Original article

Traditional use and safety of herbal medicines☆

Davyson de L. Moreira*, Sabrina Schaaf Teixeira, Maria Helena D. Monteiro,
Ana Cecilia A.X. De-Oliveira, Francisco J.R. Paumgartten

Laboratório de Toxicologia Ambiental, Escola Nacional de Saúde Pública, FIOCRUZ, Rio de Janeiro, RJ, Brazil

ABSTRACT

In the European Union, traditional herbal medicines that are regarded as "acceptably safe, albeit not having a recognized level of efficacy" fit into a special category of drugs ("traditional herbal medicine products") for which requirements of non-clinical and clinical studies are less rigorous. A regulation proposal published by the Brazilian National Health Surveillance (Anvisa) defines a similar drug category ("traditional phytotherapeutic products") for registration purposes. Regarding herbal medicines, both agencies seem to be lenient regarding proof of efficacy, and consider long-standing folk use as evidence of safety and a waiver of a thorough toxicological evaluation. Nonetheless, several herbal products and constituents with a long history of folk usage are suspected carcinogenic and/or hepatotoxic. Herbal products have also been shown to inhibit and/or induce drug-metabolizing enzymes. Since herbal medicines are often used in conjunction with conventional drugs, kinetic and clinical interactions are a cause for concern. A demonstration of the safety of herbal medicines for registration purposes should include at least *in vitro* and *in vivo* genotoxicity assays, long-term rodent carcinogenicity tests (for drugs intended to be continuously used for > 3 months or intermittently for > 6 months), reproductive and developmental toxicity studies (for drugs used by women of childbearing age), and investigation of the effects on drug-metabolizing enzymes.

Introduction

Traditional or folk medicine comprises practices, approaches, knowledge and beliefs not based on scientific evidence that are applied to treat, diagnose and prevent illness within a society. It is defined by a culture's knowledge and values and thus is context-specific, as are social constructions and negotiations of risk. When modern societies adopt such long-standing health practices outside of their traditional context, these practices become "complementary, non-conventional or alternative medicine" (Crellin, 2001).

The extent to which the traditional use of an herb ensures that a corresponding herbal drug is safe, however, is a debachart matter. A new draft regulation published by

the Brazilian National Health Surveillance Agency (Anvisa) brought this controversial topic to the center stage. The proposed regulation, which has recently undergone a public consultation for reviews and comments, defines two categories of herbal drugs for registration: "phytotherapeutic medicines" and "traditional phytotherapeutic products" (TPTP) (Anvisa, 2013). A product fits into the latter category if a long-standing (traditional) use is identified that has not been proven unsafe and is recognized in the literature or demonstrated by ethno-pharmacological and/or ethno-botanical studies. Once the traditional use is recognized, safety and efficacy data from pre-clinical and/or clinical studies are no longer essential requirements to obtain approval for commercialization.

The proposed new rules for herbal medicine registration in Brazil are, to some extent, similar to the regulation released by the European Parliament in 2004. According to EC Directive 2004/24, herbal medicines with traditional use that are acceptably safe, albeit not having a recognized level of efficacy, can be classified as "traditional herbal medicines products" (THMP), as detailed by Calapai (2008), Quintus and Schweim (2012) and Silano et al. (2004). In order for a medicinal product,or its corresponding products (*i.e.*, products having the same active ingredients, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration), to be classified as THMP, it must have been in medicinal use for a period of at least 30 years, of which more than 15 years must relate to the European Union. Herbal drugs in the THMP category undergo a simplified registration procedure. Aspiring herbal products are required to demonstrate the traditional use of the herb, but this requirement is lifted if the product complies with the European positive list established by the Committee on Herbal Medicinal Products (HPMC) (Knöss and Chinou, 2012). Herbal monographs prepared by HPMC are not binding, and member state agencies may not agree with every single aspect of the monograph. For instance, applicants that refer to a HPMC monograph may be required to provide additional points on safety (*e.g.*, on genotoxicity).

In summary, both the European Medicines Agency (EMA) and the Brazilian National Health Surveillance Agency (ANVISA) recognize a special class of phytopharmaceuticals and take tradition into account for pre-marketing demonstrations of safety and efficacy, thereby opening a wider door for the registration of manufactured herbal products as medicines.

Medicinal herb products: drugs or food supplements?

In contrast to European and Brazilian agencies, the United States Food and Drug Administration (US FDA) makes no distinction between herbal and conventional medicines regarding the requirements for pre-marketing demonstration of safety and efficacy (Wu et al., 2008). Owing to this fact, herbal products with presumed beneficial effects generally do not meet the criteria for approval as medicines, and are commercialized in the USA as food supplements.

The notion that herbal drugs require less rigorous and comprehensive safety and efficacy evaluation is questionable.

There is no scientific rationale to assume that plants, their parts and/or derived products, including those of long-standing popular use, are intrinsically safe and/or beneficial; or that, compared to conventional medicines, they would require fewer and simpler pre-clinical and/or clinical studies. For the sake of coherence in drug regulations, all medicines, regardless of their origin and development, should meet equally rigorous safety and efficacy standards for marketing authorization.

So far, the strongest argument against the application of the same rule for herbal and conventional medicines has been that insufficiently tested, or even untested, herbal medicinal products have not been removed from the market in the USA. As a matter of fact, these products continue to be widely sold and consumed as herbal and dietary supplements (HDS), a category of consumer products more loosely regulated by the US FDA. A statement of comprehensive and rigorous pre-marketing safety and drug effectiveness is not an essential requirement for HDS. The US Dietary Supplement and Health Education Act of 1994, and the Final Rule for Current Good Manufacturing Practices for Dietary Supplements of 2007, demand that HDS manufacturers define dietary ingredients as vitamins, minerals, herbs, and amino acids, provide standards in identification and purity, and ensure that claims made regarding their products are accurate and not misleading. Despite legal restrictions on placing alleged therapeutic properties on the product label, HDS are used in conjunction with conventional medicines or on their own to treat a variety of morbid conditions. Based on this, supporters of keeping a separate category of phytotherapeutics for regulation purposes argue that this special group of medicines, compared to dietary supplements, undergo a more thorough evaluation of safety and at least some assessment of efficacy, and are also under more stringent rules regarding quality assurance and manufacturer adherence to GMP.

Drug safety and efficacy

In reference to medications, safety is the likelihood of not causing harm under the proposed conditions of use, while efficacy is the capacity to induce a clinical benefit. Both safety and efficacy depend on the drug's therapeutic indication; in principle, a substance has no clinical usefulness if it is "safe" but lacks efficacy or if it is active on a relevant therapeutic target but its use is unsafe. Although these are recognized as equally essential attributes of any medicine, safety has taken precedence over proof of efficacy in drug regulation history. In the US, for instance, the Federal Food Drug and Cosmetic Act of 1938 required that safety of new drugs had to be proven by pre-marketing testing, whereas similar requirements to demonstrate drug efficacy were introduced only 25 years later by the Kefauver-Harris Amendments of 1962.

The idea that safety should come first in therapeutic interventions is conveyed by the famous Latin expression "*primum non nocere*" ("first, not do harm"), the origin of which is uncertain (Smith, 2005). Similarly, the classical version of the Hippocratic Oath that physicians take upon entering medical practice contains a promise that expresses a similar idea (doctors are required to "keep [patients] from harm").

Although the "*non-maleficence*" maxim has become a central axiom of therapeutics, ethically, it cannot be dissociated from the beneficence principle. If a clinical benefit superior to that offered by a placebo is attainable by using currently available therapeutic interventions, then not to prescribe the most effective therapeutic option available has a prejudicial impact on the patient's health.

According to the prevailing concept of evidence-based medicine (EBM; "...*use of current best evidence in making decisions about the care of individual patients*") (Sackett et al., 1996), controlled and randomized clinical trials, and an unbiased systematic review with and without a meta-analysis, rank first in the hierarchy of sources of evidence for the safety and efficacy of therapeutic interventions. Clinical efficacy cannot be presumed on the basis of pharmacological actions described in animal and/or in vitro experiments, nor on physicians'/experts' opinions only. It has to be demonstrated by adequately designed and conducted phase III studies, or exceptionally by phase II trials.

Randomized clinical trials controlled with placebos reveal a number of potential adverse effects associated with drug treatment. If patients allocated to the control group receive a reference medicine instead of a placebo, the incidences of putative adverse effects are compared between the reference and the test drug groups. At any rate, controlled and randomized clinical trials generally provide the best evidence of safety obtainable before marketing. Some aspects of drug safety, however, are not fully addressed by clinical trial protocols; thus, a comprehensive evaluation of safety also requires non-clinical assays, such as long-term carcinogenicity tests (cancer inducing potential), reproductive and developmental toxicity studies (teratogenic potential) among others. It should be noted that some rare but severe adverse events arising from interactions with drugs and nutrients, or that occur only in subgroups of patients not represented in the randomized study groups, are likely to be detected only under the actual event of use by a much larger population. Therefore, post-marketing pharmacovigilance (PV) is essential for a thorough evaluation of drug safety. The same holds true for the assessment of drug effectiveness or efficacy under the real (post-marketing) conditions of use (Box 1).

Suspicions of ineffectiveness, however, do not seem to have the same weight as safety concerns when reconsideration of a drug marketing authorization is on the chart. While the uncovering of unexpected severe adverse reactions by PV often results in the withdrawal of a drug from the market, the suspicion of reduced effectiveness or even ineffectiveness has seldom prompted regulators to take such drastic action.

Examples of medicinal products that, despite regulation by Anvisa, are exempt from scientific-based demonstration of efficacy are the homeopathic drugs (so-called "dynamized" medications). A systematic review of placebo-controlled trials of homeopathy brought about findings that were compatible with the notion that the clinical effects of homoeopathic medications are indeed placebo effects (Lind et al., 2001; Shang et al., 2005). Owing to the extreme dilution of such "dynamized" medications, they are presumed safe, thus, no pre-clinical studies are required either. The Anvisa requirements to register a homeopathy medicine are manufacturing in compliance with the methods of preparation and control described by the current edition of the Brazilian Homeopathic Pharmacopeia (2011) or other homeopathic pharmacopeias, and "proven therapeutic action" is reported in officially recognized homeopathy compendia.

The leniency of regulators and physicians regarding the demonstration of the efficacy of herbal drugs seems to be rooted in the general belief that herbal products are markedly safe. Because of this, even when phytotherapeutic drugs have a reduced efficacy, or are not clinically superior to a placebo, many regulators and physicians believe that they might exhibit favorable risk to benefit ratios. If an herbal medicine's clinical superiority over a placebo remains unproven, however, even low risks of slight to mild adverse health effects seem unaccepchart (*i.e.*, lack of a clinical benefit implies that risk to benefit ratios are unfavorable, even if risks are low).

Tradition and safety of herbal medicines

Many supporters of herbal medicines argue that products with a long history of popular use are generally safe when used properly at common therapeutic doses (Fong, 2002). A crucial question underlying this statement is the extent to which the absence of evidence of toxicity could be taken as evidence of the absence of toxicity or safety of herbal medicines. Whether the absence of records of adverse effects is an indication of lack of toxicity depends on the type of toxic effect and the likelihood of observing such an adverse outcome under the conditions prevailing in the traditional usage. Acute symptoms and short-term toxic effects, such as gastro-intestinal disturbances and dermatological effects, are likely to be recognized and associated to herbal medicine. Therefore, the absence of such observations provides some evidence of safety in these particular endpoints. Long-term adverse outcomes, such as cancer, liver and kidney damage, reproductive dysfunctions, birth defects and several morbidities that are more difficult to detect, however, are unlikely to be associated with the popular use of a medicine, unless an adequately designed epidemiology study (preferably, a prospective cohort study) is undertaken. Thus, the absence of evidence of these adverse effects within the context of traditional usage of herbal medicines is not evidence of the absence of potential to cause them. As far as drugs are concerned, safety is assumed only when the null hypothesis (absence of toxicity) has not been disproved after being challenged by properly designed and comprehensive set of pre-clinical and clinical studies, that had enough statistical power to reject it if it were false.

Carcinogenic effects of traditional herbal medicines

During R&D of conventional drugs, carcinogenic potential is assessed through a battery of in vitro and in vivo short-term genotoxicity tests, and long-term rodent carcinogenicity assays. Carcinogenicity tests in rats and mice are the longest and most costly non-clinical safety studies commonly required for a new drug marketing approval. A waiver of long-term

carcinogenicity studies for marketing approval can be obtained if results of short-term genotoxicity tests are negative and the drug is intended to be used continuously for less than three months, or intermittently for less than six months. Long-term carcinogenicity studies have seldom been performed with herbal products, and the data of their genotoxic potential are scant as well. Owing to their limited duration, clinical trials do not shed light on the carcinogenic potential of drugs. In principle, evidence on the carcinogenicity of traditional herbal medicines could be obtained from observational epidemiological studies. Nonetheless, epidemiological studies have rarely been undertaken to address this question.

As shown in Chart 1, a number of traditionally used medicinal plants and their constituents are suspected of being human and/or rodent carcinogens. Because a vast majority of herbal medicines and their constituents have not undergone any screening for carcinogenicity, it is fair to assume that plants and substances listed in Chart 1 are just the tip of the iceberg. At any rate, evidence that plants with hundreds of years of folk usage may induce cancer illustrates that proven traditional use on its own does not ensure that an herbal medicine is safe.

Liver toxicity associated with herbal medicines

Severity of drug-induced liver toxicity (DILI) ranges from mild dysfunction leading to raised serum levels of alanine aminotransferase (ALT) unaccompanied by increases in bilirubin levels and clinical symptoms reversible upon treatment discontinuation, to jaundice and overt hepatic failure that could culminate in liver transplantation or death. DILI can be broadly divided into two types: liver toxicity that depends on the dose and can be predicted by pre-clinical and clinical studies; and an idiosyncratic DILI that is a rare, but severe form of liver damage that occurs only in susceptible individuals (presumably involving immuno-allergic mechanisms) and cannot be predicted by pre-marketing safety studies.

Similar to conventional drugs, herbal medicines are capable of causing both predicchart and idiosyncratic DILI. Some herbal drugs that have been associated with severe hepatotoxic events through traditional use are listed in Chart 2. It should be noted that the degree of evidence for establishing a causal link between intake of a medicinal herb and liver impairment is variable, as it is for conventional drugs. In addition to the difficulties and limitations of pharmacovigilance, the vigilance related to herbal products faces additional problems, such as: self-medication, products that contain a diverse number of different plants, use in combination with classical pharmaceutical agents, the widespread belief that natural products are intrinsically safe so that patients often forget to disclose this information to their physicians, and poor quality issues, including misidentification of the plants, selection of the wrong part of the plant, adulteration, mislabeling, inadequate storage conditions, and contamination by fungi, pesticides, metals and other potential toxins (Larrey and Faure, 2011; Shaw et al., 2012).

The fact that several hepatotoxic plants and their constituents have a long-standing use in folk medicine is also consistent with the notion that traditional use on its own does not guarantee the safety of a phytopharmaceutical.

Kinetic interactions of herbal medicines with conventional medicines

Herbal medicines are often used concomitantly with conventional drugs, making potential pharmacokinetic interactions a cause for concern. Herbal drug co-administration with medicines of narrow therapeutic indices (*e.g.*, digoxin, warfarin) raises even deeper safety concerns. Common herbal medicines known to interact with conventional drugs include St. John's wort (*Hypericum perforatum* L.), ginkgo (*Ginkgo biloba* L.), ginger (*Zingiber officinale* Rosc.), ginseng (*Panax ginseng* C.A. Meyer) and garlic (*Allium sativum* L.) (Chart 3). St. John's wort, an herbal antidepressant, is possibly the most notorious example. It is a potent inhibitor of CYP3A4, and when co-administered with drugs metabolized by this enzyme, it decreases their clearance and increases their plasma concentrations (AUC). Because St. John's wort also induces the expression of CYP3A4 and the transmembrane transporter protein PgP (P-glycoprotein) in the liver and intestines, previous and repeated administrations have opposite effects; enhancement of clearance and decrease in AUC. The kinetic and clinical effects of a number of drugs that are substrates for CYP3A4 are altered by St. John's wort, and these drugs include cyclosporine, midazolam, oxycodone, methadone, imatinib, finasteride, bupropion, tracolimus, digoxin, atorvastin, and verapamil, among others.

As shown in Chart 3, herbal products and their constituents can alter the activity and/or expression of drug-metabolizing enzymes and transmembrane transporters, and by doing so, they can modify drug elimination, metabolic activation (*i.e.*, conversion of a precursor into its active metabolite), pre-systemic clearance, bioavailability, and kinetic parameters such as AUC, C_{max} and T_{max}. All these effects may eventually lead to changes in toxicity and/or clinical efficacy of conventional drugs. Therefore, knowledge of the potential of herbal medicines to inhibit (when co-administered) and/or induce the expression (after previous and/or repeated administration) of key drug-metabolizing enzymes (*e.g.*, CYP3A4, 2D6, 2C9, 2C19, 2A6) is of the utmost importance for safety when used in conjunction with conventional drugs.

Concluding remarks

Within the prevailing concept of evidence-based medicine, traditional use and expert opinion are at the lowest levels in the hierarchy of evidence for the safety and efficacy of drugs. The highest evidence for safety and efficacy is that arising from randomized clinical trials and an unbiased systematic review with or without a meta-analysis.

The lack of controlled and randomized clinical trials of herbal medicines with a long history of use in Brazil and/or other countries is the rule rather than the exception. In the last decade, several clinical studies (including a few controlled and randomized trials of traditional Chinese herbal medicines) were undertaken, and others are ongoing (Fu et al., 2013; Hao et al., 2013; Li et al., 2012; Liu et al., 2013). In addition to the shortcomings in clinical trial design, execution and data

Chart 1

Examples of traditional herbal medicines and/or their constituents with suspected carcinogenic effects.

Plant species	Constituent	Traditional use	Evidence		Reference
			Humans or animals	Findings	
Aristolochia sp.	Aristolochic acid (AA)	Chinese traditional medicine; arthritis, rheumatism, hepatitis, other indications.	Human	Nephrotoxicity, upper tract urothelial carcinoma; meta-analysis: OR = 5.97 (95% CI, 2.78-12.84) for AA-related cancers; TP53 mutations.	Chen et al., 2013; Hollstein et al., 2013; Wu and Wang, 2013.
Thuja sp., *Artemisia* sp., *Salvia officinalis* L.	α-β-thujone (essential oils)	Traditional medicine, flavoring food additives, absinthe (liqueur).	Rodents	Inhibitor of GABA-A receptor, seizures. Preputial gland and adrenal gland tumors in male rats (no treatment-related tumors in female rats and mice).	Halicioglu et al., 2011; NTP, 2011a, Pelkonen et al., 2013.
Mentha × *piperita* L., *M. longifolia* (L.) Huds., *Nepeta cataria* L.	Peppermint and pennyroyal oils; pulegone	Traditional medicine, flavoring food additives.	Rodents	Hyaline glomerulopathy (male, female, mice, rats); Urinary bladder neoplasms (female rats), hepatocellular neoplasms (mice), osteoma/osteosarcoma (female mice), no tumors in male rats.	NTP, 2011b
Sassafras albidum (Nutt.) Nees, *Areca catechu* L., *Piper betle* L.	Sassafras oil; safrole	Traditional medicine, Native Americans and the British, betel quid chewing in Asia.	Human Rodents	Oral squamous carcinomas (humans), hepatocellular carcinomas; DNA-adduct formation and potent rodent carcinogen.	Amarasinghe et al., 2010; Chen et al., 1999; Hsieh et al., 2001; Kapadia et al., 1978; Liu et al., 2000.
Pteridium sp. (braken), ferns and lycopods	Sesquiterpenois and analogues; ptaquiloside	Food (East Asia and American Indians), food and traditional medicine (New Zealand, the Maoris).	Human Rodents Cattle *in vitro*	Stomach and upper alimentary tract cancers, urinary bladder cancer, neoplasia of several tissues (rodents), thyamine deficiency, acute haemorrhage associated with myeloid aplasia, blindness and retinal degeneration, genotoxicity, teratogenicity.	Alonso-Amelot and Avendaño, 2002; Potter and Baird, 2000; Shahin et al., 1999; Tomšík, 2013.
Symphytum officinale L. (comfrey)	Pyrrolizidine alkaloids	Traditional medicine, Africa, China, Ayurveda, and others.	Human Rodents	Hepatotoxicity, hepatic venous occlusive disease, liver cancer, genotoxicity, DNA adducts.	Chen et al., 2010; Mei et al., 2011; Roeder, 2000; Roeder and Wiedenfeld, 2011; 2013; Steenkamp et al., 2000.
Euphorbia tirucalli L.	Phorbol esters	Traditional medicine, Africa.	Human Rodents	Burkitt's lymphoma after co-exposure E. tirucalli + Epstein Barr virus, known tumor promoting agent in rodents.	Aya et al., 1991; Imai et al., 1994.
Gingko biloba L.	Leaf extract	Chinese traditional medicine, widespread use worldwide.	Human Rodents	Dose-related increase in liver tumors including hepatocellular carcinoma (B6C3F1 mice). Evidence of carcinogenic potential in the thyroid gland (rats, mice); mutagenic (S. typhimurium TA98, TA100, E. coli WPS uvrA/pkM 101, with and without S9).	Hoenerhoff et al., 2013; NTP, 2013.
Rubia tinctorum L. (madder root)	Hydroxyanthra-quinones, lucidin	Traditional medicine and dye. Ayurveda, and in Europe for kidney stones.	Rodents *in vitro*	⬚ liver and kidney malign tumors and DNA adducts, in male and female rats. Mutagenic in S. typhimurium TA 100 and TA 98 assay, V79 HGPRT assay, malignant transformation assay with C3H/M2 cells.	Blömeke et al., 1992, Westendorf et al., 1988; 1998, Yasui and Takeda, 1983.
Senna alata L. (Roxb)	Sennosides	Traditional medicine (Africa, Nigeria, Ghana, Guinea).	Rodents *in vitro*	Mutagenic to S. thyphimurium TA98 and TA 1537 with S-9.	Hong and Lyu, 2011.
Mixture of plants called Imbiza ephuzwato, Stameta™ BODicare®	(?)	Tradional medicine multi-purpose remedies and tonics (South Africa, The Zulu).	*in vitro*	Plant mixtures were mutagenic in S. thyphimurium TA 98 assay with S9 activation.	Ndhlala et al., 2010; 2011.

Areca catechu (betel quid) also contains carcinogenic arecatannins.

Chart 2
Traditional herbal medicines associated with human liver injury.

Plant species	Constituent	Clinical/Experimental observations	References
Larrea tridentata (DC.) Coville (chaparral)	nordihydro-guiarectic acid (?)	Leaves from a desert shrub which are traditionally used in Southwestern USA and Mexico for a variety of therapeuthic indications. Reports of hepatocellular injury and cholestatic hepatitis (jaundice, marked increase of ALT) after weeks of use symptoms generally resolved on ingestion cessation.	Sheikh et al., 1997.
Teucrium chamaedrys L., *T. polium* L., *T. viscidum* Blume, *T. capitatum* L., (germander)	furano-diterpenoids	Europe and Middle East, blossoms traditionally used to treat various conditions. Reports of hyperbilirubinemia, anorexia, nausea, marked elevations of ALT, after 2 months of use. Some cases, fulminant hepatitis requiring liver transplantation.	Larrey et al., 1992; Lekehal et al., 1996; Mimidis et al., 2009.
Piper methysticum G. Forst. (kava kava)	piper-methysticin (?)	South Pacific traditional use as a recreational and cerimonial drink. Reports of hepatocellular and cholestasis pattern of liver injury, highly variable cummulative doses and latency periods. some underwent liver transplantation. Idiosyncratic DILI.	Moulds and Malani, 2003; Olsen et al., 2011; Teschke, 2010.
Symphytum officinale L. (comfrey) *Senecio* sp., *Heliotropium* sp., *Crotalaria* sp.	pyrrolizidine alkaloids	Europe, Asia, South Africa, USA, Jamaica, worldwide traditional medicine. venous occlusive disease, abdominal pain, ascites, slight jaundice and hepatomegaly (similar to Budd-Chiari Syndrome).	Steenkamp et al., 2000; Zuckerman et al., 2002.
Atractylis gummifera L.	atractylosides, gummiferin	Mediterranean region use as antipyretic, emetic, diuretic, chewing gum. Acute hepatitis, nephrotoxicity, hepatorenal failure.	Daniele et al., 2005; Larrey, 1997.
Callilepsis laureola DC.(Impila)	atractylosides	South Africa use in Zulu traditional medicine. Acute liver and kidney injury, abdominal pain, diarrhea, vomiting, high mortality.	Popat et al., 2001; 2002.
Chelidonium majus L.	celandine	Europe and temperate regions of Asia. Used to treat dyspepsia, biliary colic, cholelithiasis. Several case reports describing acute liver injury, moderate elevations of ALT, marked cholestasis, recovery after herbal medicine discontinuation.	Benninger et al., 1999; Seeff, 2007.
Mixture of plants (Herbalife® products)	(?)	Widespread use as food supplement. Case series of fulminant liver failure, hepatocellular damage, veno-occlusive disease and cholestasis.+	Bunchorntavakul and Reddy 2013; Manso et al., 2011; Schoepfer et al., 2007; Teschke et al., 2012.

+The comment of Herbalife® manufacturers on the report of DILI cases possibly associated to their product is found in a letter by Appelhans et al. (2013) and authors' reply in Reddy and Bunchorntavakul (2013).

Chart 3
Pharmacokinetic interactions of herbal medicines and edible plants with conventional drugs.

Plant species	Constituent	Kinetic interactions	Clinical/Experimental findings	References
Gingko biloba L.	flavonoids; terpene lactones (ginkgolides)	CYP3A4 (ind/inh), 2C9, 2C19 (ind, HD); P-glycoprotein (ABCD1) (ind/inh).	↑ CYP2C19-hydroxilation of omeprazole, ↓ plasma levels of omeprazole, ↓ plasma levels and AUC of midazolam.	Chen et al., 2011; Hermann and von Richter, 2012; Li et al., 2013.
Allium sativum L. (garlic)	alliin, allicin; flavonoids; isoflavonoids; terpenes	CYP2E1 (inh), pgP (ABCD1) (ind).	↓ AUC saquinavir.	Gurley et al., 2002; 2005; Hajda et al., 2010.
Silybum marianum (L.) Gaertn. (milk thistle)	flavolignans, silymarin mixture	CYP3A4 and 2C9 (inh), UGT1A1, 1A6, 1A9, 2B7, 2B15.	↓ clearance: metronidazole and hydroxymetranidazole, ↑ AUC of losartan.	Chen et al., 2011; Sridar et al., 2004.
Hypericum perforatum L. (St. John's wort)	hypericin, hyperforin; favonoids; biflavonois	CYP3A4 and 2B6 (ind / inh); CYPC19, UGT, GST, PgP (ABCD1) (ind).	↓ (ind) / ↑ (inh) AUC: cyclosporine, tracolimus, imatinib, warfarin, digoxin, verapamil, nifedipine, finasteride, glicazide, theophylline, bupropion, amitriptyline, midazolam, atorvastatin, nevirapine, indinavir, methadone, omeprazole and others.	Chen et al., 2011; Li et al., 2013.
Citrus × paradisi Macfad. (grape fruit juice)	Narigin (?)	CYP3A4.	↑ AUC: dihydropyridines, terfenadine, saquinavir, cyclosporin, midazolam, triazolam, verapamil, lovastatin, cisapride and astemizole.	Bailey et al., 1998; Fuhr, 1998.

ind: enzyme induction (previous and or repeated administration); inh: enzyme inhibition (concomitant administration); HD: high doses; UGT: UDP-glucuronosyltransferases.

analysis, recent studies have also identified deficiencies in the quality of herbal medicines trial reports. In most cases, reports on clinical trials of herbal drugs do not contain all of the information recommended by CONSORT (Consolidated Standards of Reporting Trials) guidelines (Claraco et al., 2003; Bian et al, 2006; Gagnier et al., 2006). The scarcity of clinical trials with high methodological quality is an insurmounchart obstacle for the production of good systematic reviews of clinical data on the safety and efficacy of herbal medicines. Methodological drawbacks and poor quality of reports in clinical trials may explain why the conclusions of published systematic reviews on the safety and efficacy of herbal drugs are generally elusive or contradictory (Linde and Willich, 2003; Davidson et al., 2013; Liu et al, 2013). These deficiencies are also the reason why most Cochrane reviews, a gold standard reference for evidence-based therapeutic interventions of herbal drugs, conclude that no well-designed, randomized, placebo-controlled trial with objective outcome measures has been conducted, and thus, there is no evidence to support effectiveness and safety for the proposed clinical indication (Linde et al., 2006; Myiasaka et al., 2006; 2007, Dat et al., 2012; Leach and Moore, 2012; Pitler and Ernest, 2012; Wider et al., 2013).

Some authors, however, rank traditional use, proven by sound historical research, one level above expert's opinion based on medical rationalism rather than on empirical evidence arising from clinical trials. Along this line, John K. Crellin (2001) advanced the notion of "social validation", and based on it, the author suggested that popular beliefs and "therapeutic wisdom" formed during successive generations are not to be neglected as a valid source of evidence. The recognition that traditional use is indeed a valid source of evidence, however, does not imply that clinical trials are in one way or another unnecessary to support the rational use of herbal medicines.

Commenting on the sources of evidence for efficacy, Verpoorte and other authors (Verpoorte et al., 2005; Carmona and Pereira, 2013) suggested that EBM approaches tend to overlook a crucial difference between herbal and conventional medicines. According to them, herbal medicines developed by communities and traditional healers suit a "holistic" view of health and the disease process, while conventional drug therapy reflects a reductionist approach focusing on a known therapeutic target (Verpoorte et al., 2005). A single target approach used to investigate efficacy of conventional drugs would miss the outcome of synergic interactions of herbal drugs on multiple targets. Similarly, some researchers argue that complex mixtures (phytocomplexes) found in herbal medicines would exhibit therapeutic effects greater than those conveyed by an isolated compound, and thus, the complex composition would be in fact an advantage of herbal drugs. The foregoing instigating hypothesis on the mode of action of "herbal drug complex mixtures" deserves to be adequately tested; however, regardless of the mechanism by which herbal medicines exert their therapeutic actions, clinical studies remain necessary to demonstrate that their use is, in fact, effective and safe.

European and Brazilian regulatory agencies show some leniency regarding the proof of efficacy of herbal drugs and alternative therapies presumed to be safe. However, any leniency regarding proof of safety of therapeutic interventions of unproven efficacy seems inadmissible. If clinical superiority over a placebo is small or unproven, safety criteria should be more stringent because, in this case, even low risks of adverse events, and those of minor severity, turn the risk-to-benefit ratio unfavorable. As mentioned previously, except for short-term and overtly manifested toxic effects, long-standing traditional use does not ensure that a medicinal plant is safe. This holds particularly true for long-term effects, such as cancer and morbidities not easily detected. There are indications that a number of traditionally used herbal medicines and/or their constituents are carcinogens and/or cause liver injury. Moreover, safety concerns also arise from possible kinetic interactions between herbal products and conventional drugs. These interactions can bring about adverse events that are not fully disclosed under the conditions of traditional use.

The safe use of medicines requires both a pre-clinical and clinical evaluation of toxicity and post-marketing pharmacovigilance. Post-marketing pharmacovigilance is essential to bring problems of effectiveness and rare adverse effects (*e.g.*, idiosyncratic DILI and immuno-allergic reactions), the occurrence of which is not anticipated by experimental and clinical studies. In contrast to newly developed conventional drugs, the safety assessment of traditionally used herbal medicines can also take into account a pre-marketing spontaneous report of ADR. Nonetheless, as mentioned previously, pharmacovigilance of herbal products faces a number of additional difficulties and needs to be considerably improved.

Finally, it should be emphasized that even though traditional use does not ensure the safety and effectiveness of herbal medicines, it is a useful guide for identification of new pharmacologically active substances in plants. A reverse pharmacology/toxicology or "bedside-to-bench" approach starting with a rigorous collection of clinical data in field surveys, as suggested by Graz (2013), may also be a fruitful strategy to improve knowledge on the safety of traditionally used herbal medicines.

Authors contributions

All authors contributed equally to critical reading of the manuscript, have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledxgments

REFERENCES

Alonso-Amelot, M.E., Avendaño, M., 2002. Human carcinogenesis and bracken fern: a review of the evidence. Curr. Med. Chem. 9, 675-686.

Amarasinghe, H.K., Usgodaarachchi, U.S., Johnson, N.W., Lalloo, R., Warnakulasuriya, S., 2010. Betel-quid chewing with or without tobacco is a major risk factor for oral potentially malignant disorders in Sri Lanka: a case-control study. Oral Oncol. 46, 297-301.

Anvisa, 2013. Consulta Pública No 34 de 6 de Agosto de 2013. Agência Nacional de Vigilância Sanitária. Diário Oficial da União, Brasília, em 7 de Agosto de 2013.

Appelhans, K., Najeeullah, R., Frankos, V., 2013. Letter: retrospective reviews of liver-rela§ted case reports allegedly associated with Herbalife present insufficient and inaccurate data. Aliment. Pharmacol. Ther. 37, 753-754.

Aya, T., Kinoshita, T., Imai, S., Koizumi, S., Mizuno, F., Osato, T., Satoh, C., Oikawa, T., Kuzumaki, N., Ohigashi, H., 1991. Chromosome translocation and c-MYC activation by Epstein-Barr virus and *Euphorbia tirucalli* in B lymphocytes. Lancet. 337, 1190.

Bailey, D.G., Malcolm, J., Arnold, O., Spence, J.D., 1998. Grapefruit juice-drug interactions. Br. J. Clin. Pharmacol. 46, 101-110.

Benninger, J., Schneider, H.T., Schuppan, D., Kirchner, T., Hahn, E.G., 1999. Acute hepatitis induced by greater celandine (*Chelidonium majus*). Gastroenterology. 117, 1234-1237.

Bian, Z.X., Li, Y.P., Dagenais, S., Liu, L., Wu, T.X., Miao, J.X., Kwan, A.K., Song, L., 2006. Improving the quality of randomized controlled trials in Chinese herbal medicine, part I: clinical trial design and methodology. J. Chin. Integr. Med. 4, 120-129.

Blömeke, B., Poginsky, B., Schmutte, C., Marquardt, H., Westendorf, J., 1992. Formation of genotoxic metabolites from anthraquinone glycosides, present in *Rubia tinctorum*. Mutat. Res. 265, 263-272.

Bunchorntavakul, C., Reddy, K.R., 2013. Review article: herbal and dietary supplement hepatotoxicity. Aliment. Pharmacol. Ther. 37, 3-17.

Calapai, G., 2008. European legislation on herbal medicines: a look into the future. Drug Saf. 31, 428-431.

Carmona, F., Pereira, A.M.S., 2013. Herbal medicines: old and new concepts, thruths and misunderstandings. Rev. Bras. Farmacogn. 23, 379-385.

Chen, C.H., Dickman, K.G., Huang, C.Y., Moriya, M., Shun, C.T., Tai, H.C., Huang, K.H., Wang, S.M., Lee, Y.J., Grollman, A.P., Pu, Y.S., 2013. Aristolochic acid-induced upper tract urothelial carcinoma in Taiwan: clinical characteristics and outcomes. Int. J. Cancer 133, 14-20.

Chen, C.L., Chi, C.W., Chang, K.W., Liu, T.Y., 1999. Safrole-like DNA adducts in oral tissue from oral cancer patients with a betel quid chewing history. Carcinogenesis. 20, 2331-2334.

Chen, T., Mei, N., Fu, P.P., 2010. Genotoxicity of pyrrolizidine alkaloids. J. Appl. Toxicol. 30, 183-196.

Chen, X.W., Serag, E.S., Sneed, K.B., Liang, J., Chew, H., Pan, S.Y., Zhou, S.F., 2011. Clinical herbal interactions with conventional drugs: from molecules to maladies. Curr. Med. Chem. 18, 4836-4850.

Claraco, A.E., Hanna, S.E., Fargas-Babjak, A., 2003. Reporting of clinical details in randomized controlled trials of acupuncture for the treatment of migraine/ headaches and nausea/vomiting. J. Altern. Complement. Med. 9, 151-159.

Crellin, J.K., 2001. Social validation: an historian's look at complementary/ alternative medicine. Pharm. Hist. (Lond). 31, 43-51.

Daniele, C., Dahamna, S., Firuzi, O., Sekfali, N., Saso, L., Mazzanti, G., 2005. *Atractylis gummifera* L. poisoning: an ethnopharmacological review. J. Ethnopharmacol. 97, 175-181.

Davidson, E., Vlachojannis, J., Cameron, M., Chrubasik, S., 2013. Best available evidence in Cochrane reviews on herbal medicine? Evid. Based Complement. Alternat. Med. doi: 10.1155/2013/163412.

Dat, A.D., Poon, F., Pham, K.B.T., Doust, J., 2012. Aloe vera for treating acute and chronic wounds. Cochrane Database Syst Rev. 2, CD008762. DOI: 10.1002/14651858.

European Parliament and Council, 2004. Directive 2004/24/EC, European Directive on Traditional Herbal Medicinal Products. *Official Journal L* 136, 30.4.2004, p. 85–90.

Fong, H.H., 2002. Integration of herbal medicine into modern medical practices: issues and prospects. Integr. Cancer Ther. 1, 287-293.

Fu, D.L., Lu, L., Zhu, W., Li, J.H., Li, H.Q., Liu, A.J., Xie, C., Zheng, G.Q., 2013. Xiaoxuming decoction for acute ischemic stroke: a systematic review and meta-analysis. J. Ethnopharmacol. 148, 1-13.

Fuhr, U., 1998. Drug interactions with grapefruit juice. Extent, probable mechanism and clinical relevance. Drug Saf. 18, 251-272.

Gagnier, J.J., De Melo, J., Boon, H., Rochon, P., Bombardier, C., 2006. Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration. J. Clin. Epidemiol. 59, 1134-1149.

Graz, B., 2013. What is "clinical data"? Why and how can they be collected during field surveys on medicinal plants? J. Ethnopharmacol. 150, 775-779.

Gurley, B.J., Gardner, S.F., Hubbard, M.A., Williams, D.K., Gentry, W.B., Cui, Y., Ang, C.Y., 2002. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin. Pharmacol. Ther. 72, 276-287.

Gurley, B.J., Gardner, S.F., Hubbard, M.A., Williams, D.K., Gentry, W.B., Cui, Y., Ang, C.Y., 2005. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, *Panax ginseng* and *Ginkgo biloba*. Drugs Aging 22, 525-539.

Hajda, J., Rentsch, K.M., Gubler, C., Steinert, H., Stieger, B., Fattinger, K., 2010. Garlic extract induces intestinal P-glycoprotein, but exhibits no effect on intestinal and hepatic CYP3A4 in humans. Eur. J. Pharm. Sci. 41, 729-735.

Halicioglu, O., Astarcioglu, G., Yaprak, I., Aydinlioglu, H., 2011. Toxicity of *Salvia officinalis* in a newborn and a child: an alarming report. Pediatr. Neurol. 45, 259-260.

Hao, C.Z., Wu, F., Lu, L., Wang, J., Guo, Y., Liu, A.J., Liao, W.J., Zheng, G.Q., 2013. Chinese herbal medicine for diabetic peripheral neuropathy: an updated meta-analysis of 10 high-quality randomized controlled studies. PLoS One. 8, e76113.

Hermann, R., von Richter, O., 2012. Clinical evidence of herbal drugs as perpetrators of pharmacokinetic drug interactions. Planta Med. 78, 1458-1477.

Hoenerhoff, M.J., Pandiri, A.R., Snyder, S.A., Hong, H.H., Ton, T.V., Peddada, S., Shockley, K., Witt, K., Chan, P., Rider, C., Kooistra, L., Nyska, A., Sills, R.C., 2013. Hepatocellular carcinomas in B6C3F1 mice treated with *Ginkgo biloba* extract for two years differ from spontaneous liver tumors in cancer gene mutations and genomic pathways. Toxicol. Pathol. 41, 826-841.

Hollstein, M., Moriya, M., Grollman, A.P., Olivier, M., 2013. Analysis of TP53 mutation spectra reveals the fingerprint of the potent environmental carcinogen, aristolochic acid. Mutat. Res. 753, 41-49.

Hong, C.E., Lyu, S.Y., 2011. Genotoxicity detection of five medicinal plants in Nigeria. J. Toxicol. Sci. 36, 87-93.

Hsieh, L.L., Wang, P.F., Chen, I.H., Liao, C.T., Wang, H.M., Chen, M.C., Chang, J.T., Cheng, A.J., 2001. Characteristics of mutations in the p53 gene in oral squamous cell carcinoma associated with betel quid chewing and cigarette smoking in Taiwanese. Carcinogenesis 22, 1497-1503.

Imai, S., Sugiura, M., Mizuno, F., Ohigashi, H., Koshimizu, K., Chiba, S., Osato, T., 1994. African Burkitt's lymphoma: a plant, *Euphorbia tirucalli*, reduces Epstein-Barr virus-specific cellular immunity. Anticancer Res. 14, 933-936.

Kapadia, G.J., Chung, E.B., Ghosh, B., Shukla, Y.N., Basak, S.P., Morton, J.F., Pradhan, S.N., 1978. Carcinogenicity of some folk medicinal herbs in rats. J. Natl. Cancer Inst. 60, 683-686.

Knöss, W., Chinou, I., 2012. Regulation of medicinal plants for public health-European community monographs on herbal substances. Planta Med. 78, 1311-1316.

Larrey, D., Vial, T., Pauwels, A., Castot, A., Biour, M., David, M., Michel, H., 1992. Hepatitis after germander (Teucrium chamaedrys) administration: another instance of herbal medicine hepatotoxicity. Ann. Intern. Med. 117, 129-132.

Larrey, D., 1997. Hepatotoxicity of herbal remedies. J. Hepatol. 26 (Suppl 1), 47-51

Larrey, D., Faure, S., 2011. Herbal medicine hepatotoxicity: a new step with development of specific biomarkers. J. Hepatol. 54, 599-601.

Leach, M.J., Moore, V., 2012. Black cohosh (*Cimicifuga* spp.) for menopausal symptoms. Cochrane Database Syst. Rev. 12, CD007244. doi: 10.1002/14651858.

Lekehal, M., Pessayre, D., Lereau, J.M., Moulis, C., Fouraste, I., Fau, D., 1996. 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 24, 212-218.

Li, L., Dou, L.X., Neilson, J.P., Leung, P.C., Wang, C.C., 2012. Adverse outcomes of Chinese medicines used for threatened miscarriage: a systematic review and meta-analysis. Hum. Reprod. Update 18, 504-524.

Li, W., Zeng, S., Yu, L.S., Zhou, Q., 2013. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. Ther. Clin. Risk Manag. 9, 259-71.

Linde, K., Jonas, W.B., Melchart, D., Willich, S., 2001. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. Int. J. Epidemiol. 30, 526-531.

Linde, K., Willich, S.N., 2003. How objective are systematic reviews? Differences between reviews on complementary medicine. J. R. Soc. Med. 6, 17-22.

Linde, K., Barret, B., Wolkart, K., Bauer, R., Meclhart, D., 2006. *Echinaceae* for preventing and treating the common cold. Cochrane Database Syst. Rev. 25, CD000530.

Liu, C.J., Chen, C.L., Chang, K.W., Chu, C.H., Liu, T.Y., 2000. Safrole in betel quid may be a risk factor for hepatocellular carcinoma: case report. CMAJ. 162, 359-360.

Liu, Z.L., Xie, L.Z., Zhu, J., Li, G.Q., Grant, S.J., Liu, J.P., 2013. Herbal medicines for fatty liver diseases. Cochrane Database Syst Rev. 8, CD009059. DOI: 10.1002/ 14651858.

Manso, G., López-Rivas, L., Salgueiro, M.E., Duque, J.M., Jimeno, F.J., Andrade, R.J., Lucena, M.I., 2011. Continuous reporting of new cases in Spain supports the relationship between Herbalife® products and liver injury. Pharmacoepidemiol. Drug Saf. 20, 1080-1087.

Mei, N., Guo, L., Fu, P.P., Fuscoe, J.C., Luan, Y., Chen, T., 2010. Metabolism, genotoxicity, and carcinogenicity of comfrey. J. Toxicol. Environ. Health. B Crit. Rev.13, 509-526.

Mimidis, K.P., Papadopoulos, V.P., Baltatzidis, G., Giatromanolaki, A., Sivridis, E., Kartalis, G., 2009. Severe acute cholestasis caused by *Teucrium polium*. J. Gastrointestin. Liver. Dis. 18, 387-388.

Moulds, R.F., Malani, J., 2003. Kava: herbal panacea or liver poison? Med. J. Aust. 178, 451-453.

Myiasaka, L.S., Atallah, A.N., Soares, B.G., 2006. Valerian for anxiety disorders. Cochrane Database Syst. Rev. 18, CD004515.

Myiasaka, L.S., Atallah, A.N., Soares, B.G., 2007. *Passiflora* for anxiety disorder. Cochrane Database Syst. Rev. 24, CD004518.

Ndhlala, A.R., Anthonissen, R., Stafford, G.I., Finnie, J.F., Verschaeve, L., Van Staden, J., 2010. In vitro cytotoxic and mutagenic evaluation of thirteen commercial herbal mixtures sold in KwaZulu-Natal, South Africa. S. Afr. J. Bot. 76, 132-138.

Ndhlala, A.R., Finnie, J.F., Van Staden, J., 2011. Plant composition, pharmacological properties and mutagenic evaluation of a commercial Zulu herbal mixture: Imbiza ephuzwato. J. Ethnopharmacol. 133, 663-674.

NTP, 2011a. Toxicology and carcinogenesis studies of alpha,beta-thujone (CAS No. 76231-76-0) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Natl. Toxicol. Program Tech. Rep. Ser. 570, 1-260.

NTP, 2011b. Toxicology and carcinogenesis studies of pulegone (CAS No. 89-82-7) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Natl. Toxicol. Program Tech. Rep. Ser. 563, 1-201.

NTP, 2013. Toxicology and carcinogenesis studies of *Ginkgo biloba* extract (CAS No. 90045-36-6) in F344/N rats and B6C3F1/N mice (Gavage studies). National Toxicology Program. Natl. Toxicol. Program Tech. Rep. Ser. 578, 1-183.

Olsen, L.R., Grillo, M.P., Skonberg, C., 2011. Constituents in kava extracts potentially nvolved in hepatotoxicity: a review. Chem. Res. Toxicol. 24, 992-1002.

Pelkonen, O., Abass, K., Wiesner, J., 2013. Thujone and thujone-containing herbal medicinal and botanical products: toxicological assessment. Regul. Toxicol. Pharmacol. 65, 100-107.

Pitler, M.H., Ernst, E., 2012. Horse chestnut seed extract for chronic venous insufficiency. Cochrane Database Syst. Rev. 14, CD003230. doi: 10.1002/14651858.

Popat, A., Shear, N.H., Malkiewicz, I., Stewart, M.J., Steenkamp, V., Thomson, S., Neuman, M.G., 2001. The toxicity of *Callilepis laureola*, a South African traditional herbal medicine. Clin. Biochem. 34, 229-236.

Popat, A., Shear, N.H., Malkiewicz, I., Thomson, S., Neuman, M.G., 2002. Mechanism of Impila (Callilepis laureola)-induced cytotoxicity in Hep G2 cells. Clin. Biochem. 35, 57-64.

Potter, D.M., Baird, M.S., 2000. Carcinogenic effects of ptaquiloside in bracken fern and related compounds. Br. J. Cancer 83, 914-920.

Quintus, C., Schweim, H.G., 2012. European regulation of herbal medicinal products on the border area to the food sector. Phytomedicine 19, 378-381.

Reddy, K.R., Bunchorntavakul, C., 2013. Letter: retrospective reviews of liver-related case reports allegedly associated with Herbalife present insufficient and inaccurate data-authors' reply. Aliment. Pharmacol. Ther. 37, 754-755.

Roeder, E., 2000. Medicinal plants in China containing pyrrolizidine alkaloids. Pharmazie. 55, 711-726.

Roeder, E., Wiedenfeld, H., 2011. Pyrrolizidine alkaloids in plants used in the traditional medicine of Madagascar and the Mascarene islands. Pharmazie. 66, 637-647.

Roeder, E., Wiedenfeld, H., 2013. Plants containing pyrrolizidine alkaloids used in the traditional Indian medicine-including ayurveda. Pharmazie 68, 83-92.

Sackett, D.L., Rosenberg, W.M., Gray, J.A., Haynes, R.B., Richardson, W.S., 1996. Evidence based medicine: what it is and what it isn't. BMJ 312. 71-72.

Schoepfer, A.M., Engel, A., Fattinger, K., Marbet, U.A., Criblez, D., Reichen, J., Zimmermann, A., Oneta, C.M., 2007. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J. Hepatol. 47, 521-526.

Seeff, L.B., 2007. Herbal hepatotoxicity. Clin. Liver Dis. 11, 577-596.

Shahin, M., Smith, B.L., Prakash, A.S., 1999. Bracken carcinogens in the human diet. Mutat. Res. 443, 9-79.

Shang, A., Huwiler-Müntener, K., Nartey, L., Jüni, P., Dörig, S., Sterne, J.A., Pewsner, D., Egger, M., 2005. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 2 366, 726-732.

Shaw, D., Graeme, L., Pierre, D., Elizabeth, W., Kelvin, C., 2012. Pharmacovigilance of herbal medicine. J. Ethnopharmacol. 140, 513-518.

Sheikh, N.M., Philen, R.M., Love, L.A., 1997. Chaparral-associated hepatotoxicity. Arch. Intern. Med. 157, 913-919.

Silano, M., De Vincenzi, M., De Vincenzi, A., Silano, V., 2004. The new European legislation on traditional herbal medicines: main features and perspectives. Fitoterapia 75, 107-116.

Smith, C.M., 2005. Origin and uses of *primum non nocere*--above all, do no harm! J. Clin. Pharmacol. 45, 371-377.

Sridar, C., Goosen, T.C., Kent, U.M., Williams, J.A., Hollenberg, P.F., 2004. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases. Drug Metab. Dispos. 32, 587-594.

Steenkamp, V., Stewart, M.J., Zuckerman, M., 2000. Clinical and analytical aspects of pyrrolizidine poisoning caused by South African traditional medicines. Ther. Drug Monit. 22, 302-306

Teschke, R., 2010. Kava hepatotoxicity-a clinical review. Ann. Hepatol. 9, 251-265.

Teschke, R., Wolff, A., Frenzel, C., Schulze, J., Eickhoff, A., 2012. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 32, 1543-1556.

Tomšik, P., 2013. Ferns and lycopods- a potential treasury of anticancer agents but also a carcinogenic hazard. Phytother. Res. (Published online) DOI: 10.1002/ptr.5070.

Verpoorte, R., Choi, Y.H., Kim, H.K., 2005. Ethnopharmacology and systems biology: a perfect holistic match. J. Ethnopharmacol. 100, 53-56.

Westendorf, J., Poginsky, B., Marquardt, H., Groth, G., Marquardt, H., 1988. The genotoxicity of lucidin, a natural component of *Rubia tinctorum* L., and lucidinethylether, a component of ethanolic *Rubia* extracts. Cell Biol. Toxicol. 4, 225-239

Westendorf, J., Pfau, W., Schulte, A., 1998. Carcinogenicity and DNA adduct formation observed in ACI rats after long-term treatment with madder root, *Rubia tinctorum* L. Carcinogenesis 19, 2163-2168.

Wider, B., Pitller, M.H., Thompson-Coon, J., Ernst, E., 2013. Artichoke leaf extract for treating hypercholesterolaemia. Cochrane Database Syst. Rev. 28, CD003335. doi: 10.1002/14651858.

Wu, K.M., Ghantous, H., Birnkrant, D.B., 2008. Current regulatory toxicology perspectives on the development of herbal medicines to prescription drug products in the United States. Food Chem. Toxicol. 46, 2606-2610.

Wu, F., Wang, T., 2013. Risk assessment of upper tract urothelial carcinoma related to aristolochic acid. Cancer Epidemiol. Biomarkers Prev. 22, 812-820

Yasui, Y., Takeda, N., 1983. Identification of a mutagenic substance, in *Rubia tinctorum* L. (madder) root, as lucidin. Mutat. Res. 121, 185-190.

Zuckerman, M., Steenkamp, V., Stewart, M.J., 2002. Hepatic veno-occlusive disease as a result of a traditional remedy: confirmation of toxic pyrrolizidine alkaloids as the cause, using an in vitro technique. J. Clin. Pathol. 55, 676-679.