

TOWARDS SAFER HERBAL MEDICINES

Peter A.G.M. De Smet

Royal Dutch Association for the Advancement of Pharmacy

The Hague

Preamble

This paper on the health risks of herbal medicines was presented at the 4th ESCOP symposium in Cologne, March 15, 1996. The general arguments and points have already been published elsewhere,[1] but many of the examples given here are new, which demonstrates the continued need to take the potential health risks of herbal medicines into appropriate consideration.

Types of adverse reactions

A commonly heard argument in favour of herbal medicines is that these products have a longstanding history of traditional use, resulting in considerable experience with and knowledge about their wanted and unwanted effects. There can be no doubt, of course, that traditional experience is a powerful tool for the identification of adverse effects which occur in the majority of users and develop rapidly after the start of therapy. In the clinical pharmacological literature, such acute effects are known as *type A reactions*. [2] A classical example is the induction of anticholinergic symptoms, such as palpitations, dryness of the mouth, and dilatation of the pupils, by herbal medicines rich in belladonna alkaloids. As is illustrated by Table 1, such reactions are pharmacologically predictable and dose-dependent, which implies that they can be anticipated, and that they could be prevented by dose reduction. Obviously, traditional experience can bring such dose-dependencies to light and it may also help to detect ways of processing which reduce the likelihood of acute problems.

However, not all adverse reactions occur immediately after the therapy has been started. The importance of delayed reactions was recently underlined by a retrospective study covering clinical safety trials with

27 different drug compounds. Nine of the 27 compounds were associated with serious drug-related adverse events that first occurred during the second half of a 12-month testing period. For 3 of the compounds, these late discoveries were so serious that they eventually affected the final dose selected, the product labeling, or the target population.[4] When reactions develop during chronic therapy in a pharmacologically predictable way, they are called *type C reactions*. [2] A herbal example is the occurrence of muscular weakness due to hypokalemia in longterm users of herbal anthranoid laxatives [5]. Type C reactions can be anticipated, but only after they have been identified, and such an identification may be less easy than with type A reactions.

It will be even more difficult for herbal prescribers and their clients to recognize all so-called *type B reactions*. These reactions are not related to the principal pharmacological properties of a drug and they do not improve when the dose is reduced - the drug has to be withdrawn completely. These type B reactions are often immunologically mediated but some have a non-immunological basis, such as a genetic cause. Although type B reactions occur in only a minority of the users, they can be so severe that withdrawal of the responsible agent from general drug use is warranted.[2,6] An example of a herbal medicine which has been repeatedly associated with type B reactions is the Japanese Kampo medicine Sho-saiko-to, consisting of Bupleuri radix, Ginseng radix, Glycyrrhizae radix, Pinelliae tuber, Scutellariae radix, Zingiberis rhizoma, and Zizyphi fructus. This formula has been used in China since the Han Dynasty (i.e. about 100 AD), and it was generally considered to be devoid of serious side effects. There is now a respectable series of case reports from Japan, however, which associate its use with allergic pneumonitis and/or hepatitis.[7-13] Sho-saiko-to is

by no means the only Oriental herbal medicine which is associated with rare but serious cases of hepatitis [14,15]. In recent years, there have also been various reports of type B hepatotoxic reactions to Western herbs, such as wall germander (*Teucrium chamaedrys*), [16] skullcap (*Scutellaria* or *Teucrium* sp.), [17] and chaparral (*Larrea tridentata*). [18,19] In the case of chaparral, the hepatotoxic potential only became apparent after an estimated 500 million capsules had been used without concern in a period of 20 years. [20] At present, 5% of the cases of presumed viral hepatitis are not confirmed on serological testing. To which extent herbal medicines play a role in such cases, is currently unknown. Doctors should definitely keep this possibility in mind, however, when they examine patients with an unexplained hepatic disease. [21]

Another category of adverse reactions that may be readily overlooked is that of the so-called *type D reactions*. This category consists of certain delayed effects, such as teratogenicity and carcinogenicity. [2] Some years ago, there was a tragic outbreak of fibrosing interstitial nephritis in Belgian women who had been treated with a slimming preparation that supposedly included *Stephania tetrandra* but in reality contained *Aristolochia fangchi*. [1] This latter plant drug contains aristolochic acids, which are not only nephrotoxic but also extremely potent rodent carcinogens. [22] Not surprisingly, the first Belgian victims have now been described, who rapidly developed urothelial malignancy after exposure to the slimming preparation contaminated with *Aristolochia*. [23,24]

Limitations of traditional experience

All in all, herbal prescribers and their consumers are likely to detect some types of adverse reactions to herbal medicines less readily than other types. Recognition will be particularly difficult, when the signs and symptoms are not unusual in the population and could thus also be ascribed to alternative causes. In other words, while long-standing experience may tell much about striking and predictable acute toxicity, it is a less reliable tool for the detection of reactions which occur uncommonly, develop very

gradually or need a prolonged latency period, or which are inconspicuous. [1] An appealing example of inconspicuous toxicity is the risk that traditional eye medicines damage the eye by a direct action of toxic substances introduced into the conjunctival sac, by the introduction of micro-organisms leading to infection, by physical trauma resulting from the application, or indirectly by delaying the patient's presentation to a clinic for therapy. [Plate 1] Epidemiological research has shown that one-quarter of the corneal ulcers and childhood blindness in rural Africa is associated with the instillation of traditional eye medicines. [25-27]

There is another reason, why safety claims on herbal medicines cannot always be based on traditional empiricism: not all herbal medicines have firm roots in traditional practices, and this may well be an underestimated issue. When traditional source plants are extracted in a non-traditional way (e.g. by resorting to a non-polar solvent such as hexane), the question arises whether this non-traditional extract is just as safe as the traditional one. Until recently, the ostrich fern (*Matteuccia struthiopteris*) was generally considered to be a non-toxic, edible plant with a history of use as a spring vegetable that went back to the 1700s. However, recent observations of serious gastrointestinal toxicity following the consumption of lightly sauteed or blanched ostrich fern shoots suggest that this vegetable is only safe when it is thoroughly cooked before use. [28]

In other cases, a herbal ingredient may have no medicinal tradition at all, and its route of administration or dose level may be quite different from that used in a traditional setting. A troubling example is that high-dose supplements of beta carotene, taken alone or with vitamin A or vitamin E, increase rather than decrease the incidence of lung cancer in people at high risk of this disease. [29,30]

Modification of herbal toxicity

The chance that a herbal medicine produces an adverse reaction depends not only on the herbal medicine and its dosage but also on consumer-bound

parameters, such as age, genetics and concomitant diseases. For instance, the risk that the alkaloid berberine in Chinese *Coptis* species elicits jaundice seems to be most substantial in infants who are deficient in glucose-6-phosphate dehydrogenase.[21,31,32]. The concurrent use of other drugs must also be considered. An overview of the adverse drug interactions between herbal preparations and conventional medicines will be published elsewhere.[33] While it is sometimes the conventional medicine that increases the toxicity of a herbal compound, it is also possible that a herbal preparation enhances the effects of a conventional drug. For instance, the root of *Salvia miltiorrhiza* (Danshen), which has been used traditionally in China for the treatment of coronary diseases, can enhance the anticoagulant activity of warfarin, when both drugs are taken together.[34,35]

Herbal product quality

Another important determinant of the toxicity of herbal medicines is, of course, their quality. While a consumer of an officially approved herbal medicine should not have to be concerned about the correct identity of the ingredients, this is a primary concern when an individual goes out into the field to collect his own herbs. Austrian physicians recently described a case of a very young boy who developed veno-occlusive disease of the liver after long-term consumption of a tea prepared from *Adenostyles alliariae*. [36] This herb had been erroneously gathered by the boy's parents instead of coltsfoot (*Tussilago farfara*) and it contains much more hepatotoxic pyrrolizidine alkaloids than coltsfoot [36,37]. Botanical identity can not only be problematic with self-collected plants, but also with commercially available materials. German researchers recently exposed, for instance, that *Sarothamni scoparii* flos does not always originate from *Sarothamnus scoparius* ("Besenginster") but may also come from *Spartium junceum* ("Spanischer Ginster") [38]. Since the lower parts of *Spartium junceum* are rich in quinolizidine alkaloids of the cytosine type [39,40], this adulteration

could be clinically relevant.[38] Problems with the botanical quality of crude plant drugs may be even more pertinent in the case of traditional Chinese medicines. A recent pharmacognostic study of crude materials imported into the UK shows that there is much room for improving their quality control [Table 2].

The quality of prepackaged herbal products may also be a problem, in particular in countries, where those products are not generally categorized as medicines. As a result, they remain exempt from governmental approval processes so that their quality may remain essentially uncontrolled.[42,43] A recent US example concerned a South American product labeled as "Paraguay Tea" that was associated with an outbreak of anticholinergic poisoning. Upon chemical analysis, the product yielded belladonna alkaloids instead of the xanthine derivatives that were expected in a preparation from *Ilex paraguayariensis*. [44]

Herbal medicines should be free not only from botanical contaminants, but also from residual pesticides or fumigation agents and from pathogenic micro-organisms or microbial toxins. There is evidence, for instance, that medicinal plant materials from India and Sri Lanka can be contaminated with toxigenic fungi (*Aspergillus*, *Fusarium*). Since aflatoxin B has sometimes been recovered from such materials in potentially unsafe amounts, it would certainly be prudent to improve their storage conditions.[45-47] Of great practical concern is the presence, intentionally or by accident, of toxic metals (such as lead and arsenic) or conventional pharmaceuticals (such as corticosteroids and non-steroidal anti-inflammatory drugs) in certain herbal medicines of Asian origin.[1,45] Although these hazards have been denounced for more than two decades now, they continue to pose an occasional threat to public health.[48-50] Recent reports from the US associate Chinese herbal medicines adulterated with non-steroidal anti-inflammatory agents with such serious reactions as acute renal failure [51] and aplastic anemia [52]. The contamination of herbal medicines with pharmaceuticals is not necessarily limited to products of Oriental origin. We recently analysed

Dutch slimming drops declared to contain *Ephedra* and 14 other ingredients, after the urine of a professional cyclist had given a positive result for norpseudoephedrine at a doping control. The level of norpseudoephedrine in the investigated product was substantially higher than that of ephedrine, which is normally not the case in Chinese *Ephedra* plants. This certainly raised the question, whether the product had been spiked.[53]

While the safety of some herbal medicines can be compromised by deficient product quality, other herbal products become more dangerous, when they have excellent quality. Yohimbe products rich in yohimbine will be less safe for over-the-counter use than products containing no or negligible amounts of this alkaloid.[54] Likewise, the Chinese *Tripterygium* preparations that occasionally surface in The Netherlands, will particularly entail the risk of serious health problems (e.g. gastrointestinal disturbances, skin rashes, immunosuppression, blood disturbances, amenorrhea, and oligospermia), when their quality is immaculate.[55]

What needs to be done

Although the main purpose of this presentation has been to provide an outline of herbal health risks, it appears useful to conclude with the issue whether there is anything that can and should be done about these risks. In my opinion, we should not bury our phytotherapeutic heads in the sand like a frightened ostrich in the hope that herbal health problems will dissolve by themselves. It is better to accept that herbal medicines entail certain health risks and to look out actively for safety problems associated with herbal medicines. To realise this, three steps have to be taken [1]:

1. We need to establish what is already known and this information has to be made readily available.

The key words here are data availability and differentiation: instead of getting bogged down in an

“all or nothing” discussion about the pros and cons of phytotherapy in general, we must discriminate, by careful analysis, which herbs have a favourable benefit/risk ratio and which ones do not. Hereby it should be taken into account that this ratio depends not only on the crude herb as such but also on the way in which it is prepared and applied.

Systematic efforts to collect, evaluate and disseminate scientific data about the safety or unsafety of herbal medicines should be continued and expanded. Herbal data collections must also include non-Western herbs, not only because Western doctors are increasingly confronted with non-Western patients who seek refuge in traditional remedies of their homeland but even more so because herbal therapy plays a vital role in the health care of developing countries. Renal toxicity due to *Aristolochia* was already reported in China in 1964,[56] i.e. almost thirty years before the Belgian outbreak of renal *Aristolochia* toxicity was described.[1]

In addition to collecting data about real herbal medicines, it would also be useful to produce and circulate exhaustive lists of those herbal products which have been shown to contain dangerous amounts of heavy metals or pharmaceuticals. It is remarkable that Oriental Chuifong Toukuwan pills continue to cause health problems,[50] when adulteration of this particular product with Western pharmaceuticals has been reported repeatedly since 1977.[45] This consideration introduces the second step that should be taken towards safer herbal medicines:

2. We need to act upon what we already know.

Nobody deserves a remedy which is worse than his disease, and herbal markets should be actively improved by banning unsafe remedies and by discouraging unsafe practices. Unfortunately, the introduction of herbal medicine-like products into the market is not adequately monitored in various countries. This unsatisfactory situation could be greatly improved by the creation of a special licensing system for herbal medicines. Such a system would not only help to keep

out preparations from herbs with known unsafety but it would also provide a valuable tool to improve herbal product quality.[42] This latter point is particularly relevant, because herbal health problems are all too often due to contaminants rather than to declared ingredients.[45]

Not only the quality of a finished herbal product is important, but also the quality of the consumer information about that product. Understandable warnings in the package insert can certainly help to reduce the risk of inappropriate uses and adverse reactions.[45] For instance, the German health authorities have limited the indication of herbal anthranoid laxatives to constipation which has not responded to bulk-forming therapy (which rules out their inclusion in slimming aids). In addition, they have imposed restrictions to the laxative use of most anthranoid-containing herbs, that is, not to be used for more than 1 to 2 weeks without medical advice, not to be used in children under 12 years of age, and not to be used during pregnancy and lactation.[5,57] This example illustrates that herbal health risks do not always require a full ban of specific herbal ingredients but can sometimes be pushed back by appropriate warnings in the product information. This example also makes clear that the quality assurance of herbal prescribing is an important issue that should not be overlooked. The same can be said, of course, about the quality of crude herbal materials. As is evident from the examples in Table 2, there still is much room for improvement in this area.

There is one other aspect about the recommendation that we need to act upon what we already know which deserves some comment here. A striking feature of certain restrictive measures is that they are limited to one particular herb, without taking into account that the toxic constituents of that herb also occur in other medicinal plants. For instance, when the German health authorities announced their ban of herbal medicines prepared from the madder root, *Rubia tinctorum*, [58] they paid no attention to the occurrence of the mutagenic anthranoids in madder root in other rubiaceaceous plants, which serve as

medicines in the Far East (*Morinda umbellata*, *Rubia cordifolia*, *Hymenodictyon excelsum* and *Damnacanthus indicus*).[59] Likewise, after a series of French cases had revealed the hepatotoxic potential of the wall germander (*Teucrium chamaedrys*), nobody raised a question about the safety of related *Teucrium* species, even though there is animal evidence to suggest that the hepatotoxicity of the wall germander resides in its terpenoids and even though other medicinally used *Teucrium* species contain similar terpenoids.[16,60] Not surprisingly, the first case of hepatitis associated with the use of *Teucrium polium* has recently been published.[61] This leads to the third and final recommendation:

3. We need to find out what we do not yet know.

Instead of mistaking the absence of reliable evidence of risk for reliable evidence of the absence of risk, experimental studies in this field should continue and should be supplemented with the new concept of herbal pharmacovigilance. By analogy with conventional pharmacovigilance, herbal pharmacovigilance aims at the detection of serious adverse reactions, at the quantification of their incidence, and at the identification of contributive and modifying factors.[62]

A classic and inexpensive tool of pharmacovigilance is spontaneous reporting, on a voluntary basis, by health professionals, consumers or other parties who observe or experience a suspected or possible adverse reaction during daily practice. In my opinion, such reporting should come not only from health care providers outside the phytotherapeutic realm, but also from herbal prescribers and herbal manufacturers. Herbal companies should be legally bound to report suspected adverse reactions to their products to the competent authorities, just as is now required from synthetic drug manufacturers.[1,42] Herbal prescribers should learn in their training programmes which general impediments keep conventional doctors from reporting reactions to synthetic pharmaceuticals [Table 3]. They should come to recognize that the reporting of suspected adverse reactions to their herbal medicines is an act of

courage, which will eventually increase rather than decrease the respectability of their profession.

It goes without saying that incoming reports have to be carefully analysed before they are made public. For instance, our leading Dutch medical journal recently published a case in which Chinese herbal pills were incriminated as the cause of a manganese intoxication resulting in severe chorea. The report specified, however, that the patient had taken a total dose of 2.5-4.2 mg of manganese via the pills over a time period of two months. This total dose is considered to be an adequate and safe *daily* dose in the United States, so the presented evidence did not justify the conclusion that the herbal pills were responsible for the observed problems.[64]

Final consideration

A general point to be emphasized at the end of this presentation is that herbal pharmacovigilance is not a negative tool but a neutral one. Certainly, when it identifies a new serious herbal health risk, it can be the bringer of some bad news. Pharmacovigilance can also be reassuring, however, by providing evidence that certain herbal health risks are absent or negligibly small. And thus it can help to bolster one of the main features of many phytotherapeutics, namely their relative safety when compared to conventional pharmaceuticals.

References

1. De Smet PAGM. Health risks of herbal remedies. *Drug Safety* 1995;13:81-93
2. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *Br J Clin Pharmacol* 1992;34:377-95
3. Innes IR, Nickerson M. Atropine, scopolamine, and related antimuscarinic drugs. In: Goodman LS, Gilman A., Gilman AG, Koelle GB, red. *The Pharmacological Basis of Therapeutics*. 5th edn. New York: Macmillan Publishing Co., 1975:514-32
4. Anonymous. ICH guidelines finalised for 2 further aspects of ADR reporting. *Inpharma* 1995;18 Mar:20-1
5. Anonymous. Kommission E - Aufbereiteungsmonographien. *Dtsch Apoth Ztg* 1993;133:2791-4
6. Bateman DN, Chaplin S. Adverse reactions. I. *Br Med J* 1988;296:761-4
7. Kubo K, Watanabe F, Sakuma S, Abe A, Kutsukake S, Shimano K, Abe M, Kuribayashi N. Hypersensitive hepatic injury induced by Shosaikoto, a liver-supporting herb medicine. *IRYO (Jap J Nat Med Serv)* 1986;40:205-6,257-60
8. Tsukiyama K, Tasaka Y, Nakajima M, Hino J, Nakahama C, Okimoto N, Yagi S, Soejima R. A case of pneumonitis due to Sho-saiko-to. *Jap J Thoracic Dis* 1989;27:-1556-1561
9. Daibo A, Yoshida Y, Kitazawa S, Kosaka Y, Bando T, Sudo M. A case of pneumonitis and hepatic injury caused by a herbal drug (Sho-saiko-to). *Jap J Thoracic Dis* 1992;30:1583-8
10. Imokawa S, Sato A, Taniguchi M. A case of Sho-Saiko-to induced pneumonitis and the review of literature. *Jap J Chest Dis* 1992;51:53-8
11. Takada N, Arai S, Kusuhara N, Katagiri M, Yanase N, Abe T, Tomita T. A case of Sho-Saiko-to-induced pneumonitis, diagnosed by lymphocyte stimulation test using bronchoalveolar lavage fluid. *Jap J Thorac Dis* 1993;31:1163-9
12. Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine, Syo-saiko-to (xiao-chai-hu-tang). *Dig Dis Sci* 1995;40:1845-8
13. Kawasaki A, Mizushima Y, Kunitani H, Kitagawa M, Kobayashi M. A useful diagnostic method for drug-induced pneumonitis: a case report. *Am J Chin Med* 1994; 22:329-36
14. Perharic L, Shaw D, Leon C, De Smet PAGM, Murray VSG. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. *Vet Hum Toxicol* 1995;37:562-6
15. De Smet PAGM. Herbal pharmacovigilance. In: De Smet PAGM, Keller K, Hänsel R, Chandler RF, red. *Adverse Effects of Herbal Drugs*. Volume 3. Heidelberg: Springer-Verlag, 1997
16. De Smet PAGM. *Teucrium chamaedrys*. In: De Smet PAGM, Keller K, Hänsel R, Chandler RF, red. *Adverse*

- Effects of Herbal Drugs. Volume 3. Heidelberg: Springer-Verlag, 1997
17. De Smet PAGM. *Scutellaria* species. In: De Smet PAGM, Keller K, Hänsel R, Chandler RF, red. Adverse Effects of Herbal Drugs. Volume 2. Heidelberg: Springer-Verlag, 1993:289-96,317
 18. Gordon DW, Rosenthal G, Hart J, Sirota R, Baker AL. Chaparral ingestion. The broadening spectrum of liver injury caused by herbal medications. JAMA 1995;273:489-90
 19. Batchelor WB, Heathcote J, Wanless IR. Chaparral-induced hepatic injury. Am J Gastroenterol 1995;90:831-3
 20. Blumenthal M. Herb industry and FDA issue chaparral warning - Experts unable to explain possible links to five cases of hepatitis. HerbalGram 1993;No.28:38-39,53,59,63,69
 21. Anonymous. "Natural" medicines: a Pandora's box. WHO Drug Information 1995;9:147-9
 22. De Smet PAGM. *Aristolochia* species. In: De Smet PAGM, Keller K, Hänsel R, Chandler RF, red. Adverse Effects of Herbal Drugs. Volume 1. Heidelberg: Springer-Verlag, 1992:79-89
 23. Cosyns J-P, Jadoul M, Squifflet J-P, Van Cangh P-J, Van Ypersele De Strihou C. Urothelial malignancy in nephropathy due to Chinese herbs. Lancet 1994;344:188
 24. Vanherweghem JL, Tielemans C, Simon J, Depierreux M. Chinese herbs nephropathy and renal pelvic carcinoma. Nephrol Dial Transplant 1995;10:270-3
 25. Yorston D, Foster A. Traditional eye medicines and corneal ulceration in Tanzania. J Trop Med Hyg 1994;97:211-4
 26. Courtright P, Lewallen S, Kanjaloti S, Divala DJ. Traditional eye medicine use among patients with corneal disease in rural Malawi. Br J Ophthalmol 1994;74:810-2
 27. Lewallen S, Courtright P. Peripheral corneal ulcers associated with use of African traditional eye medicines. Br J Ophthalmol 1995;79:343-6
 28. Anonymous. Ostrich fern poisoning - New York and Western Canada, 1994. Morb Mortal Weekly Rep 1994;43:677-84
 29. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35
 30. Marwick C. Trials reveal no benefit, possible harm of beta carotene and vitamin A for lung cancer prevention. JAMA 1996;275:422-3
 31. Yeung CY, Lee FT, Wong HN. Effect of a popular Chinese herb on neonatal bilirubin protein binding. Biol Neonate 1990;58:98-103
 32. Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonate 1993;63:201-8
 33. De Smet PAGM, D'Arcy PF. Drug interactions with herbal and other non-orthodox drugs. In: Wellington PJ, D'Arcy PF, red. Drug interactions. Heidelberg: Springer Verlag, 1996:327-52
 34. Lo ACT, Chan K, Yeung JHK, Woo KS. The effects of Danshen (*Salvia miltiorrhiza*) on pharmacokinetics and pharmacodynamics of warfarin in rats. Eur J Drug Metab Pharmacokin 1992;17:257-62
 35. Tam LS, Chan TY, Leung WK, Critchley JA. Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. Aust NZ J Med 25:258
 36. Sperl W, Stuppner H, Gassner I, Judmaier W, Dietze O, Vogel W. Reversible hepatic veno-occlusive disease in an infant after consumption of pyrrolizidine-containing herbal tea. Eur J Pediatrics 1995;154:112-6
 37. De Smet PAGM. Drugs used in non-orthodox medicine. In: Dukes MNG, Beeley L, red. Side Effects of Drugs - Annual 13. Amsterdam: Elsevier, 1989:442-73
 38. Schier W, Sachsa B, Schultze W. Aktuelle Verfälschungen von Arzneidrogen. 5. Mitteilung - Birkenblätter, Orthosiphonblätter, Besenginsterblüten, Wohlriechendes Gänsefußkraut und Isländisches Moos. Dtsch Apoth Ztg 1994;134:4569-76
 39. Greinwald R, Lurz G, Witte L, Czygan F-C. A survey of alkaloids in *Spartium junceum* L. (Genisteeae-Fabaceae). Z Naturforsch Sect C Biosci 1990;45:1085-9
 40. Barboni L, Manzi A, Bellomaria B, Quinto AM. Alkaloid

- content in four *Spartium junceum* populations as a defensive strategy against predators. *Phytochemistry* 1994;37:1197-1200
41. Anonymous. Drug development from natural products. *Pharm J* 1995;255:430-1
 42. De Smet PAGM. Should herbal medicine-like products be licensed as medicines. Special licensing seems the best way forward. *BMJ* 310:1023-4
 43. Tyler VE. Herbal remedies. *J Pharm Technol* 1995;11:214-20
 44. Hsu CK, Leo P, Shastry D, Meggs W, Weisman R, Hoffman RS. Anticholinergic poisoning associated with herbal tea. *Arch Intern Med* 1995;155:2245-8
 45. De Smet PAGM. Toxicological outlook on the quality assurance of herbal remedies. In: De Smet PAGM, Keller K, Hänsel R, Chandler RF, editors. *Adverse Effects of Herbal Drugs*. Volume 1. Heidelberg: Springer-Verlag, 1992:1-72
 46. Abeywickrama K, Bean GA. Toxicogenic *Aspergillus flavus* and aflatoxins in Sri Lankan medicinal plant material. *Mycopathologia* 1991;113:187-90
 47. Abeywickrama K, Bean GA. Cytotoxicity of *Fusarium* species mycotoxins and culture filtrates of *Fusarium* species isolated from the medicinal plant *Tribulus terrestris* to mammalian cells. *Mycopathologia* 1992;120:189-93
 48. Shaw D, House I, Kolev S, Murray V. Should herbal medicines be licensed? *BMJ* 1995;311:451-2
 49. Espinoza EO, Mann M-J, Bleasdel B. Arsenic and mercury in traditional Chinese herbal balls. *N Engl J Med* 1995;333:803-4
 50. Gertner E, Marshall PS, Filandrinos D, Potek AS, Smith TM. Complications resulting from the use of Chinese herbal medications containing undeclared prescription drugs. *Arthritis Rheum* 1995;38:614-7
 51. Abt AB, Oh JY, Huntington RA, Burkhart KK. Chinese herbal medicine induced acute renal failure. *Arch Intern Med* 1995;155:211-2
 52. Nelson L, Shih R, Hoffman R. Aplastic anemia induced by an adulterated herbal medication. *Clin Toxicol* 1995;33:467-70
 53. Ros JJW, Pelders MG, De Smet PAGM. Positive doping case associated with the use of an ephedra-labelled health food product. Submitted for publication
 54. De Smet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *BMJ* 1994;309:958
 55. De Smet PAGM. Chinese *Tripterygium*-tabletten veel te gevaarlijk voor zelfmedicatie. *Pharm Weekbl* 1995;130:910
 56. Zhu Y-P, Woerdenbag HJ. Traditional Chinese herbal medicine. *Pharm World Sci* 1995;17:103-12
 57. Anonymous. Anthranoid-haltige Humanarzneimittel. *Pharm Ztg* 1994;139:2432
 58. BGA-Pressedienst. Widerruf der Zulassung für Krappwurzelhaltige Arzneimittel angeordnet. Berlin: Bundesgesundheitsamt, 15/1993
 59. Kawasaki Y, Goda Y, Yoshihira K. The mutagenic constituents of *Rubia tinctorum*. *Chem Pharm Bull* 1992;40:1504-9
 60. Kouzi SA, McMurtry RJ, Nelson SD. Hepatotoxicity of germander (*Teucrium chamaedrys* L.) and one of its constituent neoclerodane diterpenes teucriin A in the mouse. *Chem Res Toxicol* 1994;7:850-6
 61. Mattei A, Rucay P, Samuel D, Feray C, Reynes M, Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration. *J Hepatol* 1995;22:597
 62. De Smet PAGM. An introduction to herbal pharmacoepidemiology. *J Ethnopharmacol* 1993;38:197-208
 63. Wiholm B-E, Olsson S. Spontaneous reporting systems outside the United States. In: Strom BL, red. *Pharmacoepidemiology*. New York: Churchill Livingstone, 1989:119-34
 64. De Smet PAGM. Manganintoxicatie door het gebruik van Chien Pu Wan tabletten. *Ned T Geneesk* 1994;138:2516-7

Table 1. Effects of atropine in relation to dosage [3]

| Dose | Effects |
|-------------------|---|
| 0.5 mg | Slight cardiac slowing; some dryness of mouth; inhibition of sweating |
| 1.0 mg | Definite dryness of mouth; thirst; acceleration of heart, sometimes preceded by slowing; mild dilation of pupil |
| 2.0 mg | Rapid heart rate; palpitation; marked dryness of mouth; dilated pupils; some blurring of near vision |
| 5.0 mg | All the above symptoms marked; speech disturbed; difficulty in swallowing; restlessness and fatigue; headache; dry, hot skin; difficulty in micturition; reduced intestinal peristalsis |
| 10.00 mg and more | Above symptoms more marked; pulse rapid and weak; iris practically obliterated; vision very blurred; skin flushed, hot, dry and scarlet; ataxia, restlessness and excitement; hallucinations and delirium; coma |

Table 2. Quality problems with some crude Chinese plant drugs imported into the UK [41]

| Plant drug | Quality problem |
|-------------|--|
| Fang ji | Plant roots supplied under this name not only contained <i>Stephania tetrandra</i> but also <i>Aristolochia fangchi</i> . |
| Mu Tong | Of two samples, one was <i>Clematis armandi</i> and the other was <i>Aristolochia manshuriensis</i> . |
| Zi Cao | One sample proved to be <i>Potentilla chinensis</i> rather than the required <i>Arnebia euchroma</i> . As a result, it contained no L-shikonin, the expected active ingredient. |
| Cheng Yiang | One sample imported from Hong Kong showed no characteristic signs of authentic <i>Aquilaria sinensis</i> and was in fact a piece of unidentified wood that had been dyed with black ink. |

Table 3. Reasons for not reporting adverse reactions to synthetic medicines [63]

| |
|---|
| <p>Complacency - the mistaken belief that only safe drugs are allowed on the market</p> <p>Fear of involvement in litigation</p> <p>Guilt - because harm to patient has been caused by the treatment the doctor has prescribed</p> <p>Ambition to collect and publish a personal series of cases</p> <p>Ignorance of the requirements for reporting</p> <p>Diffidence about reporting more suspicions which might lead to ridicule</p> <p>Lethargy - an amalgam of procrastination, lack of interest of time, inability to find a report form etc</p> |
|---|