

## Unpredictable Adverse Reactions to Herbal Products

Cristiano Colalto\*

Specialization School of Pharmacology, Department of Pharmacology, Chemotherapy and Medical Toxicology, Università degli Studi di Milano, Milan, Italy

I wish to highlight a number of issues regarding adverse drug reactions classified as type-B under the WHO's system for herbal products. These reactions are rare, unpredictable, dose-independent, and can cause patients serious harm. It is vital to raise awareness about this phenomenon, and improve safety in use for the consumer, who generally tends to consider any herbal product as natural and therefore safe.

Growing consumer interest in natural therapy has led to an increase in sales of herbal-medicine based products. These can offer a valid and efficacious pharmacological alternative in the case of many diseases, and can help clinics draw up new and interesting treatment protocols. Furthermore, continuing research in ethnobotanics is leading to the discovery of new molecules present in nature for the treatment of various major pathologies [1]. However, the other side of the coin is represented by the side effects that herbal products can cause - for a wide range of reasons. Many studies have shown that herbal products can cause adverse reactions in users, through a variety of mechanisms of action. The WHO's Uppsala Monitoring Centre - which pools indications from over 100 countries worldwide - has a database of over 4 million reports, of which 21,000 involve adverse effects caused by natural products [2]. In addition, a study examining data from the American poison control centres has shown that patients using supplements, herbal and homeopathy products fall into a group that is most linked to hospital admissions [3,4].

The adverse effects in question include intoxication due to interactions with drugs, light skin reactions due to hypersensitivity to one of the components, etc. When describing adverse reactions it is important to distinguish between type-A (drug actions), which are predictable and dose-dependent, and type-B (patient reactions), which are rare, unpredictable and dose-independent. Type-A represent about 80% of all adverse drug reactions, and can be predicted on the basis of the drug's pharmacology. Instead, type-B reactions are independent of the drug's pharmacology, and in most patient cases occur at any dose. These idiosyncratic reactions can affect any organ, and at times occur through Ig-E mediated reactions. These can be systemic, but in the clinical presentation generally affect a dominant organ (liver, kidney or skin), and precisely for this reason are difficult to recognise, since they can be interpreted as a single organ pathology rather than a hypersensitivity reaction [5]. This type of reaction has been described in detail for many pharmaceuticals, including phenytoin, phenobarbital, carbamazepine, abacavir, diclofenac and acetaminophen, and in some cases appears to be due to particular metabolites produced during the hepatic metabolism of these drugs [5-8]. In particular, a recent review has shown clearly how these type of hypersensitivity syndrome can be traced to particular alleles identified in pharmacogenetics studies; work in this area can help improve the predictability of possible adverse reactions [9].

As for pharmaceuticals, herbal products can also cause rare and unpredictable adverse dose-independent reactions that can severely compromise a person's health. The reactions triggered by herbal

products are thus difficult to diagnose and identify, partly because it is counterintuitive to consider a product that is "natural" and therefore "safe" as capable of causing reactions of this type. This aspect has also been considered in a very recent publication by Debbie Shaw and colleagues of the Chinese Medicine Advisory Service of the Medical Toxicology Information Services, Guy's Hospital, London. The study highlights the difficulties pharmacovigilance faces in getting hold of information about herbal-product safety [10]. Pharmacovigilance can be defined as the study of the safety of drugs on the market and in clinical practice in large communities of people, and can be extended to cover herbal products and the various related effects and adverse reactions. One of the chief difficulties associated with these products is knowing exactly the composition of the extract present, which can vary even by factors as a result of the methods of cultivation, collection, extraction, production, as well as incorrect botanical identification, etc. [10].

As with synthesised drugs, herbal products also have pharmacovigilance problems associated with the under-reporting of adverse reactions. The US Department of Health and Human Services notes that the pharmacovigilance system for use of food supplements (including products based on medicinal plants) records few adverse reactions [11]. A study by Barnes and collaborators examines how patients fail to tell their health workers about adverse reactions from herbal products. The study notes that 69% of patients do not report an adverse event associated with the use of herbal products to a physician [12] - a figure close to the 61.7% given in a similar Italian study [13]. According to the US Department of Health and Human Services, it is this same lack of availability to physicians and pharmacists of pharmacological, clinical and pre-clinical information that is hampering identification of adverse events associated with herbal products, and limiting awareness-raising [11]. While rare and unpredictable reactions to herbal products affecting consumers in the form of hepatitis or skin rash are already difficult to identify, these are impossible to determine if the health worker does not have toxicological and pharmacological knowledge about medicinal plant extracts. For this reason it is vital to disseminate knowledge gained from pharmacovigilance cases, making it available and easy to access.

Description of reactions in the scientific literature is invaluable to health workers, and aids their recognition in clinical practice. For

**\*Corresponding author:** Cristiano Colalto, Specialization School of Pharmacology, Department of Pharmacology, Chemotherapy and Medical Toxicology, Università degli Studi di Milano, Milan, Italy, E-mail: [cristiano.colalto@gmail.com](mailto:cristiano.colalto@gmail.com)

**Received** February 27, 2012; **Accepted** February 29, 2012; **Published** March 03, 2012

**Citation:** Colalto C (2012) Unpredictable Adverse Reactions to Herbal Products. J Drug Metab Toxicol 3:e105. doi:[10.4172/2157-7609.1000e105](https://doi.org/10.4172/2157-7609.1000e105)

**Copyright:** © 2012 Colalto C. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

example, a study from Germany involving evaluation of 21 reports demonstrated that the Greater celandine (*Chelidonium majus*) can be responsible for hepatotoxicity [14]. In this case, the authors showed that there is still a lack of clear evidence for the causality link in the ability of this plant to cause reactions of this type. As the researchers explain, there are many variables that can confound the clinical picture and the slender number of events occurring and available for analysis does little to advance knowledge about the phenomenon.

One group of Swiss researchers investigated ten cases of severe hepatotoxicity caused by herbal products from a well-known European house, over a six-year time period [15]. From retrospective analysis, the authors categorised two cases as certain, seven as probable, and two as possible. Of the ten patients, two had suffered earlier viral hepatitis, while a third patient was an alcoholic. The symptoms appeared on average five months after assumption; one patient had to undergo a liver transplant. The authors describe the difficulties encountered in identifying the reactions; they succeeded only after having probed patients diagnosed with hepatotoxicity through a questionnaire. In fact, the assumption of these self-medication herbal products is often overlooked in a patient's clinical history, and is never associated with adverse effects. It is clearly important, therefore, for physicians to try to determine if there has been any assumption of these products, and to carry out risk assessments with reference to the scientific literature. The recent article by Glisson and Walker recommends that physicians communicate closely with patients and engage in regular scientific updating, to help them identify the clinical risks connected with the use of these products [16]. The study by Schoepfer and co-workers notes clearly that while rough assessment shows these hepatotoxicity events to be very rare, of the order of  $1.8/10^6$ /year, a true estimate is difficult for the reasons outlined above [15]. Furthermore, the authors found it difficult to establish the causes, given the unwillingness of manufacturers to provide useful data about composition, origin and analysis of their products. One possible cause of the hepatotoxicity might be ascribed to the presence of N-nitroso-fenfluramine contained in a Chinese plant called "Chaso" or "Onshido" [17], as a weight-loss aid, present in some products on the market and analysed by the Swiss team [15].

Another product of Chinese origin, called Shou-Wu-Pian and formulated from *Polygonum multiflorum*, has been described by the UK Medicines and Healthcare Products Regulatory Agency as causing adverse reactions in some patients in Great Britain [18,19]. Although the mechanism of action in this case does not seem to involve mechanisms of autoimmune hepatitis, but the roles of the individual substances present in the product are not clear. This is partly because products from some parts of Asia are not always subject to stringent safety testing, and at times are found to contain impurities or heavy metals [20].

Further evidence of risk of idiosyncratic reaction due to assumption of herbal products is described in a recent review that focuses on green tea (*Camelia sinensis*) [21]. The scientific literature in fact relates over 30 individual cases where assumption of products based on green tea or its derivatives has led to hepatitis, sometimes severe. In general, improvement has been achieved through suspension, but death ensued in one case where the product was found to be adulterated. In these cases, there is strong correlation between assumption time and onset of symptoms, there being positive rechallenge in some. Even

though green tea extracts contain many types of molecule, the authors assume the hepatitis to be attributable to the catechin and gallic acid esters, such as epigallocatechin-3-gallate (EGCG), through possible mechanisms that involve the metabolism of this component [21].

Rare episodes of hepatitis and pancreatitis have been described in relation to assumption of Saw palmetto (*Serenoa repens*) by patients affected by benign prostatic hyperplasia [22-24]. Only in one case was analysis of the sample carried out to exclude the possibility of contamination. It is instead very important in cases of adverse reaction to perform qualitative/quantitative analysis of the suspected product, to allow adulteration of the product to be excluded and to put the herbal product "in the clear" [25].

Addressing the complexity and intrinsic variability of the ingredients present in herbal extracts, a recent article suggested resolving the problem of suspected adulteration and pollution by applying the rigid standards of Good Manufacturing Practice (GMP) and Good Agricultural and Collection Practices (GACP) to the field of herbal remedies and supplements [26]. Standardisation of products would make consumer use safer, and ensure that product effects are certain. Despite entailing greater costs, manufacturers of natural products should therefore improve the quality of cultivation and production, and also ensure that international regulations on natural products are unified to new pharmaceutical quality standards [27]. As well as giving the consumer greater confidence, this action would make pharmacovigilance data more easily cross-checked. Standardisation of extracts in fact would put the pharmacological and toxicological information from one same plant on a single basis. At present, herbal products can be split into pharmaceuticals and supplements, each with its specific quality of production. For each product, data about extract quality and quantity expressed as a titre (where present) have to be determined; where there is suspicion of adverse reaction, analysis of the suspect product is difficult.

This regulatory situation makes objective examination even more difficult, because it fails to clarify the already complicated and uncertain attribution of the patient harm to a specific plant rather than to the product. This complication is absent in the case of synthesised pharmaceuticals because here rigid standardisation regulations and quality controls are imposed by drug regulatory bodies *inter alia*.

In herbal-product clinical risk assessment, the first step is the correct identification and assessment of risk, through examination of the patient and available scientific evidence. The presence of risk factors for the herbal product and for the user need to be evaluated - while this may be difficult it is imperative, since these factors can determine a reaction's severity and incidence [28]. It is therefore vital that the health professional follows a thorough process of this type, also in view of the increasing presence on the market of these herbal products without parallel rise in scientific, pharmacological and toxicological knowledge. Studies in pharmacogenetics and pharmacogenomics are providing invaluable input here: new information gained can help provide some predictability to the phenomena of idiosyncratic reaction to xenobiotics, so improving clinical risk assessment and safety in patient phytotherapy.

#### Disclosure

The author declares that there are no conflicts of interest of a financial nature regarding the topics covered in this present article.

## Acknowledgement

The author wish to thank Dr Susan Biggin for esteemed suggestions and language input in preparation of the manuscript.

## References

- Rishton GM (2008) Natural products as a robust source of new drugs and drug leads: past successes and present day issues. Am J Cardiol 101: 43-49.
- World Health Organisation (2004) WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. WHO, Geneva.
- Woolf AD (2006) Safety evaluation and adverse events monitoring by poison control centers: a framework for herbs & dietary supplements. Clin Toxicol 44: 617-622.
- Vassilev ZP, Chu AF, Ruck B, Adams EH, Marcus SM (2009) Evaluation of adverse drug reactions reported to a poison control center between 2000 and 2007. Am J Health-Syst Pharm 66: 481-487.
- Knowles SR, Uetrechet J, Shear NH (2000) Idiosyncratic drug reactions: the reactive metabolite syndromes. Lancet 356: 1587-1591.
- Aithal GP (2004) Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Expert Opin Drug Saf 3: 519-523.
- Tujios S, Fontana RJ (2011) Mechanisms of drug-induced liver injury: from bedside to bench. Nat Rev Gastroenterol Hepatol 8: 202-211.
- Boelsterli UA (2003) Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Toxicol Appl Pharmacol 192: 307-322.
- Phillips EJ, Chung WH, Mockenhaupt M, Roujeau JC, Mallal SA (2011) Drug hypersensitivity: Pharmacogenetics and clinical syndromes. J Allergy Clin Immunol 127: 60-66.
- Debbie S, Graeme L, Pierre D, Elizabeth W (2012) Pharmacovigilance of herbal medicine. J Ethnopharmacol.
- U.S. Department of Health and Human Services, Office of Inspector General (2001) Adverse event reporting for dietary supplements: an inadequate safety valve.
- Barnes J, Mills SY, Abbot NC, Willoughby M (1998) Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. Br J Clin Pharmacol 45: 496-500.
- Cuzzolin L, Zaffani S, Benoni G (2006) Safety implications regarding use of phytomedicines. Eur J Clin Pharmacol 62: 37-42.
- Teschke R, Glass X, Schulze J, Eickhoff A (2012) Suspected Greater Celandine hepatotoxicity: liver-specific causality evaluation of published case reports from Europe. Eur J Gastroenterol Hepatol 24: 270-280.
- Schoepfer AM, Engel A, Fattinger K, Marbet UA, Dominique Criblez, et al. (2007) Herbal does not mean innocuous: Ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J Hepatol 47: 521-526.
- Glisson JK, Walker LA (2010) How physicians should evaluate dietary supplements. Am J Med 123: 577-582.
- Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, et al. (2003) Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. Ann Intern Med 139: 488-492.
- But PP, Tomlinson B, Lee KL (1996) Hepatitis related to the Chinese medicine Shou-Wu-Pian manufactured from *Polygonum multiflorum*. Vet Human Toxicol 38: 280-282.
- Mazzanti G, Battinelli L, Daniele C, Mastroianni CM (2004) New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derives from *Polygonum multiflorum*. Ann Intern Med 140: 30.
- Ernst E (2002) Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends Pharmacol Sci 23: 136-139.
- Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, et al. (2009) Hepatotoxicity from green tea: a review of the literature and two unpublished cases. Eur J Clin Pharmacol 65: 331-341.
- Hamid S, Rojter S, Vierling J (1997) Protracted cholestatic hepatitis after the use of prostate. Ann Intern Med 127: 169-170.
- Jibrin I, Erinle A, Saidi A, Aliyu ZY (2006) Saw palmetto-induced pancreatitis. South Med J 99: 611-612.
- Lapi F, Gallo E, Giocaliere E, Vietri M, Baronti R, et al. (2010) Acute liver damage due to *Serenoa repens*: a case report. Br J Clin Pharmacol 69: 558-560.
- Palmer ME, Haller C, McKinney PE, Klein-Schwartz W, et al. (2003) Adverse events associated with dietary supplements: an observational study. Lancet 361: 101-106.
- Jordan SA, Cunningham DG, Marles RJ (2010) Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol 243: 198-216.
- Zhanga J, Widerb B, Shanga H, Lia X, Ernst E (2012) Quality of herbal medicines: Challenges and solutions. Complement Ther Med 20: 100-106.
- Colalto C (2010) Herbal interaction on absorption of drugs: mechanisms of action and clinical risk assessment. Pharmacol Res 62: 207-227.