substances [4]; the second is a Draft compendium of botanicals and botanical preparations that have been considered for food and/or food supplement use and have been reported to have also a medicinal use [5].

The two EFSA documents [4, 5] were compiled by incorporating lists of plants that have been studied and evaluated by various international and European agencies and by other National Food Safety authorities of European Union member states.

The ISS working group selected 121 plants from the list of 1200 plants compiled by the Italian Ministry of Health in accordance with the first EFSA Compendium, plants that contain toxic, or addictive or psychotropic substances.

The criteria for the evaluation of the selected 121 plants were:

- the use of plant or of its specific part;
- the high therapeutic activity of the secondary metabolites of the examined plant;
- the reported human toxicity;
- the use of plant other than for food or medicinal reasons (*i.e.* its use in cosmetics, processing materials, etc.);
- the toxicity data adopted to assess safe levels or risks associated with intake.

The main criteria for inclusion in the list of food supplements was the food use of plants.

In this evaluation the consulted literature sources and web sites of relevant scientific agencies were: *Drogen Kunde*, Heinz A Hoppe, 1975, Band 2 [6]; *Chemotaxonomie der Pflanzen*, R Hegnauer, 1992 and 2001 [7]; *The ayurvedic pharmacopoeia of India*, 2001 [8]; *Traditional Chinese medicines*, GWA Milne, 2003 [9]; *Handbook of medicinal herbs*, James A Duke, 2000 [10]; *Handbook of ayurvedic medicinal plants*, LD Kapoor, 2000 [11]; *Physicians' desk reference for herbal medicines* [12]; Monographs of European Scientific Cooperative on Phytotherapy (ESCOP); Joint FAO/WHO Expert Committee on Food Additives (JECFA); Committee of Experts on Flavouring Substances of the Council of Europe (CEFS); Commissione Unica per la Dietetica e la Nutrizione, Italian Ministry of Health [13]; European Medicines Agency (EMA) [14]; European Food Safety Authority (EFSA's Scientific Documents on Botanicals) [15].

Plants for which no dietary and/or therapeutic uses are found in the available literature but which are used in other fields such as the manufacture of paints, lacquers, perfumes etc., were excluded from the list.

The “flavouring” compounds present in significant quantities in many of the plants examined were taken into account. It was necessary to consider the qualitative-quantitative composition of plants, as some flavouring components do not require special precautions for their use in food, while for others, due to their potential toxicity, a maximum daily intake (MDI) expressed in mg/kg bw/day has to be defined. If a full MDI cannot be set, a temporary maximum daily intake (TMDI) should be set, based on the available toxicological data [16, 17].

Some of the substances considered are described by the Council of Europe in *Active principles (constituents of toxicological concern) contained in natural sources of flavourings*; these are chemically defined substances that, in certain natural flavourings of vegetable origin and on the basis of existing toxicological data, should not be used as flavouring substances in their own right [16]. Another report of the Council of Europe, *Natural sources of flavourings*, published in 2008 was also consulted [17]. Three classes of “active principles” are reported (I, II, III). The first comprises substances suspected of being genotoxic carcinogens, for which no MDI is established because they should not generally be detectable by modern analytical test methods in foodstuffs and beverages. For the second class of substances no MDI could be set because existing toxicological data are insufficient, however a temporary MDI (TMDI) may be set in certain circumstances. Active principles of the third class are substances which are considered toxic and for which an MDI has been set.

Examples of substances belonging to class I are estragole and methyleugenol; examples of class II substances are eucalyptol, hydrocyanic acid and thujone; class III: menthofuran and pulegone.

Maximum limits in foodstuffs as consumed have been set on the basis of existing toxicological data and/or with reference to a MDI or a TMDI [16, 17].

JEFCA, the panel on food contact materials, enzymes, flavourings and processing aids (CEF) of EFSA, the Council of Europe and other competent organisations have defined an acceptable daily intake (ADI) for other substances that are not included in the list of “active principles” of flavourings.

In this study the ISS working group defined for plants containing flavourings the limits within which it is possible to consider them suitable for use in food supplements, on the basis of available scientific information.

Other secondary metabolites taken into account were coumarins for which the EFSA limits were considered [18].

Plants containing furocoumarins were excluded from the list on account of the possible occurrence of acute phototoxic effects following their oral intake in combination with sunlight or UVA light [19].

Plants containing alkaloids were mostly judged unfit for use in food, and were generally omitted from the list [20, 21].

RESULTS AND DISCUSSION

From the evaluation process some of the 121 selected plants were approved for use, others were considered suitable only within certain limits, and the remaining plants were considered not suitable for use in botanical supplements. The ISS working group defined the limitations for the use of some plants linked to a series of chemical components which may represent a danger for the health of the consumer. The limitations to use were set for the plants containing potentially dangerous substances listed in the second 2008 EFSA compendium of botanicals for food and/or food supplements and that have been reported to have also a medicinal use [5].

During the performance of the present study, after one year of activity the EFSA's Working Group on Botanicals and Botanical Preparations merged the two compendia into a single volume: the resulting compendium now focuses on toxicity aspects, listing botanicals reported to contain toxic, addictive, psychotropic or other substances of toxicological concern [22]. It was therefore necessary to update the list of plants prepared by the ISS working group in light of the information contained in the new 2009 EFSA compendium.

For plants containing anthraquinones (e.g. *Aloe* spp., *Cassia* spp., *Harungana madagascariensis*, *Pteramnia antidesma*, *Rhamnus frangula*, *Rhamnus purshiana* (Cascara), *Rheum hybridum* (Rhubarb), *Rheum officinale*, *Rheum palmatum*) no evaluation was performed because the Italian Ministry of Health is already preparing its own assessment.

Plants with limitations to use

This section discusses chemical components for which it has been necessary to set some quantitative limitation to their presence in the herbal raw material of dietary supplements. Most such substances are “potentially toxic chemically defined substances” which occur in natural flavouring source materials that are periodically evaluated by CEFS, EFSA and other competent agencies on the basis of existing data.

Table 1 shows the limitations to use for the substances that the ISS working group decided to include in this category.

With regard to the presence of sinefrine and hypericin in plants and/or botanical extracts, the limitations to use were established by the Commission on Nutrition and Dietetic Products of the Italian Ministry of Health.

Coumarin - Coumarin is a naturally occurring flavouring substance present in numerous plants included in the list: *Anthoxanthum odoratum*, *Eryngium campstre*, *Ferula assa foetida*, *Fortunella species*, *Gallium odoratum*, *Gaultheria procumbens*, *Herniaria glabra*, *Melittis melissophyllum*.

Table 1 | List of the natural substances evaluated by the ISS working group and their limit to use

Substance/plant	Limit
Coumarin	0.1 mg/kg bw/die [18]; (e.g. 6 mg/die at body weight of 60 kg)
Estragole	for category of food [17]
Eucalyptol	10 mg/kg of food with some exceptions [17]
Eugenol	2.5 mg/kg bw/die [25]; (e.g. 150 mg/die at body weight of 60 kg)
Glycyrrhizic acid	100 mg/die [27]
Hydrocyanic acid	0.023 mg/kg bw/die [17]; (e.g. 1.4 mg/die at the body weight of 60 kg)
Menthofuran and pulegone	1.1 mg/kg bw/die [17]; (e.g. 6 mg/die at body weight of 60 kg)
Menthol	4 mg/kg bw/die [37]; (e.g. 240 mg/die at body weight of 60 kg)
Methyleugenol	Advise: contraindicated for pregnant women, infants, children [17, 40]
<i>Quillaja saponaria</i>	1 mg/kg bw/die [43]; (e.g. 60 mg/die at body weight of 60 kg)
Quinine	Advise: contraindicated for pregnant women, infants, children and individuals that are taking anticoagulant preparations [44]
Safrole	Advise: contraindicated for pregnant women, infants, children [47]
<i>Saponaria officinalis</i>	1 mg/kg bw/die [43]; (e.g. 60 mg/die at body weight of 60 kg)
<i>Smilax</i> spp	1 mg/kg bw/die [43]; (e.g. 60 mg/die at body weight of 60 kg)
Thujone	1.01 mg/kg bw/die [17]; (e.g. 0.6 mg/die at body weight of 60 kg)
Trans-anethole	2 mg/kg bw/die

Coumarin is listed as an “active principle” by the Council of Europe [17], and the EFSA’s Scientific Panel on food additives, flavouring, processing aids and materials in contact with food has recently review its toxicity, focusing on its potential to induce DNA-adduct formation in kidney and liver of rats [18].

On the basis of additional *in vivo* studies of coumarin metabolism in different species, including humans, the EFSA panel demonstrated that *in vivo* coumarin does not bind covalently to DNA in target organs, supporting a non-genotoxic mechanism of action for tumour induction [23]. The panel therefore concluded that the available data allowed the derivation of a tolerable daily intake (TDI) that would take into account the hepatotoxic responses. After applying safety factors to the no-observed-adverse-effect level (NOAEL) of 10 mg/kg bw/day for liver toxicity in a 2-year study on dogs, a TDI of 0-0.1 mg coumarin/kg bw/day was established.

Taking the estimated theoretical added maximum daily intake (TAMDI) of coumarin via food, the total daily intake would be 1.3-1.5 mg/day (0.02 mg/kg bw/day), this value is below the TDI [18].

Estragole - Estragole occurs naturally in many common plants and culinary herbs, including the following listed plants: *Anethum graveolens*, *Cinnamomum verum*, *Commiphora mukul*, *Cuminum cyminum*, *Foeniculum vulgare*, *Glycyrrhiza glabra*, *Hyssopus officinalis*, *Illicium verum*, *Melilotus officinalis*, *Myrrhis odorata*, *Ocimum basilicum*, *Ocimum gratissimum*, *Paullinia cupana*, *Pimenta dioica*, *Pimenta racemosa*, *Pimpinella anisum*, *Salvia sclarea*, *Syzygium aromaticum*.

The highest concentrations of estragole, approximately 5-85%, are found in volatile oil derived from *Ocimum basilicum* [24].

Evidence of estragole’s carcinogenic potential includes observations of genotoxicity in several short-

term tests, DNA adduct formation *in vivo* and *in vitro*, chemical-structural analogies with recognized carcinogens. The formation of DNA adducts *in vivo* and *in vitro* by metabolites of estragole has been demonstrated and the major hepatic DNA adducts have been characterised. Administration of estragole to adult female mice in the diet for 12 months induced increased incidence of hepatocellular carcinomas compared with control mice [24].

Estragole was classified as a weak genotoxic carcinogen (type I active principle) for which no (T)MDI can be set, and in general it should be non-detectable using modern analytical test methods; however, long-term carcinogenicity studies in rats and mice of both sexes are needed.

An approximate estimate of the total intake of estragole from all sources appears to be in the order of one milligram per person per day; this is below the LD50 derived from available carcinogenicity studies in mice by a factor of about 3000. Nevertheless, further studies are needed to define both the nature and implications of the dose response curve in rats at low levels of exposure to estragole. In any case, efforts should be made to reduce the amount of estragole in food as far as possible [16, 17].

Eucalyptol - Eucalyptol is widely distributed in plants. In the list the main sources are: *Achillea millefolium*, *Alpinia galanga*, *Artemisia abrotanum*, *Artemisia absinthium*, *Artemisia vallesiaca*, *Artemisia vulgaris*, *Crocus sativus*, *Cuminum cyminum*, *Cupressus sempervirens*, *Curcuma longa*, *Cymbopogon citratus*, *Cymbopogon flexuosus*, *Cymbopogon laniger*, *Cymbopogon martini*, *Cymbopogon nardus*, *Cymbopogon schoenanthus*, *Cymbopogon winterianus*, *Elettaria cardamomum*, *Eucalyptus citriodora*, *Eucalyptus globulus*, *Eucalyptus odorata*, *Eucalyptus smithii*, *Hyptis suaveolens*, *Laurus nobilis*, *Melissa officinalis*, *Mentha piperita*, *Myristica*

fragens, *Rosmarinus officinalis*, *Satureja montana*, *Thymus serpyllum*, *Thymus vulgaris*. In some plants eucalyptol is the primary constituent of essential oil (*Eucalyptus*, *Rosmarinus*, *Elettaria*) and is also present in considerable quantities in others too. Eucalyptol can be hazardous via ingestion, skin contact or inhalation, and it can have acute health effects on behaviour, respiratory tract and nervous system.

The available toxicological studies relating to eucalyptol are limited and inadequate to derive a TMDI: eucalyptol has been classified as a class II active principle. The estimated daily intake of eucalyptol from foods and beverages of approximately 4.5 mg per person is a factor of 1000 below the lowest exposure of eucalyptol by ingestion of eucalyptus oil reported to result in severe intoxications or death in humans (2.45-6.25 g eucalyptol per person) [16].

For a more precise risk characterisation to set an MDI, further data on exposure and toxicity would be needed.

The general limit in food and beverages is 10 mg/kg with some exceptions [17].

Eugenol - Eugenol is a chemically defined flavouring substance used in foodstuffs and is a component of the essence of *Croton eluteria*, *Dianthus caryophyllus*, *Ocimum gratissimum*, included in the list.

On the basis of the latest evaluations performed by JECFA in 2005 (65th meeting) the initially established ADI of 0-2.5 mg/kg bw/day (1982) for eugenol was maintained [25]. The Committee considered the results of a 19-week study in rats and a later bioassay in rodents in which the NOEL was 300 mg/kg bw per day, which is more than 16 000 and 5000 times the estimated daily exposure to eugenol from its use as a flavouring agent in Europe (18 µg/kg bw) and in the US (56 µg/kg bw/day), respectively [26]. The Committee therefore concluded that eugenol, as a flavouring substance, should not present a safety concern at the estimated daily exposure and the Panel of EFSA agreed with the JECFA's conclusions [25, 26].

The results concerning acute toxicity indicate that eugenol and derivatives given orally have little acute toxicity [25, 26].

Glycyrrhizinic acid - Glycyrrhizinic acid (glycyrrhizin), a triterpenoid saponin glycoside, is one of the compounds obtained from the root extract of the liquorice plant: *Glycyrrhiza glabra*, included in the Italian Ministry's list. The crude dried aqueous extracts may contain 4-25% glycyrrhizinic acid in the form of salts. Humans may be exposed to glycyrrhizinic acid via dried crude root extract or via food into which the extract of *Glycyrrhiza glabra* has been incorporated.

Glycyrrhizinic acid and its ammonium salt are listed in the Community register of chemically defined flavouring substances, on account of their sweet taste, and liquorice has been well known for centuries, in traditional medicine, for its anti-inflammatory efficacy.

Moderate chronic or high acute exposure to glycyrrhizinic acid, ammonium glycyrrhizinate and their metabolites has been demonstrated to cause transient systemic alterations, including increased potassium excretion, sodium and water retention, body weight gain, alkalosis, suppression of the renin-angiotensin-aldosterone system, hypertension and muscular paralysis. Glycyrrhizinic acid and its derivatives block gap junction intracellular communication in a dose-dependent manner in animal and human cells, at high concentrations it is cytotoxic. Glycyrrhizinate and its hydrolysis products were considered to be non-genotoxic in *in vivo* and *in vitro* cytogenetic assays. Glycyrrhizinic acid and glycyrrhizinic acid have anti-inflammatory effects in rats and mice [27, 28].

In 1991 the Scientific Committee on Food of the European Commission did not derive an ADI because of inadequate data, but considered it prudent that the regular ingestion of glycyrrhizinic acid should not exceed 100 mg/day. In the light of subsequent toxicological information the Committee recommended an upper limit of 100 mg/day for ingestion of glycyrrhizin, while noting that human toxicity studies were still insufficient to derive a definite ADI for glycyrrhizinic acid [27].

Hydrocyanic acid - Hydrogen cyanide occurs naturally as cyanogenic glycosides in at least 2000 plants, of which the following are listed: *Amygdalus communis*, *Indigofera tinctoria*, *Linum usitatissimum*, *Prunus armeniaca*, *Prunus laurocerasus*, *Prunus persica*, *Sambucus ebulus*, *Sambucus nigra*.

The most important cyanogenic glycosides are linamarin, found in *Linum usitatissimum* (over 500 mg HCN/kg of seed), prunasin and amygdalin in *Prunus* spp. (up to 470 mg/kg of kernel) [17].

Hydrogen cyanide can be produced by a hydrolytic reaction catalysed by one or more enzymes from the plants containing cyanogenic glycosides. When the enzymes are activated by crushing and moistening or chewing of kernels the hydrolysis reaction to cyanide is rapidly completed, particularly in an alkaline environment [29].

Fruit cyanogenic glycosides, such as amygdalin and prunasin in almonds, in seeds of apricots, plums and peaches, are hydrolysed by the gut microflora to release cyanide slowly and incompletely, with subsequent adsorption, so that the acute toxicity level for cyanogenic glycosides will be lower.

However, oral LD50 values have been reported in the range of 3-4 mg cyanide/kg bw for rats, 6 mg cyanide/kg bw for mice and about 2.6 mg cyanide/kg bw for rabbits. Symptoms of acute intoxication following oral doses of cyanide are cardiovascular, respiratory and neurological alterations. Several studies have shown that the brain is the most sensitive organ.

The panel on contaminants of EFSA in its latest opinion (September 2007) concluded that the data for hydrogen cyanide were not adequate to identify a NOAEL for chronic exposure in humans, because

they were highly confounded by other nutritional and environmental factors. Adequate long-term toxicity studies to derive a NOAEL were also lacking and therefore a TDI could not be derived [29].

In 2008 the group of experts on flavouring substances of the Council of Europe placed hydrogen cyanide in the category of “active principles II” (constituents of toxicological concern) for which a TMDI may be set. Based on the NOAEL of 4.5 mg cyanide/kg bw/day found in the 13-week study in rats and on a safety factor of 200, a TMDI of 0.023 mg cyanide/kg bw/day was established [17].

Maximum use level for hydrocyanic acid in foods was set at 1 mg/kg in Italian Decree n. 107/92 [30]; in the following Regulation (EC) No. 1334/2008 [31] maximum level was not reported, with exceptions for specific classes of foodstuffs; in the report of 2008 the expert committee on flavouring substances of the Council of Europe defined a limit of 0.5 mg/kg for hydrocyanic acid in foods [17].

Menthofuran and pulegone - Pulegone and menthofuran show a qualitatively similar hepatotoxicity so that the evaluation of these two substances should be considered together. Metabolic studies have established the role of pulegone in the cytochrome P450-catalyzed bioactivation that occurs via at least two independent pathways: 1) the formation and subsequent activation of menthofuran from pulegone; and 2) the formation of reactive intermediate(s) from pulegone, but not menthofuran, which can be detoxified through a mechanism requiring reduced glutathione.

These substances are contained in the following list plants: *Barosma betulina*, *Barosma crenulata*, *Barosma serratifolia*, *Nepeta cataria*, *Hedeoma pulegioides*, *Mentha arvensis*, *Mentha piperita*.

Mint oil (Ph Eur) contains maximum 2.0% pulegone and peppermint oil contains maximum 4.0% pulegone and between 1.0 and 9.0% menthofuran [32].

Pulegone and menthofuran may not be added as such to foodstuffs; maximum levels in beverages and special kinds of foodstuffs, to which flavourings or other food ingredients with flavouring properties have been added, are set in European Regulation (EC) No 1334/2008 but no limit is given for generic food [31].

The Committee of Experts on Flavouring Substances of the Council of Europe [17] classifies pulegone and menthofuran under “active principles III” for which an MDI has been set: in the report of 2008 a limit of 20 mg/kg is indicated in foods and beverages, with some exceptions, and an MDI of 0.1 mg/kg bw/day, based on a no-observed-effect-level (NOEL) of 20 mg/kg bw/day in the 28-days oral toxicity study in rats [33] with a safety factor of 200 was reported. However, no ADI can be derived because of limited and inadequate toxicological studies, in the opinion of the EFSA's panel on food additives, flavouring, processing aids and materials in contact with food [34].

In 2005 the EFSA panel evaluated pulegone and menthofuran and found that the available database for the two substances was still inadequate to estab-

lish an ADI, even though the new 95-day toxicological data on pulegone enabled the establishment of NOAELs in rats and mice [34].

Menthol - This substance is a naturally occurring compound of plant origin, which gives plants of the mentha species (*Mentha piperita*, *Mentha arvensis*) their typical flavour. The chemical substance exists in four pairs of optical isomers, but in nature the (-)-menthol (or L-menthol) is the most commonly found isomer. Exposure to menthol occurs through the use of peppermint oil, since menthol is its primary component (35-60%) [35]. Peppermint oil is used in cosmetic formulations, in the manufacture of chewing gum, confectionery, toothpaste and pharmaceutical products. Potential exposure to menthol isomers from drinking water and ambient air is presumed to be negligible [36].

L-, D/L- and the unspecified menthol isomers are well absorbed by the oral route of exposure, humans metabolize menthol primarily by conjugation with glucuronic acid and elimination in the urine, cytochrome P450-mediated oxidation occurs yielding various alcohol and hydroxy acid derivatives, which would also be eliminated in the urine unchanged or conjugated with glucuronic acid. All menthol isomers are of very low acute oral toxicity with LD50 values normally greater than 2000 mg/kg bw. Clinical signs of intoxication are unspecific and include apathy and reduced activity.

Menthol was first evaluated at the eleventh meeting of the expert committee on food additives, when it was allocated an ADI of 0.2-2 mg/kg bw/day; at the eighteenth meeting, an ADI of 0-0.2 mg/kg bw/day was also established [37]. In 1998 the safety evaluation on menthol was reviewed by the JECFA at its 51st meeting, where it was noted that the highest dose of (±)-menthol tested in long-term studies in mice and rats had no specific toxic effect. As the survival of mice was reduced at the high dose of 600 mg/kg bw/day, the committee allocated an ADI for L-menthol and D/L-menthol in the range of 0-4 mg/kg bw/day on the basis of the NOEL of 380 mg/kg bw per day in the long-term study in rats, applying a safety factor of 100 and rounding to one significant figure [37].

Methyleugenol - Methyleugenol is a natural constituent of many aromatic plants and their essential oils; among the listed plants it occurs in particular in: *Acacia senegal*, *Alpinia galanga*, *Artemisia abrotanum*, *Cinnamomum verum*, *Cymbopogon citrates*, *Cymbopogon flexuosus*, *Cymbopogon laniger*, *Cymbopogon martini*, *Cymbopogon nardus*, *Elettaria cardamomum*, *Hamamelis virginiana*, *Hyssopus officinalis*, *Laurus nobilis*, *Melaleuca alternifolia*, *Melaleuca leucadendron*, *Myristica fragrans*, *Ocimum basilicum*, *Ocimum gratissimum*, *Peumus boldus*, *Pimenta dioica*, *Pimenta racemosa*, *Pistacia lentiscus*, *Rosmarinus officinalis*, *Satureja montana*, *Syzygium aromaticum*, *Zingiber officinalis*.

The consumer is exposed to methyleugenol through the consumption of foodstuffs flavoured with the mentioned plants, for instance soft candy, non-alco-

holic beverages, meat products etc.

Methyleugenol belongs to the same chemical class as safrole, estragole, eugenol and myristicin.

When administered orally, it was found to be carcinogenic in rats and mice: it significantly increased the incidences of liver neoplasms and neuroendocrine tumours of the glandular stomach in male and female rats. Mechanisms of tumour induction by methyleugenol in other organs (kidney, mammary gland, and skin) or induction of mesotheliomas are not known. Mechanistic data indicate that liver tumours induced by methyleugenol and structurally related allylbenzenes such as safrole, result from the metabolism of these compounds to DNA-reactive intermediates [38].

Methyleugenol is rapidly absorbed following oral administration to rats and mice; its metabolism occurs via the cytochrome P450 system and involves side-chain hydroxylation, side-chain epoxide diol formation, and *O*-demethylation. Studies carried out to investigate the metabolism of methyleugenol have suggest that the risk due to dietary ingestion varies in the human population: it seems that methyleugenol is eliminated more rapidly in males than in females, suggesting that metabolic induction is greater in males [39].

No studies on the potential carcinogenicity of methyleugenol in humans have been reported, no data are available that would suggest the mechanisms thought to account for tumour induction by methyleugenol in experimental animals would not also operate in humans [38]. In the *Tenth Report on Carcinogens* (2002), published by the Department of Health and Human Services, methyleugenol is defined as “*reasonably anticipated to be a human carcinogen*” based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicate an induction of liver tumours (malignant and/or combination of malignant and benign) in mice and rats via DNA-adduct formation.

The Scientific Committee on Food of the European Commission in its opinion of 26 September 2001 confirmed the genotoxicity and carcinogenicity of methyleugenol and recommended that reductions in exposure and restrictions in use levels should be ensured [40].

In 2008 the latest evaluation of the experts on flavouring substances of the Council of Europe considered methyleugenol as an active principle I, for which no (T)MDI has to be set, on account of its genotoxic potential, but whose limit has to be considered as the limit of determination [17].

Quillaja saponaria extracts - Quillaia extracts (QE) are obtained by aqueous extraction of the milled inner bark or whole wood of *Quillaja saponaria* Molina (family Rosaceae), included in the list. The extracts contain over 100 triterpenoid saponins, the glycosides of the chief hydrophobic aglycone quillaic acid (about 8.5-17% in the freshly prepared unpurified extract); other compounds are tannins, polyphenols and calcium oxalate [12].

There are two types of purified extracts (types 1 and 2) with differing contents of saponins: type 1 contains 10-30% and type 2 may contain 65-90% quillaia saponins on a dried basis [41].

Based on the ability of saponin micelles to form insoluble aggregates with cholesterol Quillaia saponins can be used for the production of low-cholesterol dairy food products; they are also used internally for coughs and other conditions of the respiratory tract because of their expectorant and purgative effects. The biological activities and the potency of individual saponins *in vivo* depend primarily on the route of administration.

JECFA established a number of specifications for QE, including limits for colour absorbance, for a pH of fresh aqueous extracts between 5 and 5.5 and set a limit no greater than 14% for ash on the dried basis for type 1 and 5% for type 2. The latter limit reflects the high levels of calcium oxalate in type 1 (about 11% by weight) [41].

Some of the more toxicological effects include haemolysis (strong *in vitro*, much weaker *in vivo*), local irritation, inflammation; more severe toxic effects are liver damage, respiratory failure, convulsions, coma [42].

QE have a wide range of industrial applications: their major use is as foaming agents in beverages such as soft drinks and as emulsifiers in foods.

Quillaia is recognised as a natural flavouring substance for use in food and beverages by the United States Food and Drug Administration (US FDA); in the European Union the Codex Committee on Food Additives and Contaminants lists unpurified QE as suitable for use as a foaming agent in “water-based flavoured drinks”, including sport or electrolyte drinks, and sets a maximum use level of 500 mg/kg [42].

In 2006 the JECFA Committee, in its sixty-fifth report, established an ADI of 0-1 mg/kg bw/day (corresponding to 60 mg/die for a person weighing 60 kg) for type 1 and type 2 extracts expressed as Quillaia saponins and the previously established temporary ADI of 0-5 mg/kg bw was withdrawn [43].

Quinine - Quinine and its isomer quinidine are the most important alkaloids of the barks of *Cinchona* spp. present in the list: *Cinchona calisaya*, *Cinchona cordifolia*, *Cinchona ledgeriana*, *Cinchona officinalis*, *Cinchona succirubra*. In medicine quinine is used to treat malaria and nocturnal calf muscle cramp; because of its characteristic bitter flavour, it is also used in foods, particularly soft drinks. Quinine is also used as a flavouring, mainly in tonics and bitter lemonades.

When large amounts of quinine are consumed, it can constitute a health problem, especially for specific groups of persons. The German Federal Institute for Risk Assessment (BfR) has recently published an updated health assessment *Quinine-containing beverages may cause health problems* [44]. The BfR identified potential risks for quinine intake in particular for pregnant women, who should therefore

be advised to avoid quinine-containing beverages on precautionary grounds because of the possible link between the consumption of these beverages during pregnancy and the occurrence of health disorders in the mother and in the child. Quinine is also counter-indicated for people with tinnitus, pre-existing damage to the optic nerve, certain types of haemolytic anaemia or who take medicinal products such as anticoagulant medicines. The main adverse reactions to quinine intake are tinnitus, visual disturbances, disorientation, haematomas.

The 2008 *Report on natural sources of flavouring* of the Council of Europe [17] reported a NOEL of 1.2 mg quinine base/kg bw/day in humans and, based on a safety factor of 10 for inter-individual variability, an MDI of 0.1 mg/kg bw/day was proposed.

Directive 2002/67/EC of 18 July 2002 on the labelling of foodstuffs containing quinine, in accordance with the opinion of the EU Scientific Committee on Food (SCF), decided "to continue the use of quinine at a certain maximum level in bitter drinks. However, consumption of quinine may be counter-indicated for certain people for medical reasons". Moreover, quinine and its salts must be mentioned by name in labelling, in the list of ingredients after the term "flavouring". The SCF concluded that exposure to quinine (at up to 100 mg/l) has no adverse effects on reproduction and is not teratogenic [45].

However, the panel on food additives of EFSA, in their opinion of 22 May 2008, recommended that the toxicological database of quinine should be re-considered, adding that more reliable exposure data are required in order to finalise the evaluation [45].

Safrole - This substance occurs naturally in a variety of spices in the Italian Ministry list such as *Hamamelis virginiana*, *Illicium verum*, *Myristica fragrans*, cinnamon, nutmeg, pepper and herbs such as basil. The most important dietary sources are nutmeg, mace and their essential oils. Safrole is also present in cola drinks [17]. Its intake estimates in flavouring substances are generally very poor because of the lack of data on the concentrations of these chemicals occurring naturally or voluntarily added in foodstuffs.

The latest evaluation of safrole by the International Agency for Research on Cancer (IARC) resulted in a classification in Group 2B: possibly carcinogenic to humans [46]. The Scientific Committee on Food of the European Commission, in its opinion of 12 December 2001, classified safrole as a genotoxic and carcinogenic substance for which no safe exposure limit could be established; consequently, reductions in the exposure and restrictions in use levels are indicated [47].

Regulation (EC) No 1334/2008 of the European Parliament sets a maximum level of safrole for specific kinds of foods but does not indicate specific limits for foodstuffs in general to which flavourings or other food ingredients with flavouring properties have been added [31].

Safrole has not been approved by the US Food

and Drug Administration for use in foods (21 CFR 121-106) [47].

Safrole and isosafrole are carcinogenic in mice and rats; they produce liver tumours following oral administration [48].

The oral LD50 was reported to be 1950 mg/kg bw for rats and 2350 mg/kg bw for mice [49]. Safrole is metabolically activated through the formation of intermediates able to react directly with DNA; DNA adducts (two major and two minor) were detected in rat liver DNA after single doses of safrole at 1 or 100 mg/kg bw. These results suggest that the cytogenetic effects may result from covalent DNA modification in the rat liver [50].

No adequate human studies of the relationship between exposure to safrole and human cancer have been reported.

Saponaria officinalis - The root active compounds of this plant consist of triterpene saponins (2 to 8%) [12]. Closely similar to the Quillaia active principles, Saponaria is used to treat inflammation of the mucous membranes of the upper respiratory tract and also as an antibiotic, antiphlogistic and cholesterol-lowering agent.

On the basis of toxicological evaluations of Quillaia the ISS group decided to adopt the same recommendations for *Saponaria* sp., i.e. a maximum use level is established at 1 mg/kg bw/day of plant (corresponding to 60 mg/die for a person weighing 60 kg) [42, 43].

Smilax spp. - The roots of *Smilax* spp., known as Salsaparilla and included in the Italian Ministry's list, are reported to contain steroid saponins in 0.5-3% content, with sarsaponin as principal aglycone [12]. The steroid saponins are responsible for the drug's irritant effect on the skin and its strong diuretic and diaphoretic effects in high doses [12]. The German Commission E reported side effects following oral administration of preparations containing Salsaparilla, including gastric irritation and temporary renal damage. Saponins also increase the adsorption of digitalic glycosides and bismuth and the elimination of some hypnotic drugs. Particular attention should therefore be paid when saponins are ingested simultaneously with these medicinal products. For this reason the Commission E considered that the therapeutic index of the roots of *Smilax* is too low and the substance should only be used within certain limits.

On the basis also of the toxicological evaluation of saponin-containing Quillaia extracts, the ISS working group decided to adopt the same limitation to use, i.e. a maximum level of 1 mg/kg bw/day of plant (corresponding to 60 mg/die for a person weighing 60 kg) [42, 43].

Thujone (alpha- and beta-) - Thujone is a terpenoid ketone that exists in nature as a mixture of alpha- and beta- isomers which occur widely in essential oils in varying proportions, most notably in *Achillea millefolium*, *Artemisia* spp., *Cymbopogon* spp., *Croton eluteria*, *Salvia officinalis*, *Satureja montana* of the list.

Essential oils are used in traditional herbal medi-

cine (as abortifacient, carminative, anthelmintic, and for digestive problems, female hormone activity, fever, cough) and in food as flavourings in the alcoholic drink industry. Thujone has a neurotoxic potential and produces convulsions in animals and humans, acting on the central nervous system. No data are available on long term toxicity, carcinogenicity or reproductive toxicity.

Several studies on the mechanism of the neurotoxicity of alpha-thujone indicate that it is a modulator of the GABA type A receptor; the effects appear to be due to the parent compound and metabolism leads to detoxification [51, 52].

Little is known about the pharmacokinetics of these terpenes in humans and no epidemiological studies investigating the association of exposure to thujone and cancer risks in humans were available, but several case study reports of the acute effects of essential oils containing thujone causing seizures in humans indicated that the animal data are of relevance to humans [53, 54].

Thujone is banned as a food additive in the US and its presence in foods and beverages is regulated in several countries.

Annex III of Regulation (EC) No 1334/2008 on flavourings sets levels for thujone in some beverages as a naturally occurring substance present in flavourings or other food ingredients to which flavouring properties have been added, but it may not be added as such to food [31].

In 2002 thujone was evaluated by the Scientific Committee on Food of EFSA, which considered that the amounts of thujone isomers in foods and beverages resulting from the addition of thujone-containing flavouring agents (e.g. sage) should be reduced to the lowest practicable level [55].

The Council of Europe confirmed in its 2008 report [17] the limit in food and beverages of 0.1 mg/kg set in 2005 [16], and allocated a TMDI of 0.01 mg/kg bw/day based on a NOAEL of 5 mg/kg, derived from a 14-week study in female rats, to which a safety factor of 500 (due to the poor quality of the database) was applied [56]. The toxicological data on thujone are limited and the quality of the available studies was considered insufficient to set a TDI/ADI. However, the total intake of thujone from all sources appears to be well within the established TMDI value.

Trans-anethole - Trans-anethole is an alkenylbenzene or para-propenylanisole (t-anethole). It provides the characteristic sweet aroma of anise seeds and leaves. T-anethole is an aromatic oxidant, present in a variety of medicinal plant extracts used by the food and beverage industry, especially anise-flavoured alcoholic beverages. The most important listed plants containing t-anethole are: *Pimpinella anisum* (Anise), *Foeniculum vulgare* (Fennel Fruit, Fennel Plant), *Illicium verum*, *Artemisia dracunculus*, *Anethum graveolens*, *Ocimum basilicum*, *Origanum majorana*, *Agastache foeniculum*, *Coriandrum sativum*, *Apium graveolens*.

The most recent ADI approved by JECFA is 0-2 mg per kg of body weight.

Trans-anethole is liposoluble and rapidly absorbed by passive diffusion from the digestive tract. Despite the widespread use of this product, there is little scientific information about side effects of high doses in experimental animals: it seems to have very weak mutagenic activity and produces slight hydroypic changes in the liver of male animals [57]. Trans-anethole is also considered a biocide because of its nematocidal activity [58] and was found to be the major insecticidal agent present in anise oil. Rare side effects are reported, e.g. a case of stomatitis after use of denture cream containing oil of anise and a case of erythema and vesiculation after cutaneous application of a cream with the essential oil of anise [57]. Recent studies demonstrate that anethole suppresses T-cell proliferation and IL-2 production in mouse splenocyte cultures. This inhibition is mediated, at least in part, through the down-regulation of NF-AT and AP-1 [59].

Plants not admitted for use in food supplements

Plants or their parts not admitted for use in food supplements are divided into four groups: plants containing substances that are definitely toxic to humans (Table 2); plants of proven therapeutic efficacy, even at low doses, which can not be used in food supplements (Table 3); plants used in the preparation of cosmetics, repellents and other no-food products (Table 4); plants whose active principles are unknown and on which the toxicological studies are insufficient to express an opinion regarding their use in food.

A brief summary of these four classes of plants is given below.

Plants that contain substances which are definitely toxic to humans (Table 2) - Among the plants that are not suitable for food use because of their content of toxic principles [60-128], there are those that contain furan diterpenoids. These plants, when ingested, have toxic effects on the liver. They are found in the genera: *Perilla* (*P. frutescens* Britton) and *Teucrium* (*T. marum*, *T. montanum*, *T. polium*, *T. scordium*, *T. scorodonia*). Their toxicity can be effective directly in the case of oxidation of furanoditerpenes by the P450 enzyme system (the metabolites produced lead to a depletion of reduced glutathione, causing bubbles in the plasma membrane and death of hepatocytes) or indirectly, when it is mediated by activation of CYP3A4, leading to the formation of reactive epoxides, which inactivate or alter the human microsomal epoxide hydrolase, triggering an immune response against this enzyme (autoimmune hepatitis).

Plants containing toxic alkaloids should be excluded from the preparation of food supplements. Among these, the genus *Alkanna* (*A. tinctoria*) contains pyrrolizidinic alkaloids and is responsible for serious liver poisoning (liver cirrhosis and ascites), and suspected of causing liver tumours, right ventricular hypertrophy and pulmonary hypertension.

Table 2 | List of not admitted plants in food supplements and their constituents of toxicological concern

Botanical name	Parts of plants of possible concern	Constituents of toxicological concern	References
<i>Alkanna tinctoria</i> Tausch.	Radix	Pyrrolizidine alkaloids	61
<i>Discorea villosa</i> L.	Rhizoma	Alkaloid:dioscorine; saponins: dioscin, diosgenine; phytoestrogens with haemolytic activity	6, 12, 19, 62-64
<i>Eschscholtzia californica</i> Cham.	Herba	Pyrrolizidine alkaloids	19, 65-69
<i>Gossypium herbaceum</i> (L.)	Radix	Ergot alkaloids, terpenoids.	6, 10, 19, 70-83
<i>Gossypium</i> spp.	Semen	Gossypol, 1,3-dicloropropene.	6, 10, 12, 70, 72, 74-84
<i>Juglans regia</i> L.	Folium	Nicotine, p-cumaric acid, eugenol, cyanidine, juglone.	85
<i>Perilla frutescens</i> Britton	Fructus	Furano diterpenoids	86
<i>Pimpinella major</i>	Radix	Furano coumarins	6, 19, 87, 88
<i>Pimpinella saxifraga</i>	Herba, radix, rhizoma	Furano coumarins	6, 19, 87, 88
<i>Physalis peruviana</i> L.	Folium	Physaline, tropane alkaloids	86, 89
<i>Polygonum multiflorum</i> Thunb.	Rhizoma, Radix	Liver toxins	60, 90-92
<i>Ruta graveolens</i>	Oleum, herba, floribus	Alkaloids, coumarins	12, 93.
<i>Sassafras albidum</i> Nees	Cortex ex radicibus, radix, folium	Safrole	12, 94, 95
<i>Spigelia marilandica</i>	Floribus, radix, rhizoma	Neurotoxin	12
<i>Stachys officinalis</i> Trev.	Herba, folium	Aucubin, aucubigenine.	96-103
<i>Teucrium marum</i> L.	Folium, summitas	Furano diterpenoids	104-107
<i>Teucrium montanum</i> L.	Herba, floribus	Furano diterpenoids	108-112
<i>Teucrium polium</i> L.	Herba, floribus	Furano diterpenoids	113-116
<i>Teucrium polium</i> L. ssp. <i>Aureum arcangeli</i>	Herba	Furano diterpenoids	
<i>Teucrium polium</i> L. ssp. <i>Capitati arcangeli</i>	Herba, floribus	Furano diterpenoids	
<i>Teucrium scordium</i> L.	Herba, floribus	Furano diterpenoids	117
<i>Teucrium scorodonia</i> L.	Herba, floribus	Furano diterpenoids	117
<i>Viscum album</i> L.	Folium, herba	Viscotoxin	118-128

Plants with clear therapeutic efficacy, even at low doses, which can not be used in food supplements (Table 3) - Some plants can not be used in food supplements because of their therapeutic effects [129-213]: among these the ISS working group identified the genera *Annona* (*A. muricata*, *A. reticulata* and *A. squamosa*) and *Asimina* (*A. triloba*), which contain acetogenins, which are active against the parasites *Leishmania braziliensis* and *L. panamensis*. These plants cause depletion of ATP levels in many cells, including tumour cells, thereby inactivating the mechanisms of cellular resistance. The seeds of *Asimina triloba* also contain the alkaloids asimicina and asimina, which have emetic and narcotic effects, respectively.

Plants containing the alkaloid berberine, such as the genus *Coptis* (*C. japonica* and also *C. teeta* and *C. trifolia* are in the list) are used effectively as hypolipidaemic agents on account of their plasma cholesterol-reducing activity.

Plants used in the preparation of cosmetics, repellents and other no-food products (Table 4) - Some plants are used for non-food applications for the presence of active odour and/or emollients can be used as natural insect repellents, or for cosmetic preparations [214-253].

Plants of the genus *Calophyllum* contain polyunsaturated fatty acids, lipoproteins, coumarins, flavonoids, tocopherols, tocotrienols, and xanthenes, and are used in cosmetics for the treatment of skin and hair conditions and so can not be permitted for use in dietary supplements.

Furanocoumarins, active ingredients consisting of a furan ring conjugated to a coumarin, are compounds with high phototoxicity. These substances, synthesised by plants for defence against insect pests, are present in the genera *Heracleum* (*H. sphondylium*) and *Opopanax* (*O. chironium*) reported in the list.

Some plants used in the field of cosmetics contain toxic principles, such as the gender *Nigella* (*N. da-*

Table 3 | List of not admitted plants in food supplements due to their therapeutic effect

Botanical name	Parts of plants of possible concern	References
<i>Annona muricata</i> L.	Folium, radix, semen	129-136
<i>Annona reticulata</i>	Folium, radix, semen	
<i>Annona squamosa</i> L.	Folium, radix, semen	
<i>Asimina triloba</i> Dunal	Semen	19, 137-141
<i>Brunfelsia hopeana</i> Benth.	Radix	12
<i>Callitris articulata</i> Link.	Gummi	12
<i>Canarium commune</i> L.	Resina, semen	142
<i>Cedrela toona</i> Roxb.	Folium, lignum, semen	143-145
<i>Combretum micranthum</i> Don.	Folium	12, 19, 146-153
<i>Copaifera officinalis</i> Linn.	Balsamum	154-160
<i>Coptis japonica</i> Makino	Radix	161-164
<i>Eryngium campestre</i> L.	Radix	12, 18, 19, 165-170
<i>Evernia prunastri</i> Ach. (L.)	Thallus	171, 172
<i>Fagus sylvatica</i> L.	Fructus, lignum, semen	6, 173
<i>Ferula galbaniflua</i> Boiss.-B.	Gummi, resin	12, 19, 174-181
<i>Levisticum officinale</i> Koch.	Radix	6, 12, 182, 183
<i>Mahonia aquifolium</i> Pursh.	Radix	6, 12, 184
<i>Momordica charantia</i>	Fructus, balsamum	6, 19, 185, 186
<i>Paeonia officinalis</i> L.	Flos, radix	10
<i>Papaver somniferum</i> L.	Semen	187-194
<i>Piper betle</i> L.	Folium	6, 195-198
<i>Ptychopetalum olocoides</i> Benth.	Cortex, cortex ex radicibus, lignum	199-203
<i>Punica granatum</i> L.	Cortex	204
<i>Quassia amara</i> L.	Lignum	205-207
<i>Saussurea lappa</i> Clarke	Radix	8, 208, 209
<i>Scutellaria laterifolia</i>	Herba	12, 210, 211
<i>Scutellaria baicalensis</i> Geor.	Folium, radix	
<i>Scutellaria galericulata</i>	Herba	
<i>Selenicereus grandiflorus</i> (L.) Britt et Rose	Flos, herba	12
<i>Smilax officinalis</i> H.B.K.	Radix	212, 213

Table 4 | List of not admitted plants in food supplements due to their use in no alimentary fields

Botanical name	Parts of plants of possible concern	References
<i>Arnica montana</i> L.	Capitula, herba c., floribus, radix folium, summitas	214-218
<i>Calophyllum inophyllum</i> L.	Resina	219-223
<i>Convolvulus scoparius</i> L.	Lignum, radix	6
<i>Heracleum sphondylium</i> (L.)	Fructus	6, 12, 19, 178, 224-229
<i>Ledum palustre</i>	Herba	230-235
<i>Liquidambar styraciflua</i> L.	Balsamum	6
<i>Malaleuca alternifolia</i>	Oleum, summitas	236, 237
<i>Nigella damascena</i> L.	Semen	238, 239, 240
<i>Opopanax chironium</i> Koch.	Gummi, resina	241, 242
<i>Pogostemon cablin</i> Benth.	Folium	243-246
<i>Tanacetum cinerariaefolium</i> Sch. Bip.	Capitula	247-250
<i>Tanacetum creticum</i>		251
<i>Tanacetum vulgare</i> L.	Capitula, herba, floribus, semen	252, 253

mascena), which synthesises damascenine, while the genus *Arnica* (*A. montana*) is used for external use, in the treatment of bruises and sprains. These plants contain sesquiterpene lactones and are therefore toxic for humans when ingested orally.

Plants used as natural repellents belonging to the genus *Tanacetum* (*T. cinerariaefolium*, *T. creticum* and *T. vulgare*) contain pyrethroids, compounds known for their activity against insects, but toxic in foods.

Plants whose active principles are unknown, and whose toxicological studies are insufficient to enable their safe use in food supplements - In examining the herbal drugs used in food supplements, we found that there is insufficient evidence to enable a proper assessment of the leaves of *Croton eluteria*. It was therefore deemed prudent to preclude the use in food of the leaves of this plant.

CONCLUSIONS

The criteria for the preparation of this paper were intended to safeguard the health of consumers of botanicals and botanical preparations as food supplements. To this end, the plants were studied from a phy-

tochemical point of view in order to highlight the components with any kind of activity in humans. Where the activity of a plant is expressed and there is sufficient documentation regarding its toxicity, the plant has been excluded from the list of admitted plants. Where the activity of one substance present in plant has one threshold level, this quantity was taken as the maximum admitted dose.

However it is clearly stated that the safety in the use of botanical preparations should be assessed considering the toxicity and the increased exposure of the consumers as main criteria. If in the future, new plants will be studied by ISS working group, the same criteria and limits will be used also for them if they contain the same constituents of the plants examined in this study.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 1 March 2010.

Accepted on 17 June 2010.

References

- European Union. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. *Official Journal of the European Communities* L 183/51, 12 July 2002.
- European Union. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending as regards herbal medicinal products Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Communities* L 136/85, 30 April 2004.
- Italia. Decreto legislativo 21 maggio 2004 n. 169. Attuazione della direttiva 2002/46/CE relativa agli integratori alimentari. *Gazzetta Ufficiale - Serie Generale* n. 164, 15 luglio 2004.
- EFSA Scientific Cooperation (ESCO), Working Group on Botanicals. *Draft compendium of botanicals that have been considered for a food and/or a food supplement use and that have been reported to contain toxic or addictive or psychotropic substances*. June 2008.
- EFSA Scientific Cooperation (ESCO), Working Group on Botanicals. *Draft compendium of botanicals and botanical preparations that have been considered for food and/or food supplement use and have been reported to have also a medicinal use*. June 2008.
- Hoppe HA. *Drogen Kunde*. Berlin-New York: Walter de Gruyter; 1975.
- Hegnauer R. *Chemotaxonomie der Pflanzen*. Basel-Boston-Berlin: Birkhäuser Verlag; 1992 and 2001.
- India. Ministry of Health and Family Welfare, Department of Indian Systems of Medicine & Homoeopathy. *The ayurvedic pharmacopoeia of India*. New Delhi: National Institute of Science Communication (CSIR); 2001.
- Zhou J, Xie G, Yan X. *Traditional Chinese medicines, molecular structures, natural sources and application*. Hampshire-Burlington: Ashgate Publishing Lmted, GWA Milne Editor; 2003.
- Duke JA. *Handbook of medicinal herbs*. Boca Raton: CRC Press; 2000.
- Kapoor LD. *Handbook of ayurvedic medicinal plants*. Boca Raton: CRC Press; 2000.
- Gruenwald J, Brendeler T, Jaenicke C, Fleming T (Ed.). *Physicians' desk reference (PDR) for herbal medicines*. 2. Ed. Montvale-w Jersey: Medical Economics Company; 2000.
- Ministero della Salute. *Alimenti particolari e integratori. Integratori alimentari*. Available from: www.salute.gov.it.
- European Medicines Agency Regulatory. *Human medicines. Herbal products*. Available from: www.ema.europa.eu.
- European Food Safety Authority. *Scientific documents. Botanicals*. Available from: www.efsa.europa.eu.
- Council of Europe, Committee of Experts on Flavouring Substances - *Active principles (constituents of toxicological concern) contained in natural sources of flavourings*. Health Protection of the Consumer Series, Strasbourg: Council of Europe Press; October 2005. Available from: www.coe.int/t/e/social_cohesion/soc-sp/public_health/flavouring_substances/Active%20principles.pdf.
- Council of Europe, Committee of Experts on Flavouring Substances. *Natural sources of flavourings. Report No. 3*. Belgium: Council of Europe Publishing; 2008.
- European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and material in contact with food (AFC) on a request from the Commission related to coumarin. Question number EFSA-Q-2003-118. *The EFSA Journal* 2004;104:1-36.
- Bruni A, Nicoletti M. *Dizionario ragionato di erboristeria e di fitoterapia*. Padova: Piccin; 2003. p. 523
- Bruni A, Nicoletti M. *Lezioni di botanica farmaceutica*. Roma: CISU; 2000.
- Stewart MJ, Steenkamp V. Pyrrolizidine poisoning: a neglected area in human toxicology. *Ther Drug Monit* 2001;23:698-708.
- EFSA Scientific Cooperation (ESCO). *Compendium of botanicals that have reported to contain toxic or addictive or psychotropic substances*. *The EFSA Journal* 2009;7:281-79.
- Swenberg JA. Covalent binding index study on coumarin. In: *Report of laboratory of molecular carcinogenesis and mu-*

- tagensis*. University of North Carolina, Chapel Hill, NC, USA and by European Flavour and Fragrance Association (EFFA); Brussels; 2003.
24. European Medicines Agency, Committee on Herbal Medicinal Products. *Public statement on the use of herbal medicinal products containing estragole*. London, 23 November 2005. Doc. Ref: EMEA/HMPC/137212/2005.
 25. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Eugenol and related hydroxyallylbenzene derivatives In: *Safety evaluation of certain food additives*. Geneva: WHO; 2005. p. 155-200. (WHO Food Additives Series n. 56).
 26. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and material in contact with food. Consideration of eugenol and related hydroxyallylbenzene derivatives evaluated by JECFA (65th meeting) structurally related to ring-substituted phenolic substances evaluated by EFSA in FGE.22 (2006). Question number EFSA-2008-32L. *The EFSA Journal* 2009; 965:1-53.
 27. European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on glycyrrhizic acid and its ammonium salt*. 4 April 2003. Available from: http://ec.europa.eu/food/fs/sc/scf/out186_en.pdf.
 28. Cosmetic Ingredient Review Expert Panel. Final Report on the safety assessment of glycyrrhizic acid. *Int J Toxicol* 2007;26(Suppl. 2):79-112.
 29. European Food Safety Authority. Opinion of the Scientific Panel on contaminants. Ethyl carbamate and hydrocyanic acid in food and beverages. Question number EFSA-Q-2006-076 *The EFSA Journal* 2007;551:1-44.
 30. Italia. Decreto Legislativo 25 gennaio 1992 n.107. Attuazione delle direttive 88/388/CEE e 91/71/CE relative agli aromi destinati ad essere impiegati nei prodotti alimentari ed ai materiali di base per la loro preparazione. *Gazzetta Ufficiale - Supplemento Ordinario* n. 39, 17 febbraio 1992.
 31. European Union. Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. *Official Journal of the European Union* 2008; L354: 34-48.
 32. European Medicines Agency, Committee on Herbal Medicinal Products. *Public statement on the use of herbal medicinal products containing pulegone and menthofuran*. London, 23 November 2005. Doc Ref: EMEA/HMPC/138386/2005.
 33. Thorup I, Würtzen G, Carstensen J, Olsen P. Short term toxicity study in rats dosed with peppermint oil. *Toxicol Lett* 1983;19(3):211-5.
 34. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with foods on a request from the Commission on pulegone and menthofuran in flavourings and other food ingredients with flavouring properties. Question number EFSA-Q-2003-119. Adopted on 7 December 2005. *The EFSA Journal* 2005;298:1-32.
 35. Nair B. Final report on the safety assessment of Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. *Int J Toxicol* 2001;20(Suppl. 3):61-73.
 36. Organization for Economic Cooperation and Development. *Menthols*. Paris: UNEP Publications; 2003. p. 14.
 37. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Menthol In: *Safety evaluation of certain food additives*. Geneva: WHO; 1999. (WHO Food Additives Series n. 42).
 38. National Toxicology Program. *Toxicology and carcinogenesis studies of methyleugenol (CAS No. 93-15-2) in F344/N rats and B6C3F1 mice (gavage studies)*. Research Triangle Park, NC: US Department of Health and Human Service; 2000. (NTP TR 491, NIH Publication n. 00-3950).
 39. National Toxicology Program. *Toxicology and carcinogenesis studies of methyleugenol (CAS No. 93-15-12) in F344/N rats and B6C3F1 mice (gavage studies)*. Research Triangle Park, NC: US Department of Health and Human Service; 1998. (NTP TR 491, NIH Publication n. 98-3950).
 40. European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on Methyleugenol (1,4-Allyl-1,2-dimethoxybenzene)*. 2001. Doc Ref: SCF/CS/FLAV/FLAVOUR/4 ADD1 FINAL-26 September 2001.
 41. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Quillaia extracts Type 1 and Type 2. Chemical and Technical Assessment. First draft prepared by Silvia Resnik (2003). Revised draft prepared by Paul M Kuznesof and Lucia M Valente Soares (2005). In: *Chemical and Technical Assessment 65th JECFA*. Available from: ftp://ftp.fao.org/es/esn/jecfa/cta_65_quillaia.pdf.
 42. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Quillaia extracts. In: *Safety evaluation of certain food additives*. Geneva: WHO; 2002. (WHO Food Additives Series n. 48). Available from: www.inchem.org/documents/jecfa/jecmono/v48je03.htm.
 43. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Quillaia Extracts. In: *Evaluation of certain food additives*. Geneva: WHO; 2006. (WHO Technical Report Series No 934). p. 28-33.
 44. Federal Institute for Risk Assessment (BfR). *Quinine-containing beverages may cause health problems*. Update BfR Health Assessment n. 020; 2005. Available from: www.bfr.bund.de/cm/245/quinine_containing_beverages_may_cause_health_problems.pdf.
 45. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and material in contact with food. *Three quinine salts from the priority list from chemical group 30*. Question number EFSA-Q-2003-172B. *The EFSA Journal* 2008;739:1-18.
 46. International Agency for Research on Cancer (IARC). *Some naturally occurring substances*. Lyon, France: IARC; 1976. (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. 10). 353 p.
 47. European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the safety of the presence of safrole (1-allyl-3,4-methylene dioxy benzene) in flavourings and other food ingredients with flavouring properties*. 12 December 2001. Available from: http://ec.europa.eu/food/fs/sc/scf/out116_en.pdf.
 48. Wislocki PG, Borchest P, Miller JA, Miller EC. The metabolic activation of the carcinogen 1'-hydroxysafrole *in vivo* and *in vitro* and the electrophilic reactivities of possible ultimate carcinogens. *Cancer Res* 1976;36:1686-95.
 49. Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG. Food flavourings and compounds of related structure. I. Acute oral toxicity. *Food Cosm Toxicol* 1964;2:327-43.
 50. Daimon H, Sawada S, Asakura S, Sagami F. *In vivo* genotoxicity and DNA adduct levels in the liver of rats treated with safrole. *Carcinogenesis* 1998;19:141-6.
 51. Meschler JP, Howlett AC. Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabimimetic responses. *Pharmacol Biochem Behav* 1999;62:473-80.

52. Höld KM, Sirisoma NS, Ikeda T, Narahashi T, Casida JE. Alpha-thujone (the active component of absinth): gamma-aminobutyric acid type A receptor modulation and metabolic detoxification. *Proc Natl Acad Sci USA* 2000;97(8):3826-31.
53. Burkhard PR, Brukhardt K, Haenggeli CA, Landis T. Plant-induced seizures: reappearance of an old problem. *J Neurol* 1999;246:667-70.
54. Strang J, Arnold WN, Peters T. Absinthe: what's your poison? *Brit Med J* 1999;319:1590-1.
55. European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on Thujone* (expressed on 2 December 2002). Doc Ref: SCF/CS/FLAV/FLAVOUR/23 ADD2 Final.
56. Margaria R. *Acute and sub-acute toxicity study on thujone*. Unpublished report of the Istituto di Fisiologia, Università di Milano 1963 (cited from CoE Datasheet RD4.2/14-44, 1999).
57. Toxnet. Anethole. *Hazardous Substances Data Bank*. Available from: <http://toxnet.nlm.nih.gov>.
58. Oka Y, Nacar S, Putievsky E, Ravid U, Yaniv Z, Spiegel Y. Nematicidal activity of essential oils and their components against the root-knot nematode. *Phytopathology* 2000;90(7):710-5.
59. Yea SS, Jeong HS, Choi CY, Park KR, Oh S, Shin JG, Yun CH. Inhibitory effect of anethole on T-lymphocyte proliferation and interleukin-2 production through down-regulation of the NF-AT and AP-1. *Toxicol in vitro* 2006;20(7):1098-105.
60. Park GJ, Mann SP, Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from *Polygonum multiflorum*. *J Gastroenterol Hepatol* 2001;16:115-7.
61. Assimpoulou AN, Papageorgiou VP. Radical scavenging activity of *Alkanna tinctoria* root extracts and their main constituents, hydroxynaphthoquinones. *Phytother Res* 2005;19:141-7.
62. Broadbent JL, Schnieden H. A comparison of some pharmacological properties of dioscorine and dioscin. *Brit J Pharmacol* 1958;13:213.
63. Sauvaire Y, Baccou JC. Extraction of diosgenine, (25R)-spirost-5-ene-3beta-ol; problems of the acid hydrolysis of the saponins. *Lloydia* 1978;41:247-56.
64. Hooker E. Final report of the amended safety assessment of *Dioscorea villosa* (Wild Yam) root extract. *Int J Toxicol* 2004;23:49-54.
65. Stermitz FR, Schneider MJ, Schell LD, McGregor S, James LF, et al. (Ed.). *Toxic international symposium*. Utah, USA: Logan; 1988. p. 204-7.
66. Schafer HL, Schafer H, Schneider W, Elstner EF. Sedative action of extract combinations of *Eschscholtzia californica* and *Corydalis cava*. *Arzneim Forsch* 1995;45(2):124-6.
67. Fabre N, Claparols C, Richelme S, Angelin ML, Fourasté I, Moulis C. Direct characterization of isoquinoline alkaloids in a crude plant extract by ion-pair liquid chromatography-electrospray ionization tandem mass spectrometry: example of *Eschscholtzia californica*. *J Chromatogr A* 2000;904(1):35-6.
68. Paul LD, Maurer HH. Studies on the metabolism and toxicological detection of the *Eschscholtzia californica* alkaloids californine and protopine in urine using gas chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2003;789(1):43-57.
69. Singh S, Jain L, Pandey MB, Singh UP, Pandey VB. Antifungal activity of the alkaloids from *Eschscholtzia californica*. *Folia Microbiol (Praha)* 2009;54(3):204-6.
70. Grag SK, Saksena SK, Chaudhury RR. Antifertility screening of plants. VI. Effect of five indigenous plants on early pregnancy in albino rats. *Indian J Med Res* 1970;58:1285-9.
71. Lee H, Lin JY. Antimutagenic activity of extracts from anticancer drugs in Chinese medicine. *Mutat Res* 1988;204:229-34.
72. Hong CY, Huang JJ, Wu P. The inhibitory effect of gossypol on human sperm motility: relationship with time, temperature and concentration. *Human toxicol* 1989;8:49-51.
73. Budavari S (Ed.). Cottonseed oil. *The Merck Index. Encyclopedia of Chemicals, Drugs and Biologicals*. Rahway, NJ: Merck and Co., Inc.; 1989.
74. Edenharder R, von Petersdorff I, Rauscher R. Antimutagenic effects of flavonoids, chalcones and structurally related compounds on the activity of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and other heterocyclic amine mutagens from cooked food. *Mutat Res* 1993;287:261-74.
75. Coutinho EM, Athayde C, Atta G, Gu ZP, Chen ZW, Sang GW, Emuveyan E, Adekunle AO, Mati J, Otubu J, Reidenberg MM, Segal SJ. Gossypol blood levels and inhibition of spermatogenesis in men taking gossypol as a contraceptive. A multicenter, international, dose-finding study. *Contraception* 2000;61:61-7.
76. Mondini C, Dell'Abate MT, Leita L, Benedetti A. An integrated chemical, thermal, and microbiological approach to compost stability evaluation. *J Environ Qual* 2003;32:2379-86.
77. Lordelo MM, Davis AJ, Calhoun MC, Dowd MK, Dale NM. Relative toxicity of gossypol enantiomers in broilers. *Poult Sci* 2005;84:1376-82.
78. Bezemer TM, Wagenaar R, van Dam NM, van Der Putten WH, Wäckers FL. Above- and below-ground terpenoid aldehyde induction in cotton, *Gossypium herbaceum*, following root and leaf injury. *J Chem Ecol* 2004;30:53-67.
79. Stipanovic RD, Puckhaber LS, Bell AA, Percival AE, Jacobs J. Occurrence of (+)- and (-)-gossypol in wild species of cotton and in *Gossypium hirsutum* var. marie-galante (Watt) Hutchinson. *J Agric Food Chem* 2005;53:6266-71.
80. Indovina P, Rainaldi G, Santini MT. Three-dimensional cell organization leads to a different type of ionizing radiation-induced cell death: MG-63 monolayer cells undergo mitotic catastrophe while spheroids die of apoptosis. *Int J Oncol* 2007;31:1473-83.
81. Indovina P, Rainaldi G, Santini MT. Hypoxia increases adhesion and spreading of MG-63 three-dimensional tumor spheroids. *Anticancer Res* 2008;28:1013-22.
82. Amara AA, El-Masry MH, Bogdady HH. Plant crude extracts could be the solution: extracts showing *in vivo* antitumor activity. *Pak J Pharm Sci* 2008;21:159-71.
83. Menegassi A, Wassermann GE, Olivera-Severo D, Becker-Ritt AB, Martinelli AHS, Feder V, Carlini CR. Urease from cotton (*Gossypium hirsutum*) seeds: isolation, physicochemical characterization, and antifungal properties of the protein. *J Agric Food Chem* 2008;56:4399-405.
84. Przybylski P, Pospieszny T, Huczynski A, Brzezinski B. EI MS and ESI MS studies of the bisesquiterpene from cotton seeds: gossypol and its aza-derivatives. *J Mass Spectrom* 2008;43(5):680-6.
85. Saad B, Dakwar S, Said O, Abu-Hijleh G, Al Battah F, Kmeel A, Aziazah H. Evaluation of medicinal plant hepatotoxicity in co-cultures of hepatocytes and monocytes. *Evid Based Complement Altern Med* 2006;3:93-8.
86. Food and Drug Administration, Centre for Food Safety and Applied Nutrition. *Perilla frutescens*. FDA Poison Plant Database. FDA; 2006.
87. Floss HG, Mothes U. On the biosynthesis of furocoumarins in *Pimpinella magna*. *Phytochemistry* 1966;5(1):161-9.

88. Wessely F, Neugebauer L. Contents of the root of *Pimpinella saxifraga*. *Monatsch Chem* 1953;84:217.
89. Kubwabo C, Rollmann B, Tilquin B. Analysis of Alkaloids from *Physalis peruviana* by capillary GC, capillary GC-MS and GC-FTIR. *Planta Med* 1993;59(2):161-3.
90. But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from *Polygonum multiflorum*. *Vet Hum Toxicol* 1996;38:280-2.
91. Mazzanti G, Battinelli L, Daniele C, Mastroianni CM, Lichtner M, Coletta S, Costantini S. New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from *Polygonum multiflorum*. *Annals Intern Med* 2004;140:W30. Available from www.annals.org/cgi/content/full/140/7/W-30.
92. Panis B, Wong DR, Hooymans PM, De Smet PA, Rosias PP. Recurrent toxic hepatitis in a Caucasian girl related to the use of Shou-Wu-Pian, a Chinese herbal preparation. *J Pediatr Gastroenterol Nutr* 2005;41:256-8.
93. Germany. Bundesinstitut für Arzneimittel und Medizinprodukte. Kommission E. *Ruta graveolens* (Raute) Monograph. *Bundesanzeiger* 1989. N. 43 on 02/03/1989.
94. Newall CA, Anderson LA, Phillipson JD (Ed.). *Herbal medicines. A guide for health-care professionals*. London: The Pharmaceutical Press; 1996.
95. Hutson D, Cupp MJ. Sassafras. In: Cupp MJ (Ed). *Toxicology and clinical pharmacology of herbal products*. Totowa, New Jersey: Humana Press Inc; 2000. p. 245-52.
96. Fontaine J, Elchami AA, Vanhaelen M, Vanhaelen-Fastre R. Biological analysis of *Harpagophytum procumbens* D.C. Part 2. Pharmacological analysis of the effects of harpagoside, harpagide and harpagogenin on the isolated guinea pig ileum. *J Pharm Belg* 1981;36:321-4.
97. Breschi MC, Martinotti E, Catalano S, Flamini G, Morelli I, Pagni AM. Vasoconstrictor activity of 8-*O*-acetylharpagide from *Ajuga reptans*. *J Nat Prod* 1992;55:1145-8.
98. Bartholomaeus A, Ahokas J. Inhibition of P-450 by aucubin: is the biological activity of aucubin due to its glutaraldehyde-like aglycone? *Toxicol Lett* 1995;80:75-83.
99. Miyase T, Yamamoto R, Ufno A. Phenylethanoid glycosides from *Stachys officinalis*. *Phytochemistry* 1996;43:475-9.
100. Kim DH, Kim BR, Kim JY, Jeong YC. Mechanism of covalent adduct formation of aucubin to proteins. *Toxicol Lett* 2000;114(1-3):181-8.
101. Vundac VB, Pfeifhofer HW, Brantner AH, Males Z, Plazibat M. Essential oils of seven *Stachys taxa* from Croatia. *Biochem Syst Ecol* 2006;34(12):875-81.
102. Akkol EK, Tatli II, Akdemir ZS. Antinociceptive and anti-inflammatory effects of saponin and iridoid glycosides from *Verbascum pterocalycinum* var. *mutense* Hub. *Mor. Z Naturforsch* 2007;62(11-12):813-20.
103. Háznagy-Radnai E, Réthy B, Czige Sz, Zupkó I, Wéber E, Martinek T, Falkay G, Máthé I. Cytotoxic activities of *Stachys* species. *Fitoterapia* 2008;79(7-8):595-7.
104. Pagnoni UM, Pinetti A, Trave R, Garanti L. Monoterpenes of *Teucrium marum*. *Aust J Chem* 1976;29(6):1375-81.
105. Sanz J, Mus M, Rossello JA. Volatile components variation in the *Teucrium marum* complex (Lamiaceae) from the Balearic Island. *Bot J Linn Soc* 2000;132(3):253-61.
106. Eisner T, Eisner M, Anashansley DJ, Wu CL, Meinwalt J. Chemical defense of the mint plant. *Teucrium marum* (Labiatae). *Chemoeology* 2000;10(4):211-6.
107. Ricci D, Fraternali D, Giampieri L, Bucchini A, Epifano F, Burini G, Curini M. Chemical composition, antimicrobial and antioxidant activity of the essential oil of *Teucrium marum* (Lamiaceae). *J Ethnopharmacol* 2005;98(1-2):195-200.
108. Brown-Woodman PDC, Mohri H, Mohri T, Suter D, White IG. Mode of action of alpha-chlorohydrin as a male anti-fertility agent. Inhibition of the metabolism of ram spermatozoa by alpha-chlorohydrin and location of block in glycolysis. *Biochem J* 1978;170(1):23-37.
109. Malakov PY, Papanov GY, Boneva IM. Neo-clerodane diterpenoids from *Teucrium montanum*. *Phytochemistry* 1992;31(11):4029-30.
110. Rodriguez B. Oxirane-opening reactions of some 6,19-oxygenated 4- α ,18-epoxy-*neo*-clerodanes isolated from *Teucrium*. Biogenesis and antifeedant activity of their derivatives. *Tetrahedron* 1994;50(18):5451-68.
111. Kisiel W, Piozzi F, Grzybek J. Terpenoids from *Teucrium montanum* subsp. *pannonicum*. *Planta Med* 1995;61(2):191-2.
112. Chen I-C, Wu Y-K, Liu H-J, and Zhu J-L. Total syntheses of (\pm)-montanin A and (\pm)-teuscorolide. *Chem Commun* 2008;4720-2.
113. Lekehal M, Pessayre D, Lereau JM, Moulis C, Fouraste I, Fau D. Hepatotoxicity of the herbal medicine germander: metabolic activation of its furano diterpenoids by cytochrome P450 3A depletes cytoskeleton-associated protein thiols and forms plasma membrane blebs in rat hepatocytes. *Hepatology* 1996;24(1):212-8.
114. De Berardinis V, Moulis C, Maurice M, Beaune P, Pessayre D, Pompon D, Loeper J. Human microsomal epoxide hydrolase is the target of germander-induced autoantibodies on the surface of human hepatocytes. *Mol Pharmacol* 2000;58(3):542-51.
115. Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy *Teucrium polium* L. *Eur J Gastroenterol Hepatol* 2006;18(6):681-3.
116. Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by *Teucrium polium* L.: report of two cases and review of the literature. *Eur J Gastroenterol Hepatol* 2007;19(6):507-11.
117. Jakupovic J, Baruah RN, Bohlmann F, Quack W. New Clerodane Derivatives from *Teucrium scordium* L. *Planta Med* 1985;51(4):341-2.
118. Grieve M. *A modern herbal*. London: Penguin Books, Lyle CF; 1984.
119. Altmann H. *Poisonous plants and animals*. London: Chatto and Windus; 1980.
120. Chevallier A. *Encyclopedia of medicinal plants*. London: Dorling Kindersley; 1996.
121. Bown D. *Encyclopaedia of herbs and their uses*. London: Dorling Kindersley; 1995.
122. Chiej R. *Encyclopaedia of medicinal plants*. Edinburgh: MacDonald; 1984.
123. Stary F. *Poisonous plants*. UK: Hamlyn; 1983.
124. Lust J. *The herb book*. USA: Bantam books; 1983.
125. Uphof JC. *Dictionary of economic plants*. Weinheim, Germany: HR Engelman; 1959.
126. Freethy R. *From agar to zenery*. Marlborough, United Kingdom: The Crowood Press; 1985.
127. Mills SY. *The dictionary of modern herbalism: A comprehensive guide to practical herbal therapy*. Wellingborough, New York: Thorsons Pub Group; 1985.
128. World Health Organisation. *Medicinal plants in the Republic of Korea* n. 21. Manila: WHO; 1998.
129. Morita H, Sato Y, Chan KL, Choo CY, Itokawa H, Takeya K, Kobayashi J, Samoquasine A. Benzoquinoline alkaloid from the seeds of *Annona squamosa*. *J Nat Prod* 2000;63(12):1707-8.

130. Chang FR, Liaw CC, Lin CY, Chou CJ, Chiu HF, Wu YC. New adjacent bis-tetrahydrofuran *Annonaceous acetogenins* from *Annona muricata*. *Planta Med* 2003;69(3):241-6.
131. Lannuzel A, Michel PP, Hoeglinger GU, Champy P, Jousset A, Medja F. The mitochondrial complex I inhibitor annonacin is toxic to mesencephalic dopaminergic neurons by impairment of energy metabolism. *Neuroscience* 2003;121(2):287-96.
132. Ahmad KF, Sultana N. Biological studies on fruit pulp and seeds of *Annona squamosa*. *J Chem Soc Pak* 2003;25(4):331-3.
133. Rahman MM, Parvin S, Haque ME, Islam ME, Mosaddik MA. Antimicrobial and cytotoxic constituents from the seeds of *Annona squamosa*. *Fitoterapia* 2005;76(5):484-9.
134. Champy P, Melot A, Guérineau Eng V, Gleye C, Fall D, Höglinger GU, Ruberg M, Lannuzel A, Laprèvote O, Laurens A, Hocquemiller R. Quantification of acetogenins in *Annona muricata* linked to atypical parkinsonism in Guadeloupe. *Mov Disord* 2005;20(12):1629-33.
135. Lannuzel A, Hoglinger GU, Champy P, Michel PP, Hirsch EC, Ruberg M. Is a atypical parkinsonism in the Caribbean caused by the consumption of Annonaceae? *J Neural Transm Suppl* 2006;70:153-7.
136. Mohanty S, Hollinshead J, Jones L, Jones PW, Thomas D, Watson AA, Watson DG, Gray AI, Molyneux RJ, Nash RJ. *Annona muricata*. Toxic or therapeutic. *Nat Prod Commun* 2008;3(1):31-3.
137. Derevinskaya TI, Pakaln DA. Some problems of the quality of drug-technical raw material of *Asimina triloba*. *Farm Zh* 1983;38:49-52.
138. Zhao G, Hui Y, Rupprecht JK, McLaughlin JL, Wood KV. Additional bioactive compounds and trilobacin, a novel highly cytotoxic acetogenin, from the bark of *Asimina triloba*. *J Nat Prod* 1992;55(3):347.
139. He K, Shi G, Zhao GX, Zeng L, Ye Q, Schwedler JT, Wood KV, McLaughlin JL. Three new adjacent bis-tetrahydrofuran acetogenins with four hydroxyl groups from *Asimina triloba*. *J Nat Prod* 1996;59:1029-34.
140. Zhao GX, Chao JF, Zeng L, Rieser MJ, McLaughlin JL. The absolute configuration of adjacent bis-THF acetogenins and asimicin, a novel highly potent asimicin isomer from *Asimina triloba*. *Bioorg Med Chem* 1996;4(1):25-32.
141. Woo MH, Kim DH, McLaughlin JL. Asitriolobins A and B: Cytotoxic mono-THF Annonaceous acetogenins from the seeds of *Asimina triloba*. *Phytochemistry* 1999;50(6):1033-40.
142. *Pharmacopoeia of the People's Republic of China*, 232, 1043. Hong Kong: Lie Young & Young Creation; 1988.
143. Kout O, Isman MB. Toxicity of the limonoid allelochemical cedrelone to noctuid larvae. *Entomol Exp Appl* 1992;64(3):281-7.
144. Wali U, Rehman R. Trial of insecticides and a fumigant against forest seed pests. *Pakistan J Forest* 1993;43(2):85-90.
145. Malairajan P, Gopalakrishnan G, Narasimhan S, Veni KJ, Kavimani S. Anti-ulcer activity of crude alcoholic extract of *Toona ciliata* Roemer (heart wood). *J Ethnopharmacol* 2007;110(2):348-51.
146. Ogan AU. The alkaloids in the leaves of *Combretum micranthum*. Studies on West African medicinal plants. VII. *Planta Med* 1972;21:210-7.
147. Bassene E, Olschwang D, Pousset JL. African medicinal plants: alkaloids of *Combretum micranthum* G. Don (Kinkeliba). *Ann Pharm Fr* 1986;44(3):191-6.
148. Ferrea G, Canessa A, Sampietro F, Cruciani M, Romussi G, Bassetti D. *In vitro* activity of a *Combretum micranthum* extract against *Herpes simplex* virus types 1 and 2. *Antiviral Res* 1993;21(4):317-25.
149. Ancolio C, Azas N, Mahiou V, Ollivier E, Di Giorgio C, Keita A, Timon-David P, Balansard G. Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. *Phytother Res* 2002;16(7):646-9.
150. Benoit F, Valentin A, Pellissier Y, Diafouka E, Marion C, Kone-Bamba D, Kone M, Mallie M, Yapo A, Bastide JM. *In vitro* antimalarial activity of vegetal extracts used in West African traditional medicine. *Am J Trop Med Hyg* 1996;54(1):67-71.
151. Karou D, Dicko MH, Sanon S, Simpore J, Traore AS. Antimalarial activity of *Sida acuta* Burm. f. (Malvaceae) and *Pterocarpus erinaceus* Poir. (Fabaceae). *J Ethnopharmacol* 2003;89(2-3):291-4.
152. Olajide OA, Makinde JM, Okpako DT. Evaluation of the anti-inflammatory property of the extract of *Combretum micranthum* G. Don (Combretaceae). *Inflammopharmacology* 2003;11(3):293-8.
153. Küster E. Cholin- and carboxylesterase activities in developing zebrafish embryos (*Danio rerio*) and their potential use for insecticide hazard assessment. *Aquatic Toxicol* 2005;75(1):76-85.
154. Ohsaki A, Yan LT, Ito S, Edatsugi H, Iwata D, Komoda Y. The isolation and *in vivo* potent antitumor activity of clerodane diterpenoids from the oleoresin of Brazilian medicinal plant *Copaifera langsdorffii* Desfon. *Bioorg Med Chem Lett* 1994;4:2889-92.
155. Paiva LAF, Rao VSN, Gramosa NV, Silveira ER. Gastroprotective effect of *Copifera langsdorffii* oleo-resin on experimental gastric ulcer models in rats. *J Ethnopharmacol* 1998;62(1):73-8.
156. Gomes NM. Antinociceptive activity of Amazonian Copaiba oils. *J Ethnopharmacol* 2007;109(3):486-92.
157. Cascon V, Gilbert B. Characterization of the chemical composition of oleoresins of *Copaifera guianensis* Desf., *Copaifera duckei* Dwyer and *Copaifera multijuna* Hayne. *Phytochemistry* 2000;55(7):773-8.
158. Paiva LA, Gurgel LA, Silva RM, Tomé AR, Gramosa NV, Silveira ER, Santos FA, Rao VS. Anti-inflammatory effect of kaurenoic acid, a diterpene from *Copaifera langsdorffii* on acetic acid-induced colitis in rats. *Vascular Pharmacol* 2002;39(6):303-7.
159. Costa-Lotufo LV, Cunha GMA, Farias PAM, Viana GSB, Cunha KMA, Pessoa C, MoraesMO, Silveira ER, Gramosa NV, Rao VSN. The cytotoxic and embryotoxic effects of kaurenoic acid, a diterpene isolated from *Copaifera langsdorffii*. *Toxicol* 2002;40(8):1231-4.
160. Krauchenco S, Nagem RAP, da Silva JA, Marangoni S, Polikarpov I. Three-dimensional structure of an unusual Kunitz (STI) type trypsin inhibitor from *Copaifera langsdorffii*. *Biochimie* 2004;86(3):167-72.
161. Namba T, Mikage M, Ushiyama T. Fundamental studies on the evaluation of crude drugs. Part 6. Electron microscopic analysis of crude drugs. Part 1. Determination of berberine in *Coptidis Rhizoma*. *J Pharm Soc Jap* 1982;102:56-62.
162. Mizuno M, Kojima H, Tanaka T, Iinuma M, Min Z, Murata H. Benzophenanthridine alkaloids from the seeds of *Coptis japonica* var. *dissecta*. *J Nat Prod* 1987;50:326.
163. Lee MK, Kim HS. Inhibitory effects of protoberberine alkaloids from the roots of *Coptis japonica* on catecholamine biosynthesis in PC12 cells. *Planta Med* 1996;62(1):31-4.
164. Park H, Kim MS, Jeon BH, Kim TK, Kim YM, Ahnn J, Kwon DY, Takaya Y, Wataya Y, Kim HS. Antimalarial activity of herbal extracts used in traditional medicine in Korea. *Biol Pharm Bull* 2003;26(11):1623-4.
165. Erdelmeier CA, Sticher O. Coumarin derivatives from *Eryngium campestre*. *Planta Med* 1985;51(5):407-9.
166. García MD, Sáenz MT, Gómez MA, Fernández MA.

- Topical antiinflammatory activity of phytosterols isolated from *Eryngium foetidum* on chronic and acute inflammation models. *Phytother Res* 1999;13(1):78-80.
167. Kartal M, Mitaine-Offer AC, Abu-Asaker M, Miyamoto T, Calisi I, Wagner H, Lacaille-Dubois MA. Two new triterpene saponins from *Eryngium campestre*. *Chem Pharm Bull* 2005;53(10):1318-20.
 168. Küpeli E, Kartal M, Aslan S, Yesilada E. Comparative evaluation of the anti-inflammatory and antinociceptive activity of Turkish *Eryngium* species. *J Ethnopharmacol* 2006;107(1):32-7.
 169. Hegnauer R. *Chemotaxonomie der Pflanzen*. Basel-Boston-Berlin: Birkhäuser Verlag; 1990.
 170. Kartal M, Mitaine-Offer AC, Paululat T, Abu-Asaker M, Wagner H, Mirjolet JF, Guilbaud N, Lacaille-Dubois MA. Triterpene saponins from *Eryngium campestre*. *J Nat Prod* 2006;69(7):1105-8.
 171. Dahlquist I, Fregert S. Contact allergy to atranorin in lichens and perfumes. *Contact Dermatitis* 1980;6(2):111-9.
 172. Loppi S, Pacioni G, Olivieri N, Di Giacomo F. Accumulation of trace metals in the lichen *Everina prunastri* transplanted at biomonitoring sites in central Italy. *Bryologist* 1998;101(3):451-4.
 173. Breckle SW, Kahle H. Effects of toxic heavy metals (cadmium, lead) on growth and mineral nutrition of beech (*Fagus sylvatica* L.). *Vegetatio* 1992;101(1):43-53.
 174. Nassar MI. Spectral study of farnesiferol B from *Ferula assa foetida* L. *Pharmazie* 1994;49:542-3.
 175. Saleem M, Alam A, Sultana S. *Asafoetida* inhibits early events of carcinogenesis A chemopreventive study. *Life Sci* 2001;68(16):1913-21.
 176. Mohamed H, El-Razek A, Ohtab S, Ahmedc AA, Hirataa T. Monoterpene coumarins from *Ferula ferulago*. *Phytochemistry* 2001;57(8):1201-3.
 177. Mallikarjuna GU, Dhanalakshmi S, Raisuddin S, Rao AR. Chemomodulatory influence of *Ferula asafoetida* on mammary epithelial differentiation, hepatic drug metabolizing enzymes, antioxidant profiles and N-Methyl-N-Nitrosourea-induced mammary carcinogenesis in rats. *Breast Cancer Res Treat* 2003;81:1-10.
 178. Zhou J, Xie G, Yan X. *Traditional chinese medicines, molecular structures, natural sources and application*. Hampshire-Burlington: AshgatePublishing Lmted, GWA Milne Editor; 2003.
 179. Rasulev BF, Saidkhodzhaev AI, Nazrullaev SS, Akhmedkhodzhaeva KS, Khushbaktova ZA, Leszczynski J. Molecular modelling and QSAR analysis of the estrogenic activity of terpenoids isolated from *Ferula* plants. *SAR QSAR Environ Res* 2007;18(7-8):663-73.
 180. Shahverdi AR, Fakhimi A, Zarrini G, Dehghan G, Iranshahi M. Galbanic acid from *Ferula szowitsiana* enhanced the antibacterial activity of penicillin G and cephalixin against *Staphylococcus aureus*. *Biol Pharm Bull* 2007;30(9):1805-7.
 181. Monti M, Pinotti M, Appendino G, Dallochio F, Bellini T, Antognoni F, Poli F, Bernardi F. Characterization of anti-coagulant properties of prenylated coumarin ferulenol. *Biochim Biophys Acta* 2007;1770(10):1437-40.
 182. Ojala T, Vuorela P, Kiviranta J, Vuorela H, Hiltunen R. A bioassay using *Artemia salina* for detecting phototoxicity of plant coumarins. *Planta Med* 1999;65(8):715-8.
 183. Yarnell E. Botanical medicines for the urinary tract. *World J Urol* 2002;20(5):285-93.
 184. Volleková A, Košťálová D, Kettmann V, Tóth J. Antifungal activity of *Mahonia aquifolium* extract and its major protoberberine alkaloids. *Phytother Res* 2003;17(7):834-7.
 185. El Sattar SA, El Batran, El Gengaihi SE, El Shabrawya OA. Some toxicological studies of *Momordica charantia* L. on albino rats in normal and alloxan diabetic rats. *J Ethnopharmacol* 2006;108:236-42.
 186. Leung L, Birtwhistle R, Kotecha J, Hannah S, Cuthbertson S. Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. *Br J Nutr* 2009;13(1):1-6.
 187. Hayes LW, Krasselt WG, Mueggler PA. Concentrations of morphine and codeine in serum and urine after ingestion of poppy seeds. *Clin Chem* 1987;33(6):806-8.
 188. Pettitt BC Jr, Dyazel SM, Hood LVS. Opiates in poppy seed: effect on urinalysis results after consumption of poppy seed cake-filling. *Clin Chem* 1987;33(7):1251-2.
 189. ElSohly HN, ElSohly MA, Stanford DF. Poppy seed ingestion and opiates urinalysis: a closer look. *J Anal Toxicol* 1990;14(5):308-10.
 190. Selavka CM. Poppy seed ingestion as a contributing factor to opiate-positive urinalysis results: the Pacific perspective. *J Forensic Sci* 1991;36(3):685-96.
 191. Unnithan S, Strang J. Poppy tea dependence. *Br J Psychiatry* 1993;163:813-4.
 192. Meadway C, George S, Braithwaite R. Opiate concentrations following the ingestion of poppy seed products – evidence for “the poppy seed defence”. *Forensic Sci Int* 1998;96(1):29-38.
 193. Soulimani R, Younos C, Jarmouni-Idrissi S, Bousta D, Khallouki F, Laila A. Behavioral and pharmacotoxicological study of *Papaver rhoeas* L. in mice. *J Ethnopharmacol* 2001;74(3):265-74.
 194. Braye K, Harwood T, Inder R, Beasley R, Robinson G. Poppy seed tea and opiate abuse in New Zealand. *Drug Alcohol Rev* 2007;26(2):215-9.
 195. Chen SJ, Wu BN, Yeh JL, Lo YC, Chen IS, Chen IJ. C-fiber-evoked autonomic cardiovascular effects after injection of *Piper betle* inflorescence extract. *J Ethnopharmacol* 1995;45(3):183-8.
 196. Chen CL, Chi CW, Chang KW, Liu TY. Safrrole-like DNA adducts in oral tissue from oral cancer patients with betel quid chewing history. *Carcinogenesis* 1999;20(12):2331-4.
 197. Chu NS. Effects of Betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001;8(3):229-36.
 198. Guha P. Betel leaf: the neglected green gold of India. *J Hum Ecol* 2006;19(2):87-93.
 199. Germany. Bundesinstitut für Arzneimitel und Medizinprodukte. Kommission E. *Ptychopetalum lignum* (Potenzholz) Monograph. *Bundesanzeiger* 1987. N. 193 on 15.10.1987.
 200. Hegnauer R. *Ptychopetalum olacoides* Benth. In: *Chemotaxonomie der pflanzen*. Basel-Boston-Berlin: Birksäure Verlag; 1990. Band IX: 156-9.
 201. Siqueira IR, Fochesatto C, da Silva AL, Nunes DS, Battastini AM, Netto CA, Elisabetsky E. *Ptychopetalum olacoides*, a traditional Amazonian “nerve tonic”, posses anticholinesterase activity. *Pharmacol Biochem Behav* 2003;75(3):645-50.
 202. da Silva AL, Bardini S, Nunes DS, Elisabetsky E. Anxiogenic properties of *Ptychopetalum olacoides* Benth. (Marapuama). *Phytother Res* 2002;16(3):223-6.
 203. Tang W, Hioki H, Harada K, Kubo M, Fukuyama Y. Clerodane diterpenoids with NGF-potentiating activity from *Ptychopetalum olacoides*. *J Nat Prod* 2008;71(10):1760-3.
 204. Gruenwald J, Brendeler T, Jaenicke C, Fleming T (Ed.). Pomegranate (*Punica granatum*). In: *Physicians' desk reference (PDR) for herbal medicines*. 2. ed. Montvale-New Jersey: Medical Economics Company; 2000. p. 605.
 205. Council of the European Community. Council Directive 88/388/EEC of 22 June 1988 on the approximation of the

- law of the Member States relating flavourings for use in food-stuffs and to source materials for their production. *Official Journal of the European Communities* L184, 15/07/1988.
206. Food and Drug Administration, Centre for Food Safety and Applied Nutrition. *Quassia amara*. *FDA Poison Plant Database*;2006.
 207. Woo GH, Shibutani M, Inoue K, Fujimoto H, Takahashi M, Lee KY, Hirose M. Promoting potential of a Jamaica Quassia extract in a rat medium-term hepatocarcinogenesis bioassay. *Food Chem Toxicol* 2007;45(7):1160-4.
 208. Pandey MM, Rastogi S, Rawat AK. *Saussurea costus*: botanical, chemical and pharmacological review of an ayurvedic medicinal plant. *J Ethnopharmacol* 2007;110(3):379-90.
 209. Yu HH, Lee JS, Lee KH, Kim KY, You YO. *Saussurea lappa* inhibits the growth, acid production, adhesion, and water-insoluble glucan synthesis of *Streptococcus mutans*. *J Ethnopharmacol* 2007;111(2):413-7.
 210. Schumacher J, Cupp MJ. Scullcap. In: Cupp MJ (Ed). *Toxicology and clinical pharmacology of herbal products*. Totowa: Humana Press Inc; 2000. p. 215-21.
 211. Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. *Altern Ther Health Med* 2003;9(2):74-8.
 212. Germany. Bundesinstitut für Arzneimitel und Medizinprodukte. Kommission E. *Salsaparillae radix* (Sarsaparillewurzel) Monograph. *Bundesanzeiger* 1990; n. 164 on 01.09.1990.
 213. Gruenwald J, Brendeler T, Jaenicke C, Fleming T (Ed.). *Salsaparilla (Smilax spp)*. In: *Physicians' desk reference (PDR) for herbal medicines*. 2. ed. Montvale-New Jersey: Medical Economics Company; 2000. p. 661.
 214. Willuhn G. *Arnica montana* L.: portrait of a medicinal plant. *Pharm Ztg* 1991;136(12):9-12, 14, 18, 21, 24-6.
 215. Woerdenbag HJ, Merfort I, Passreiter CM, Schmidt TJ, Willuhn G, van Uden W, Pras N, Kampinga HH, Konings AW. Cytotoxicity of flavonoids and sesquiterpene lactones from *Arnica* species against the GLC4 and the COLO 320 cell lines. *Planta Med* 1994;60(5):434-7.
 216. American College of Toxicology. Sage (Ed.). Final report on the safety assessment of *Arnica montana* extract and *Arnica montana*. *Int J Toxicol* 2001;20(2):1-11.
 217. Barnes J, Anderson LA, Phillipson JD. *Herbal medicines: a guide for healthcare professionals*. 2. ed. London and Chicago: Pharmaceutical Press; 2002.
 218. Haller CA, Anderson IB, Kim SY, Blanc PD. An evaluation of selected herbal reference texts and comparison to published reports of adverse herbal events. *Adverse Drug React Toxicol Rev* 2002;21(3):143-50.
 219. Potti GR, Kurup PA. Antibacterial principle of the root bark of *Calophyllum inophyllum*: isolation and antibacterial activity. *Indian J Exp Biol* 1970;8(1):39-40.
 220. Itoigawa M, Ito C, Tan HT, Kuchide M, Tokuda H, Nishino H, Furukawa H. Cancer chemopreventive agents, 4-phenylcoumarins from *Calophyllum inophyllum*. *Cancer Lett* 2001;169(1):15-9.
 221. Le Coz CJ. Allergic contact dermatitis from tamanu oil (*Calophyllum inophyllum*, *Calophyllum tacamahaca*). *Contact Dermatitis* 2004;51(4):216-7.
 222. Yimdo MC, Azebaze AG, Nkengfack AE, Meyer AM, Bodo B, Fomum ZT. Antimicrobial and cytotoxic agents from *Calophyllum inophyllum*. *Phytochemistry* 2004;65(20):2789-95.
 223. Said T, Dutot M, Martin C, Beaudeau JL, Boucher C, Enee E, Baudouin C, Warnet JM, Rat P. Cytoprotective effect against UV-induced DNA damage and oxidative stress: role of new biological UV filter. *Eur J Pharm Sci* 2007;30(3-4):203-10.
 224. Blazek Z. Content and localization of furocoumarins in some types of the genus *Heracleum*. *Cesk Farm* 1969;18(6):250-7.
 225. Brázdovicová B, Kostálová D, Strocinská E, Tomko J. Isolation and identification of oroselol and other furocoumarin derivatives from *Heracleum sphondylium* L. roots. *Cesk Farm* 1982;31(9):346-7.
 226. Oakley AM, Ive FA, Harrison MA. String trimmer's dermatitis. *J Soc Occup Med* 1986;36(4):143-4.
 227. Tirillini B, Ricci A. Furocoumarin production by callus tissues of *Heracleum sphondylium* L. *Phytother Res* 1998;12: S25-6.
 228. Weimarck G, Nilsson E. Phototoxicity in *Heracleum sphondylium*. *Planta Med* 1980;38(2):97-111.
 229. Cies'la L, Bogucka-Kocka A, Hajnos M, Petruczynik A, Waksmundzka-Hajnos M. Two-dimensional thin-layer chromatography with adsorbent gradient as a method of chromatographic fingerprinting of furanocoumarins for distinguishing selected varieties and forms of *Heracleum* spp. *J Chromatogr A* 2008;1207(1-2):160-8.
 230. Tattje DH, Bos R. Composition of essential oils of *Ledum palustre*. *Planta Med* 1981;41(3):303-7.
 231. Germany. Bundesinstitut für Arzneimitel und Medizinprodukte. Kommission E. *Raphani sativi radix* Monograph. *Bundesanzeiger* 1986. 177a.
 232. Monografie sulle droghe vegetali. In: REFIT (Repertorio Fitoterapico) 2. ed. Milano: OEMF; 1996. p. 428-9.
 233. Frohne D, Pfander HJ. *Giftpflanzen: Ein Handbuch für Apotheker, Ärzte, Toxikologen und Biologen (Gebundene Ausgabe)*. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH; 1997.
 234. Daschinamzhilov ZhB, Yatzenko TV, LyarsKaya LV, Aseeva TA, Nikolaev SM, Badluev OA, Sambueva ZG. Hepatoprotective effect of herbal medicine "dig-da-shitan" on liver damaged by ethanol. *Rastitel'nye Resursy* 2007;43(1):130-5.
 235. Guan S, Lu J, Liu J. Protective effects of ursolic acid extract from *Ledum palustre* against genetic damage on mice. *Aibian Jibian Tubian* 2009;21(1):68-9.
 236. Hammer KA, Carson CF, Riley TV, Nielsen JB. A review of the toxicity of *Melaleuca alternifolia* (tea tree) oil. *Food Chem Toxicol* 2006;44:616-25.
 237. Bronstein AC, Spyker DA, Cantilena LR jr, Green JL, Rumack BH, Heard SE. Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. *Clin Toxicol* 2007; 46: 927-1057.
 238. Fico G, Tome F. Alkaloids in *Nigella damascena* seeds. An hypothesis on their biological role. *Eur J Pharm Sci* 1998;6(Supp.1):S79.
 239. Fico G, Panizzi L, Flamini G, Braca A, Morelli I, Tomè F, Cioni PL. Biological screening of *Nigella damascena* for antimicrobial and molluscicidal activities. *Phytother Res* 2004;18:468-70.
 240. Landa P, Marsik P, Havlik J, Kloucek P, Vanek T, Kokoska L. Evaluation of antimicrobial and anti-inflammatory activities of seed extracts from six *Nigella* species. *J Med Food* 2009;12:408-15.
 241. Appendino G, Bianchi F, Bader A, Campagnuolo C, Fattorusso E, Tagliatalata-Scafati O, Blanco-Molina M, Macho A, Fiebich BL, Bremner P, Heinrich M, Ballero M, Muñoz E. Coumarins from *Opopanax chironium*. New dihydrofuranocoumarins and differential induction of apoptosis by imperatorin and heraclenin. *J Nat Prod* 2004;67:532-6.
 242. Goswami S, Gupta VK, Sharma A, Gupta BD. Supramolecular

- structure of S-(+)-marmesin - a linear dihydrofuranocoumarin. *Bull Mater Sci* 2005;28:725-9.
243. De Vincenzi M, Mancini E. Monographs on botanical flavouring substances used in foods. Part VI. *Fitoterapia* 1997;68:49-61.
244. Gruenwald J, Brendeler T, Jaenicke C, Fleming T (Ed.). Patchouli (*Pogostemon cablin*). In: *Physicians' desk reference for herbal medicines*. 2. ed. Montvale-New Jersey: Medical Economics Company; 2000. p. 575.
245. Zhu BC, Henderson G, Yu Y, Laine RA. Toxicity and repellency of patchouli oil and patchouli alcohol against Formosan submediterranean termites *Coptotermes formosanus* Shiraki (Isoptera: Rhinotermitidae). *J Agric Food Chem* 2003;51:4585-8.
246. Pavela R. Insecticidal properties of several essential oils on the house fly (*Musca domestica* L.). *Phytopar Res* 2008;22:274-8.
247. Casida JE. Pyrethrum flowers and pyrethroid insecticides. *Environ Health Perspect* 1980;34:189-202.
248. Pandita PN, Sharma SD. Pyrethrin content and dry-flower yield of some strains of dalmatian pyrethrum (*Tanacetum cinerariifolium*). *Indian J Agric Sci* 1990;60:693.
249. Wandahwa P, VanRanst E, VanDamme P. Pyrethrum (*Chrysanthemum cinerariaefolium* Vis) cultivation in West Kenya: Origin, ecological conditions and management. *Ind Crops Prod* 1996;5:307-22.
250. Keskitalo M, Angers P, Earle E, Pehu E. Chemical and genetic characterization of calli derived from somatic hybridization between tansy (*Tanacetum vulgare* L.) and pyrethrum (*Tanacetum cinerariifolium* (Trevir.) Schultz-Bip.). *Theor Appl Genet* 1999;98:1335-43.
251. Savona G, Piozzi F, Bruno M, Dominguez G, Rodriguez B, Servettaz O. Teucretol, a neo-clerodane diterpenoid from *Teucrium creticum*. *Phytochemistry* 1987;26:3285-8.
252. Lahlou S, Tahraoui A, Israili Z, Lyoussi B. Diuretic activity of the aqueous extracts of *Carum carvi* and *Tanacetum vulgare* in normal rats. *J Ethnopharmacol* 2007;110:458-63.
253. Lahlou S, Tahraoui A, Israili Z, Lyoussi B. Acute and chronic toxicity of a lyophilised aqueous extract of *Tanacetum vulgare* leaves in rodents. *J Ethnopharmacol* 2008;117:221-7.