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Pharmacovigilance of Herbal Medicines: Current State and Future Directions

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Speaker Abstracts

Herbal Medicines: An Introduction

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The 2004 European Directive on Traditional Herbal Medicines and proposals for the regulation of the herbal medicine profession should go far to improve standards of care in this field, but much remains to be done. The public frequently hold misconceptions as to the safety of herbal medicine products, considering that since they are 'natural', they must also be safe. Health care professionals are frequently not aware that their patients may be taking both conventional and herbal medicines and that important interactions can occur between them.

MHRA is active in publicising the importance of herbal safety issues. Regular communication via Herbal Safety News, and media briefings on current problems as they arise serve to raise the profile of clinical issues. Extension of the Yellow Card Scheme to encourage reports on unlicensed herbal medicines and the introduction of patient Yellow Card reporting are further moves which are being energetically followed.

Central to the safety of herbal medicines is control of their quality; variations in manufacturing standards, adulteration and contamination are all problems which must be detected and dealt with.

The public and the healthcare professions require authoritative and clear information on herbal medicines as in any other therapeutic field. Episodes such as the adulteration of slimming medicines with Aristolochia resulting in renal damage, and the occurrence of drug interactions with St John's Wort serve to emphasise the importance of communication.

Strategies for Risk Management for Herbal Medicines

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Risk management involves a structured approach to the identification of hazards and an assessment of the risk associated with them. Identified risks need to be monitored and managed, and communication with those who may be exposed to them is also an essential aspect of the whole process.

Herbal medicines are widely used in the community. However, they can occasionally be associated with Type A (dose-related) or Type B ("idiosyncratic") toxicity. This may be due to toxicity associated with one or more ingredient, but sometimes with adulteration or substitution of ingredients with other agents. Interactions may also occur between herbal medicines and other medicines. In some cases interactions may result in type A toxicity, but in the case of enzyme inducers (e.g. St John's Wort), inefficacy of another therapeutic agent has been associated with serious consequences.

Identification of safety issues requires appropriate and sensitive pharmacovigilance procedures, including optimum use of existing spontaneous reporting systems. Identification of risk is most difficult in relation to adverse events that are either infrequent or share features with other common medical conditions in the community. Adverse events which occur in association with chronic use or are delayed in onset may also cause identification difficulties.

Risk assessment should then follow, with characterisation, estimation and evaluation of the risk when possible. Assessment of public concern is an integral component of risk assessment. Monitoring of who may be affected should be followed by an examination of existing precautions and whether they are adequate. Specific groups who may be at particular risk (e.g. pregnant or nursing mothers, children, the elderly or perioperative patients) should be considered. Effective monitoring should be underpinned by a reliable, robust and responsive regulatory system.

Risk management may then involve specific hazard and risk-reduction measures. These should be proportional and consistent and as evidence-based as possible. They should be supported when necessary by strong regulatory mechanisms, underpinned by a transparent legal framework and effective sanctions.

Communication with the public, who expect to be actively involved in identifying, characterizing, and solving issues that affect their lives, is also essential throughout the risk management process. Communication can be improved by ensuring that consumers and health professionals have easy access to accurate information about the issues associated with the use of herbal medicines. Education and training programmes for health professionals should incorporate the subject of herbal medicines at undergraduate and as part of continuous professional development.

Risk Modification: An Important Principle in Herbal Safety

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This presentation will examine the important role that risk modification can play in herbal safety. On the one hand, it will discuss product-related risk modifiers, such as basic product quality, contamination and adulteration. On the other hand, it will review consumer-related risk modifiers, such as overuse, age, infrequent genotypes, frailness, comorbidities, organ dysfunctions, pregnancy, lactation, and specific circumstances (e.g., undergoing surgery, being exposed to UV irradiation, driving, or concomitant exposure to additional herbal or conventional medicines). Building on earlier reviews,[1,2] new concerns and examples of continuing concerns will be presented, and areas where there still is room for improvement will be identified.

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Drug-Herbal Interactions: Mechanisms and Clinical Relevance

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Herbs are often taken concomitantly with therapeutic drugs, raising the potential for drug-herbal interactions. There are an increased number of reports on drug-herbal interactions, although many of which are from case studies and limited clinical observations. Drugs that commonly interact with herbs mainly include anticoagulants (e.g. warfarin and aspirin), sedatives and antidepressants (midazolam, alprazolam and amitriptyline), oral contraceptives, anti-HIV agents (indinavir, ritonavir and saquinavir), cardiovascular drug (digoxin), and immunosuppressants (cyclosporine and tacrolimus). Most of these drugs have narrow therapeutic indices and are substrates for cytochrome P450s (CYPs) and/or P-glycoprotein (PgP). Herbs that commonly interact with drugs include St John's wort, ginseng, ginkgo, milk thistle, and dong gui. Both pharmacokinetic and pharmacodynamic components play an important role in drug-herbal interactions. Pharmacokinetic drug-herbal interactions are caused due to altered absorption, metabolism, distribution and excretion of drugs. The altered drug concentration by concomitant herbal medicines is always due to induction or inhibition of CYPs and drug transporters such as PgP. For example, St John's wort is a potent inducer of CYP3A4 and PgP and it decreased the blood concentrations of cyclosporine, midazolam, amitriptyline, digoxin, indinavir, warfarin, and theophylline. Milk thistle decreased the trough concentrations of indinavir, while piperine increased the area under the plasma concentration-time curve of phenytoin, theophylline and rifampin. Pharmacodynamic herbal-drug interactions occur when both herbal components and drug act on the same drug target or physiological system. For example, ginkgo or dong gui can cause bleeding when combined with warfarin. Cases have been reported where the combination of St John's wort and selective serotonin re-uptake inhibitors (e.g. sertraline) caused symptoms characteristic of central serotonergic syndrome in the elderly. Synergistic therapeutic effects may lead to unfavourable toxicities and complicate the dosing regimen of long-term medications, while antagonistic interactions will result in decreased efficacy and therapeutic failure. Drug-herbal interactions may lead to altered drug clearance, response and toxicity. Toxicity arising from drug-herbal interactions may be minor, moderate, or even fatal, depending on a number of factors associated with the patients, herbs and drugs. Prediction of drug-herbal interactions by following pharmacokinetic principles and using proper models, timely identification of drugs that interact with herbs in the early stages of drug development, and therapeutic drug monitoring may minimize toxic drug-herbal interactions. A fourth approach for circumventing toxicity arising from drug-herbal interactions is design of drugs with minimal potential for herbal interaction. Herbs should be appropriately labelled to alert consumers to potential interactions with prescribed drugs.

Chemical and Molecular Basis of *Aristolochia* and Other Herbal Toxicities

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The use of a herbal weight-loss product, containing *Aristolochia* species has been associated with the development of a novel nephropathy, and urothelial cancer.[1] The observed nephropathy and urothelial carcinoma has been traced to the ingestion of aristolochic acid (AA) and is now called aristolochic acid nephropathy (AAN). The major components of the plant extract AA, aristolochic acid I (AAI) and aristolochic acid II (AAII), both are nitrophenanthrene carboxylic acids, which are genotoxic mutagens forming DNA adducts after metabolic activation. Several mammalian enzymes have been shown capable to activate both AAI and AAII *in vitro* and in cells. The activating metabolism has been elucidated and is consistent with the formation of a cyclic nitreniumion with delocalised charge leading to the preferential formation of purine adducts bound to the exocyclic amino groups of deoxyadenosine and deoxyguanosine. The predominantly formed DNA adduct 7-(deoxyadenosin-N^6-yl)aristolactam I (dA-AAI) *in vivo* which is the most persistent of the adducts in target tissue, is a mutagenic lesion leading to AT→TA transversions *in vitro*. This transversion mutation is found in high frequency in codon 61 of the H-*ras* oncogene in tumours of rodents induced by AAI, suggesting that dA-AAI might be the critical lesion in the carcinogenic process in rodents.[1] In contrast, the molecular mechanism of renal interstitial fibrosis in humans after chronic administration of AA remains to be explored. AA is a powerful nephrotoxic and carcinogenic substance with an extremely short latency period not only in animals but also in humans. In particular the highly similar metabolic pathway of activation and resultant DNA adducts of AA which are detectable by the ^{32}P-postlabeling method, allows the extrapolation of carcinogenesis data from laboratory animals to the human situation. These findings draw one of the strongest links yet between use of a herbal product and cancer in humans. Therefore, all botanical-containing products known or suspected of containing AA should be banned from the market worldwide. Pyrrolizidine alkaloids are common constituents of hundreds of plant species widely distributed in the world. Although no epidemiological data relating the use of herbal preparations containing pyrrolizidine alkaloids to cancer incidence in humans are available, some pyrrolizidine alkaloids are clearly tumourigenic in rodents through a genotoxic mechanism mediated by specific adduct formation.[2]

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Herbal Medicines in Pregnancy and Breast Feeding

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Background: Herbal medicine is a complementary therapy that uses plants or plant extracts to treat illness. Many well established medicines come from plants, the active ingredients of which are chemicals that are similar to those in purified medicines and have similar potential to cause serious adverse effects.

Methods: Herbal medicines are not currently subject to the same regulations as conventional drugs as regards testing for purity and safety.[1] The methodology used in collecting data is very variable and often ill defined making interpretation of results difficult.

Results: The last decade has seen a dramatic rise in the availability and use of herbal medicines. The public and some health professionals often regard them as natural, gentle and safe, but scientific evidence is lacking.[2,3] Safety claims about herbal preparations seem especially attractive to pregnant women who are often concerned about the health of their unborn child. Their estimated use in pregnancy is 7–55%, with echinacea and ginger used most frequently.[4] However, few studies have assessed the efficacy and safety of herbal drugs in pregnancy or the factors related to their use.[1-6] Recent reviews of the efficacy and safety of ginger to reduce morning sickness have produced conflicting data.[7] There is a paucity of data concerning the effects of herbal medicines during breast feeding. It is largely unknown whether or not herbal components are excreted into breast milk or if they reach concentrations that could be harmful to the nursing infant. A recent study of the use of herbal drugs in pregnancy in 400 postpartum women showed that 144 (36%) of them reported herbal use during pregnancy with an average of 1.7 products per woman.[3] In total, 249 products containing 46 different herbs. The proportion of women using herbal drugs increased throughout each trimester. Preparations that were considered potentially harmful or had no safety data were used by 39%. Herbal galactagogues were used by 43% of the women who had breastfed a prior child.

Conclusion: Rigorous scientific studies of the safety of herbal medicines in pregnant and lactating women are lacking. The widespread use of herbal medicines by this group of women indicates a need for safety and efficacy data. Ensuring the quality of herbal products by regulatory authorities is urgently required. Applying pharmacological principles to herbal drug kinetics in the pregnant and breast feeding mother and baby may help to define those babies at risk of toxicity.

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Regulation of Herbal Medicine Practitioners in the UK: Implications for Safety and Safety Monitoring of Herbal Medicines

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Whilst the use of herbal medicines continues to be a popular treatment option for growing numbers of individuals, safety concerns have highlighted the lack of adequate regulation of herbal products and practitioners supplying them.

In 2004 the Department of Health consulted on proposals for the statutory regulation of the herbal medicine profession. The consultation was based on an earlier report by the Herbal Medicine Regulatory Working Group (HMRWG) chaired by Professor Michael Pittilo. The proposals for statutory regulation were strongly support by the public, herbal practitioners and other healthcare professionals in the UK. Alongside the DH consultation the MHRA consulted on outline proposals for updating the regime under Section 12(1) of the Medicines Act 1968 under which practitioners make up and supply unlicensed herbal remedies following a face to face consultation. The responses showed general recognition that the existing arrangements for herbal medicines supplied under Section 12(1) failed to adequately protect patients. Furthermore, the exemptions from the normal licensing provisions could potentially create risks to public health in particular, due to the lack of systematic quality controls and appropriate patient information.

The statutory regulation of herbal practitioners has the potential to improve public health protection in a number of significant ways. Herbalists on the register will have met various requirements relating to training and/or experience and continuing professional development and can be subject to remedial action or discipline by their professional body if they are found to fall short of the standards required.

Herbalists will have a responsibility to provide clear information to patients on the medicines they supply and will have a responsibility to report any suspected adverse reactions or potential drug-herb interactions to MHRA. Furthermore, the herbalist's professional body can set out for its members a code of practice relating to the making up and use of Section 12(1) remedies. Use of potent herbal ingredients which are currently controlled under The Medicines (Retail Sale and Supply of Herbal Remedies) Order 1977, SI 2130 could be restricted to supply only by a registered herbalist.

Regulation will protect the public by setting and monitoring standards, training, conduct and performance of herbal practitioners. The opportunity to integrate herbal practitioners more fully into the healthcare system offers enormous advantages for patient safety.

Herbal ATC Classification

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The use of herbal medicines is accepted as the most common form of traditional medicine. They include:

Crude plant material such as leaves, flowers, fruit, seed, stem, wood, bark, roots, rhizomes or other plant parst, which may be entire, fragmented or powdered, also *plant material* such as herb, gums, fixed oils, fresh juice, essential oils, resins. They also include herbal preparations.

The first stage in assuring the quality, safety and efficacy of herbal medicines is identification of the plant species by scientific accepted botanical verifications. Not only the scientific plant name and the authority but also the plant parts used for each preparations.

It should not be forgotten that new preparative methods may alter the chemical, toxicological and even pharmacological profiles of traditionally used herbal medicines, so if there is documentation of historical use of a herb, it must be respected.

In order to standardise herbal classification Uppsala Monitoring Centre has produced a book "Accepted botanical names of therapeutic herbs and their synonyms". This accepted book is essential for those who wants to communicate professionally with people in the herbal field or understand writing and articles about herbal.

The *A*natomical *T*herapeutic *C*hemical classification system for herbal medicine, Herbal *ATC*, has been proposed by De Smet 1998. The system is based on the same main principles as the ATC classification system for substances used in conventional medicine.

In order to assign an HATC to a crude drug, it should be designated by the complete accepted Latin name including the author(s) of the plant from which the crude drug is derived, followed by plant part or extract.

Example 1: Single ingredient (*Panax ginseng C.A. Mey., root*)

- HN06: PSYCHOANALEPTICS
- HN06W: HERBAL PSYCHOANALEPTICS
- HN06WA: Herbal adaptogens
- HN06WA5002: Panax ginseng C.A. Mey., root

Example 2: Multiple ingredients (*Kytta-Sedativum*)

- Indications: Hypnotic and sedative
- *Kytta-Sedativum* Contains: Valeriana officinalis L., root; Humulus lupulus L., cone; Passiflora incarnata L., herb; Crataegus laevigata (Poiret) DC., fruit; and Viscum album L., herb
- H N05C: HYPNOTICS AND SEDATIVES
- HN05CM9004: Other hypnotics and sedatives

The Uppsala Monitoring Centre has published two books: Guidelines for Herbal ATC Classification and a Herbal ATC Index.

Plant Names as Obstacles and Solutions to Accessing Reliable Information about Plants with Medicinal Activity

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The ways in which scientific plant names are used, and misused in the literature can create obstacles to effective communication about herbal plants. Searching the internet or a library using a scientific plant name may result, for example, in your failing to find all relevant publications. Worse still, it may lead you to erroneous conclusions since you may access information relating to a completely different plant from that which you are investigating.

Professionals in the pharmaceutical industry and health care sectors may benefit from greater awareness of the potential pitfalls when using or publishing information about medicinal plants. These pitfalls arise because of the diverse, and sometimes complex, ways in which plant names have been applied and misapplied in the past. These will be illustrated and explained with examples from a development project based in Northeast Brazil[1] that promotes the safe and sustainable use of medicinal plant remedies.

Common plant names suffer from similar complications though, unlike formal scientific names which have international scope, will be quite properly used in different ways by different people in different places.

The international nature and formal rules concerning the use of scientific names therefore help us access the information that we need. Several electronic catalogues of scientific plant names already exist[2-4] each with a different remit and purpose which I will describe. As useful as these tools are, a failure to grasp their precise function may mislead.

Increasingly botanists are aware of their responsibilities to the broader community to facilitate access to information about plants reliably and to make this as easily as possible. Current initiatives seek to build new global electronic catalogues which will provide new ways for professionals and information systems in other disciplines to access them.[5, 6] Input is sought from this audience to help define your precise needs for an effective plant name index.

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Authenticating Chinese Medicinal Plants on the UK Market: Issues, Needs and Developments

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Traditional Chinese Medicine (TCM) has been quick to exploit the West's renewed interest in plant-based medicine. As such it has become one of the fastest growing sectors of the global herbal medicine industry with an annual world market estimated at US$16 billion (128 billion RMB). Upwards of 3,000 TCM clinics are now established in the UK with their pharmacies prescribing remedies made from 200-300 Chinese plant species. Demand for Chinese species from other sectors such as Western phytopharmacy, cosmeceuticals and nutriceuticals brings the total to around 500 species.

Regrettably, lack of mandatory authentication testing is enabling incorrect, contaminated or counterfeit herbs, especially within the TCM sector, to reach the consumer. And, despite an increase in responsible TCM suppliers introducing voluntary quality control checks, problem herbs continue to pose significant problems for public safety as well as the professional reputation of the TCM industry.

Why are some herbs frequently substituted or adulterated with another? Nomenclatural confusion, regional preferences, supply shortages, or accidental harvesting of look-alike species are all possible causes. Furthermore, TCM is an evolving therapy, and recent clinical research sometimes leads to an 'official' species being replaced with another species considered safer or more efficacious. Herbal authentication facilities need to take account of these and many other factors if their responses are to be appropriate for today's market.

Kew's Chinese Medicinal Plants Authentication and Conservation Centre (CMPACC),[1] a joint initiative with the Institute of Medicinal Plant Development in Beijing, was established in 1998 as a non-profit-making scientific resource. Its aims are i) to build a provenanced reference collection of authentic Chinese materia medica and ii) to use this collection to adapt and research new authentication methods relevant to Western needs.

Using examples from CMPACC's work, this presentation outlines current herbal authentication issues and the challenges that lie ahead.

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Quality of Herbal Medicinal Products and Implications for Safety and Efficacy

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In herbal medicinal products (HMPs) the herbal substance or the herbal preparation (HP) in its entirety represents the active substance. Consequently, the quality of the herbal active substance must be assured in such a way that consistent therapeutical activity without any meaningful toxicity is guaranteed from batch to batch. This requirement can only be successfully fulfilled if a reproducible quality profile being predominantly determined by a consistent spectrum of constituents of the HMP is obtained.

Great efforts are necessary to guarantee such a constant and adequate quality of HMPs.

Therefore, the plant material should be carefully selected and a standardised manufacturing process of the HP as well as the HMP in accordance with the principles of GMP should be applied. To prove the constant composition of HMPs adequate chromatographic and analytical methods have to be applied. In some cases, reference standards have to be either procured commercially or isolated and documented on an inidivual basis (e.g. echinacoside, eleutherosides). To prove the safety of HMPs several special purity tests are of great importance including tests for microbial contamination, pesticides, heavy metals, mycotoxins, fumigants, radioactive contamination and residual solvents. Also negative markers or unwanted constituents such as allergens or toxins (e.g. pyrrolizidine alkaloids, aristolochic acids) should be absent.

Finally, stability testing of HMPs is necessary to prove that the composition of the herbal substance remains constant over the intended shelf-life by applying suitable fingerprint chromatography. So it is assured that no relevant changes in the pattern and concentration of constituents occur.

In this lecture, the state-of-the-art methodology used for assuring consistent quality of HMPs without exaggerated and unnecessary efforts on cultivation of herbal substances, manufacturing of HPs and/or HMPs and quality control will be presented and discussed.

Adverse Event Reporting by Herbal Practitioners: The National Institute of Medical Herbalists Yellow Card Reporting Scheme

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The National Institute of Medical Herbalists (NIMH), founded in 1864, is the largest professional body of herbal practitioners in the UK. At the beginning of 1994, in collaboration with the Medicines and Healthcare products Regulatory Agency (MHRA), NIMH implemented a Yellow Card reporting scheme in recognition of the need to develop a formal pharmacovigilance system for prescribed herbal medicines by qualified herbal practitioners.

Trained herbal practitioners prescribe whole plant extracts based on a system of traditional medicine and empirical knowledge. Herbal medicines are prescribed on an individual basis involving a detailed case history including medical and drug history, allergies, nutritional status and lifestyle factors. Patients are monitored by way of follow-up reviews to assess changes and progress. Any suspected adverse reactions would be recorded and addressed accordingly.

Adverse events in modern herbal therapeutics are usually transient and minor, and might include events such as changes in bowel performance, diuresis, or increased mucus production. Such events are likely to be essentially linked with the disease process and may be a positive change as part of the healing process.

Since the implementation of the NIMH Yellow Card system in 1994, a total of 42 reports have been submitted and recorded, averaging 3-4 reports per year. No serious or life threatening adverse events have been reported by practitioners.

The increasing number of high profile reports on safety issues concerning herbal medicines have directly related to the increasing sales of over the counter (OTC) herbal products, highlighting the quality and safety issues concerning self prescribing of OTC products. Trained herbal practitioners prescribe herbs appropriate to the individual with far less risk of causing potentially damaging adverse events.

The Register of Chinese Herbal Medicine 'Yellow Card Scheme'

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Background: The Register of Chinese Herbal Medicine plays a key role in the professional development of practitioners of Chinese Herbal Medicine. The first such body of its kind, it was set up in 1987 to regulate the practice of Chinese herbal medicine in the UK. Part of the work of the RCHM has been to put in place a 'yellow card' scheme.

Aims: The yellow card scheme was developed to help gather safety data on Chinese herbal medicines through identifying suspected adverse reactions to herbs. The World Health Organisation states that the largest group of adverse reactions to herbal medicines is those associated with the concurrent use of orthodox drugs,[1] yet there is little known about herb/drug interactions. Active use of the scheme would further knowledge in this area.

Method: All RCHM practitioners are issued with a yellow card form for completion when a suspect adverse reaction occurs. The forms are accompanied with guidance notes on filling in the form. The personal details of both practitioner and patient are kept confidential. The only person who sees the details of cases is the yellow card co-ordinator. Personal details are removed from the card and all other information is put onto the yellow card database.

The practitioner who has submitted the card is asked whether they wish the case to be analysed by another practitioner. If so, the case history is forwarded for examination.

Results: To date the scheme has had some response with approximately 3% of practitioners completing yellow cards.

Conclusion: The results show that there are a relatively low number of reported adverse reactions to Chinese Herbs.

Discussion: Why are there low numbers of reported adverse reactions? Is it that Chinese herbs are intrinsically safe and have few side effects or is it that practitioners are reluctant to fill in yellow cards?

Is there more success at yellow card reporting within the allopathic sector?

What are the obstacles to filling in yellow cards? Is it lack of understanding of the scheme? Is there difficulty in recognising an adverse reaction? Is there a lack of trust of the medicines regulators? Is there a lack of motivation from practitioners?

How can the scheme be improved? What incentives can be given to practitioners to fill out yellow cards? Are there any alternatives to this scheme? How should the routine testing of liver enzymes be reported? Who will be responsible for this scheme after SSR?

Reference

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Adverse Events and Aromatherapy Practice: A UK Initiative on Reporting

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In the UK aromatherapy is largely a body therapy, split between clinical and aesthetic use. The profession has traditionally looked to cosmetics industry guidelines on the use of essential oils to help inform safe practice. However reports on toxicity from the European Union[1,2] are leading to tightening of cosmetic industry recommended usages for various whole oils and single components[3]. A strict adherence to these guidelines, by clinical aromatherapists, could restrict the use of many essential oils in topical applications. Aromatherapy has a different pattern of use of these materials compared to the cosmetics industry and there is a need to monitor their use in therapeutic practice. This will inform safe practice, education, and regulation.

Skin reactions are the most likely adverse event (AE) during aromatherapy treatment, but very little research has been carried out on their true frequency. Most evidence comes from reported case histories[4] or studies on subjects with a history of skin sensitivity[5]. Although (AEs) to aromatherapy are occasionally reported via the yellow card system, most practitioners do not have access to this system and there is likely to be under-reporting of minor events.

The Adverse Reactions in Aromatherapy, (ARIA), system for reporting AEs is being developed by the The International Federation of Professional Aromatherapists (IFPA), and Thames Valley University, for the following reasons:

- To gather data on the frequency and severity of AEs to aromatherapy practice.
- To build a database of AEs in order to identify any patterns related to modes of application, essential oil supply, storage and handling, etc. that can be used to improve education and safe practice.

A self-reporting form for practitioners, covering skin reactions only, was piloted in 2004[6] and received positive feedback from a small group of volunteers. During the nine month period of the pilot only one, minor AE was reported from 4229 total treatments. 94% of respondents reported that they had never or rarely in the past experienced skin reactions to clients, but reported a slightly greater risk to themselves, with 18 % reporting occasional experience of AEs.

The next phase of the ARIA project is now underway. This entails rolling out the reporting system to a larger number of practitioners and developing a related reporting form for types of AE other than skin reactions. The database is also in development. The long-term aim of gathering information and feeding this back into education and practice can now begin.

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Safety of Herbal Medicines: The Practitioners' View

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The high and increasing patronage of traditional medicine (TM) products (usually herbal medicines) in developing as well as developed countries[1] has been accompanied by an increased[2] (though still low) attention to safety of these products yet few studies have attempted to identify the views of practitioners on the safety of herbal medicines. TM practice often adopts a holistic framework wherein issues of safety including adverse or undesirable effects may either be attributed to factors other than any administered medicinal products or may be accepted as a necessary and unavoidable part of the disease and healing process; thus an essential premium to be paid in order to get well. The widespread practice of TM and increasing commercialization of herbal medicines makes objective and active monitoring of safety imperative in all countries. However, in rural and less developed parts of Africa, where the traditional healer is often an opinion leader and sometimes a religious figure of high standing, objective assessment of safety is impossible, especially when products are formulated and dispensed extemporaneously. Lack of knowledge and identity of the multiple constituents of some herbal remedies, their extemporaneous use and non-provision (by practitioners) of printed patients' information leaflets or SPCs makes systematic "post-market" surveillance impossible, a fact observed by workers in both developed[2] and developing[3] countries.

Safety perceptions of TM practitioners vary widely and a detailed collation and analysis of the range of perceptions as well as their association with level of education, traditional medicine practice type (fully commercial, small-scale, not for profit), socio-economic standing and position of the practitioner within the community (religious/traditional leader) are essential in order to understand why practitioners accept or reject participation in formal schemes for structured safety monitoring of adverse reactions to herbal medicines. The perceptions of practitioners in southern Ghana obtained via investigator-administered questionnaires, focus group discussions and key informant interviews indicate wide variation on the views of practitioners on the safety of herbal medicines but nearly all of them agree on the need to develop appropriate, practical and culturally relevant tools and systems for systematic collection of safety data.

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The ESCOP Perspective on ADRs and ADR reporting

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In 1994 ESCOP obtained 3-year funding from the BIOMED programme of the European Commission for a series of projects under the title "Determining European standards for the safe and effective use of phytomedicines". A major project was the production of definitive new monographs on medicinal plants, since continued as ongoing submissions to the Herbal Medicinal Products Committee of the European Medicines Agency.

The programme also included a review of the state of pharmacovigilance for herbal medicinal products in Europe. ESCOP noted that although there were Europe-wide requirements on manufacturers of licensed medicines to report adverse drug reactions (ADRs), and mandatory reporting schemes for physicians in a few Member States of the European Union, there were generally very limited opportunities for health professionals and members of the public to report adverse effects involving herbs. It was noted that compliance for voluntary schemes was low and that there were additional reasons why they were likely to be even less effective for herbals. Two projects reinforced this view.

1) A survey of urologists in the Germany, among whom phytomedicines were widely prescribed, found that these physicians were at least ten times less likely to report ADR's for phytomedicines than for other prescriptions. 2) A substantial research study was conducted to assess the experience of, and attitudes to, herb safety among consumers in the UK. In over 500 user interviews across the country, it was demonstrated that they were significantly less likely to report both serious and minor adverse reactions involving herbal remedies compared with conventional medication.[1]

In an attempt to improve reporting prospects ESCOP devised a novel herb-specific "Yellow Card" which was eventually printed in 5 languages on the ESCOP website with an invitation for anyone to report adverse events.[2] In spite of a widespread publicity campaign there was however little uptake and there was insufficient funding to develop the project after the end of the BIOMED project. In intervening years the increase in formal reporting mechanisms and requirements and in awareness of the issue has arguably reduced the attraction of a separate voluntary scheme.

ESCOP is now exploring ways to provide a central coordination for the herbal sector's monitoring of adverse events, especially as pharmacovigilance requirements for the new European Directive on Herbal Medicinal Products with Traditional Use come into effect.

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Safety of Herbal Medicines and Herbal ADR Reporting: Perspective of a Herbal Medicine Manufacturer

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The latest European rules and regulations on pharmacovigilance that are by now implemented into national laws in most EU countries require additional pharmacovigilane procedures in pharmaceutical companies many of which are costly and bind additional manpower such as the necessity of electronic expedited reporting of serious adverse reactions. For a herbal medicine manufacturer this process is particularly challenging since the product status of herbal medicines still varies from country to country, in Europe as elsewhere. Inasmuch as herbal medicines are proper remedies by law the same safety requirements apply as for chemically based drugs in the countries concerned. In this legal environment many human and financial ressources are bound to guarantee the same safety level for herbal medicines as for chemical entities. The only difference is that the active substance is a plant extract the composition of which is well defined in herbal medicines. Where drug status is prevented by law or regulatory power safety issues are usually subjected to a lower level of risk averse legal framework which e. g. may allow an ill-defined composition. To a certain extent, this may be modified in the major part of Europe due to the implementation of directive 2004/24/EC into most national laws as far as traditional herbal medicines are concerned. Perceptions followed by consumers and health professionals that go along with e.g. a dietary supplement status make a high profile safety standard as is required for herbal medicines difficult. Therefore, particular safety concerns may arise, such as adulteration, mixing up products deriving from different parts of the same plant without this being labelled on the product or indicated in the case report even when published, combining varieties of plants on undue or absent scientific grounds, and even the impossibility to identify the product contents due to a lack of manufacturing and labelling requirements. Furthermore, in most countries academic education for physicians and pharmacists does not include teaching on herbal medicines to an extent thorough enough to take the particularities of herbal medicines into appropriate account so that case reports on herbal medicines are in general of low quality even when published. As far as there are comparisons between herbal and chemically defined medicines available, herbal medicines are generally safer. A prerequisite to this is well-defined extract quality and a safety-supervision as required for any remedy.

Spontaneous Reporting of Herbal ADRs: The Global Experience

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For almost four decades spontaneous ADR reports on herbal remedies have been collected by the WHO Programme for International Drug Monitoring. Despite the vast use of herbal remedies globally, the proportion of herbal ADR reports is merely a small fraction of the total number of ADR reports in the WHO ADR database (Vigibase).

Herbal pharmacovigilance brings with it specific challenges with respect to reporting, classification and assessment of data. To improve the quality of herbal signal detection, Vigibase has undergone some major improvements in recent years. One of the fundamental criteria for allowing detection of herbal signals is the identification of the drug. In the previous system duplicates of the same herbal substance (only with two different names) were entered, which increased the risk of missing herbal signals. The enhanced structure of the database allows for linkage of common names and botanical synonyms to one preferred botanical name, as well as more unspecific names where the preferred name can not be found. Each herbal substance specified as the plant name (preferably the accepted Latin botanical name), plant part and extraction method has its own Herbal Code Number (HCN), equivalent to CAS numbers for chemical substances (table I). The HCN makes it possible for all substances from the same plant to be linked together.[1] By reducing the risk of duplicate substances, signal detection is enhanced.

Table I. An example of the Herbal Code Number (HCN) structure

Herbal substance	HCN
Glycyrrhiza glabra L.	90210 000 00
Glycyrrhiza glabra L. root	90210 005 00
Glycyrrhiza glabra L. root extract	90210 005 03

As a second step towards better herbal signal detection, the Herbal Anatomical Therapeutic Chemical (HATC) classification system[2] has been implemented into Vigibase. Where the regular ATC system lacked herbal specific codes, the HATC structure allows for investigations of groups of herbals with similar therapeutic, pharmacological and chemical properties, which could give an indication of a possible group effect.

Herbal pharmacovigilance is improving, but still there are many challenges ahead. The quality and quantity of herbal spontaneous ADR reporting must continue to improve internationally to allow more effective herbal signal detection.

Some herbal signals will be presented as examples, as well as the structure of the herbal database.

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Safety Monitoring of Herbal Medicines in Ghana: Challenges and Opportunities

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Patronage of traditional medicine products is high in Ghana and an estimated 70% of the population use herbal medicines either alone or concomitantly with allopathic medicines.

Pharmacovigilance of herbal medicines is a key component of Ghana's pharmacovigilance system which uses one spontaneous reporting form to capture ADRs to allopathic medicines, herbal medicines and vaccines. National initiatives to improve traditional medicine practice and the quality of traditional medicine products started with the passage of the Centre for Scientific Research into Plant medicine Decree in 1975 (NLCD 344) followed recently by the Traditional Medicines Act 2000 (Act 575) to regulate practice and practitioners. There is also increased regulatory action geared towards improvement in quality, safety and efficacy of herbal medicines. However, increasing commercialisation including improved packaging and branding, frequent direct-to-consumer advertising and strategic positioning of products between the grey area that straddles medicines and food supplements raise challenges both for pharmacovigilance and drug regulation. Serious adverse reactions including four fatalities in association with herbal medicines usage (alone or in combination) have been reported since 2003 but causality assessment has been difficult as the suspected products are frequently unknown (reported simply as "herbal medicine") or, where known, have been used in combination with other herbal or allopathic medicines. Increased consumption of registered and unregistered local and foreign herbal aphrodisiacs presented as alcoholic bitters or in conventional dosage forms raises important public health concerns calling for rapid deployment of responsive safety monitoring tools and systems.

The development of a separate reporting form and system for herbal medicines have been agreed with herbal medicine practitioners though the value of such a system, whilst remaining untested, appears unclear due to reticence by practitioners to be transparent in providing information on safety and content of products. In some instances, ADRs (e.g. rashes, diarrhoea) are claimed to be a natural extension of the therapeutic response of the products.

Rigid enforcement of existing legislation, increased competition and regular consumer education are powerful facilitating forces encouraging systematic safety data collection and reporting by manufacturers and consumers. Active collaboration between various stakeholders and the National Pharmacovigilance Centre to improve safety data collection and analysis has started with the ultimate aim of developing safe and efficacious herbal medicines for diseases of public health importance in Ghana including malaria, tuberculosis and opportunistic infections in HIV/AIDS.

Safety Monitoring of Traditional Chinese Medicines in China

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As China's scientific and technical treasure and historic and cultural crystallization, Traditional Chinese Medicine (TCM), during the long history, has been a powerful tool of prevention and treatment against diseases. In the past, it played a vital role in ensuring the multiplying and thriving of the Chinese Nation. At present, TCMs or herbal medicines are still making new contributions to health care of the Chinese people as well as people of the world. Thus, the safety of herbal medicines has become more and more concerns to both national health authorities and the general public.

From 1989, China set about establishing ADR Monitoring System, the safety monitoring of TCMs was included and is equal to chemical, even paid more attention. Traditionally, TCMs include Materia Medica, Prepared Slices of Medicinal Herbs, Decoction of Chinese Medicines, and Chinese Patent Medicines. According to the Regulation of ADR Reporting and Monitoring Management, four types of these should be surveilled. However, in fact, the majority adverse events reports on TCM are from Chinese Patent Medicine. The main causes are more and more modern people using the Chinese Patent Medicines (compared with other three types of TCMs), and Chinese Patent Medicines, to some extent, are more happened adverse events than Decoction of Chinese Medicines.

Except for traditional forms, modern Chinese medicines nearly include all modern preparation forms, such as capsule, inhalant, dripping pills, transdermal patch, even injection and injectable powder. The case reports of injection occupy more high proportion in the adverse events on Chinese Patent Medicines.

The analysis and identifying the causes of these adverse events is more difficult, which may relate to a variety of issues, such as the different preparation forms, problems of quality, adulteration, mistaken use of wrong species, overdose, medication errors, prolonged use, irrational use and interactions with chemicals and foods. At the same time, the ingredients are very complicated. So, the capacity of technical institution, National Centre or Regional Centre, and the ability of personnel for detecting signal and identifying the causes are crucial. They need to have technical expertise and rich knowledge and theory on TCMs.

Herbal Medicines: Spontaneous Reporting and Challenges in Risk-to-Benefit Assessment

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In Germany all products containing herbal preparations and fitting with the EU definition of medicinal products are formally authorized. Accordingly all mandatory pharmacovigilance activities laid down in the national and EU pharmaceutical legislation apply for herbal products as well as for homeopathic and anthroposophic drugs. Suspected serious ADRs must be reported promptly by the MAHs, and PSURs must be submitted to BfArM as usual. Around 3100 herbal medicines are authorized in Germany, and the ADR data base contains about 2500 reports since 1990 on suspected ADRs associated with the use of herbal preparations (without combinations of herbal remedies with chemically defined substances). Single case reports are medically assessed with regards to the observed ADR per quality, seriousness, causality, possible risk factors, and quality resp. completeness of the report. Most ADR reports relate to the following SOCs: gastrointestinal disorders 44.5%, hepatobiliary disorders 8.8%, nervous system 21.2%, respiratory disorders 11.1%, skin disorders 43.8%, vascular disorders 9.6% (all other less relevant SOCs below 10% each). There are statistical tools implemented in the BfArM data base to detect signals for new ADRs or safety issues. If a new safety issue makes a full risk-to-benefit-assessment of specific herbal drugs necessary, a well established formal risk assessment procedure is applied.

Spontaneous reports, data from clinical or epidemiological studies as well as from toxicological studies are sources used to describe and quantify the risk. Evidence for the benefit of the herbal drug(s) is derived from clinical studies if available. Major challenges in risk-to-benefit assessment of herbal drugs are causality assessment (because of the complex and varying composition of herbal drugs), determining toxic and non-toxic concentrations resp. dosages of herbal medicines, and balancing risk against weak benefit resp. soft indications, and therapeutic alternatives. Depending on the robustness of data the risk-to-benefit ratio is determined for herbal plants, preparations and medicinal products. Aristolochia (carcinogenic), herbal drugs containing pyrrolizidine alkaloids, Kava-Kava, Chelidonium (all liver toxic), St. John wort (relevant interactions), and anthranoid laxatives (tolerance, misuse) are examples.

International Data Mining for Signals of Herbal ADRs

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Data mining can be defined as "The analysis of (often large) observational data sets to find unsuspected relationships and to summarize the data in novel ways that are both understandable and useful to the data user[1]." Data mining techniques are routinely applied in the detection of previously unsuspected adverse drug reactions in the WHO database[2]. The database now contains more than 3.5 million suspected adverse drug reaction (ADR) reports. The large volume of data on many conventional drugs makes the use of quantitative techniques a necessity. A quantitative measure the Information Component (IC) is calculated for all suspected drug- adverse reaction combinations in the data and positive values are used to filter the data set and focus clinical review on case series most likely to contain new adverse reactions.

The volume of data in the WHO database on herbal drugs is small relative to that on conventional drugs but increasing. Consequently signal detection and the use of quantitative methods are becoming more and more important. Appropriate classification of herbal products is critical for an effective data mining strategy. There are 593 suspected ADR case reports of *Gingko biloba* L. in the WHO database. Seven of these, originating from three different countries, list haematoma as a suspected adverse reaction. The combination has a positive IC value (2.4) and is reported in the literature[3, 4].

For some case reports the reporting name of the drug is less than adequate. For example there are 107 reports referring to the common name ginseng in the WHO database, and of these three are suspected ginseng induced manic reactions (IC=2.4). While there are individual case reports in the literature with *Panax ginseng* C. A. Mey.[5, 6] all of the seven reports in the WHO database refer to a non-specific ginseng. These reports might refer to Panax ginseng but if it refers to another common name ginseng such as Siberian ginseng (*Eleutherococcus senticocus* (Rupr. & Maxim.) Maxim.), this might potentially represent a new signal.

Some of the properties of herbal pharmacovigilance make the application of data mining particularly challenging, but also add to its potential benefit. Herbal drugs are likely to differ in reporting patterns to conventional drugs and therefore comparison to a background of herbal drugs is also useful. Herbal signals can already be detected in spontaneously reported suspected ADRs, and our capability will increase in the future as the volume of herbal data continues to accumulate. Data mining will have an important role to play.

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Periodic Safety Update Reports (PSUR) for Herbal Medicinal Products: An Industry Perspective

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Chapter 1.4 of the *Rules Governing Medicinal Products in the European Union, Volume 9 – Pharmacovigilance, Part I – Medicinal Products for Human Use* stipulates the requirements for the elaboration of Periodic Safety Update Reports (PSUR). In the PSUR all relevant clinical and non-clinical safety data generated or retrieved in the report period and data on serious, unlisted ADRs for both the report period and as cumulative summary tabulations starting from the International Birth Date must be assessed regarding their relevance for the benefit/risk balance of the product. In principal, the assessment of safety data for Herbal Medicinal Products (HMPs) should be based on the same standards as for chemically defined products. However, for HMPs particular aspects have to be considered at various steps of the process.

Literature research for HMPs requires awareness of the variety of even the systematic names for the same plant. To detect all relevant information secondary compounds have to be included into the research strings where relevant like (e.g., sennosides or hypericin). Causality assessment of case reports for HMPs is more complicated due to often poorly defined quality of the herbal preparation (e.g., extraction solvent?, DER?, dosage?) and frequent use of complex combination products. Different causality assessment algorithms are at the producer's choice which may affect the classification differently.

Thus, PSURs are a challenge for the industry from a quantitative and qualitative perspective. Harmonisation of submission dates for preparations from the same plant offers opportunities to cope with both. Based on harmonized PSUR submission dates agreed with the BfArM the german HMP industry has started with the shared utilization of literature based parts of the PSUR. With the vision of harmonized EU herbal monographs ahead a harmonization of assessment criteria and submission dates for herbal PSURs seems worthwhile to discuss.

Potential of Observational Data in Herbal Pharmacovigilance

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Observational data, data from patients' clinical records, provided in a suitably anonymised format, is a key tool used by the pharmaceutical industry, regulators and academics to research associations between events that might be Adverse Drug Events (ADRs) and the particular medicines under investigation.

The research typically uses data on those who have taken a medicine (X) and looks for relevant events that take place during or even after this exposure. Relevant events are also looked at in a sample of data subjects who have not taken the medicine (X)- the unexposed, but who are matched, typically by age, sex and GP practice. The comparison between those exposed and those unexposed provides a useful indication of the relative safety of the medicine. This cohort study design as well as other designs will be reviewed.

GPRD (General Practice Research Database) is the world's most researched database[1] on medicines' safety issues as it has been running since 1987 and contains information on over 9 million patients[2] who are registered with a GP practice that uses one of the main UK primary care computer systems. GPRD is run and managed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Currently "events" and "exposures" that happen to a patient when they visit their GP or obtain hospital or other NHS care are recorded in the system. OTC, Pharmacy only medications and herbal medicines provided by non NHS practitioners or purchased directly are not presently recorded.

But, with the massive changes in NHS IT via the on-going Connecting for Health program it is not difficult to see how data on exposure to herbal medicines could be collected and therefore linked to events in the patient's full clinical record. For example pharmacists have for years been keeping patient medication records (PMRs) and with electronic prescribing and transmission of data such records are likely to become available for research. If those prescribing and or dispensing herbal medicines kept PMRs and these were available and linkable to the patients NHS record, identical principals of Pharmacovigilance can be applied as currently with prescribed drugs.

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Methodology of a Feasibility Study to Assess the Application of Prescription Event Monitoring (PEM) to Monitor the Safety of Herbal Medicines

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Background: It is important for public safety that herbal medicines are monitored as closely as conventional drugs. Herbals are used extensively in the general population, sometimes in patients with chronic illnesses at high risk of adverse events (AEs). In the UK, the National Institute of Medical Herbalists (NIMH) has a spontaneous reporting scheme, in conjunction with the Yellow Card scheme, specifically for herbalists to report suspected adverse herbal reactions (AHR). However, the limitations, such as under-reporting, of such schemes are well known. This feasibility study proposes an active surveillance system, based on Prescription Event Monitoring (PEM), to monitor the safety of herbal medicines, dispensed to patients by NIMH practitioners. Hypericum perforatum is the model herb because of known risks of selected AHRs.

Objectives: 1) To develop a systematic process for monitoring the safety of herbal medicines prescribed by herbalists; 2) to identify and quantify common AEs associated with H. perforatum; 3) to compare recorded AE data between herbalists and primary care physicians (GPs).

Methods: The proposed study will use an observational, cohort design. Exposure data will come from herbalists' records of new prescriptions containing H. perforatum. Patients will be given study details and a consent form, which should be returned to the co-ordinating centre (DSRU) if they wish to participate. Outcome data will come from health events recorded by herbalists on simple questionnaires sent out six months after starting treatment and on a separate questionnaire by the GP, during the same calendar period. The pilot project (9-12 months duration) aims to recruit 100 patients. Recruitment rates and demographic characteristics of patients and herbalists will be presented. Event Incidence Densities (IDs) [no.1st reports / 1000 patient-months of exposure] will be calculated. Information on suspected AHRs, reasons for stopping treatment and other events of interest will also be requested.

Results: Testing of questionnaires is being undertaken by NIMH practitioners.

Discussion: This pilot study will define the methodological constraints and advantages of the application of PEM in monitoring herb use in the primary care setting, in order to design a formal system that would provide a systematic surveillance system of AEs related to herbals, as prescribed by herbalists. Such a system would allow for quantitative signal detection approaches as well as qualitative case-by case analyses for the assessment of herbal safety and thus complement the results of other pharmacoepidemiological studies exploring the same issue. This methodology could be further developed to monitor the safety of proprietary herbal preparations.

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EVAMED – A Prescription-Based Electronic System for Reporting Adverse Drug Events in Complementary Medicine

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Objective: Although there is evidence that herbal medicines can cause serious adverse reactions (ADRs), there is still a lack of knowledge about ADRs of Complementary and Alternative Medicines (CAM) in general practice. Hence, there is a need for a qualified reporting system for adverse events of CAM based on the number of patients treated with a given medicine. Therefore, we developed an electronic system for the continuous report of all prescriptions as well as ADRs if they occurred. The project (EvaMed) focusses on products of anthroposophical medicine. Data for allopathic medicines were documented as well and evaluated according to the defined internal standard.

Material and methods: Based on the web-oriented postgreSQL-database system, EvaMed can easily be connected to the data of usual practice-software of physicians. Both, documentation and classification of ADRs are based on the WHO-standards of adverse reaction terminology (WHO-ART) and the grade of severity (from 1=light to 4=severe).

Results: Since September 2004, data of 35 German anthroposophically oriented physicians have been collected. So far, a total of 135.292 prescriptions for 32.671 patients (60% female, children: 51%) were documented. They comprised 253.352 prescribed medicines (42% allopathic, 43% anthroposophical, 8% homeopathic, 7% herbal). Until September 2005 ADRs were reported in 82 cases (WHO-grade I: 34, WHO-grade II: 36, WHO-grade III: 11 and WHO-grade IV 1). Out of those 82 cases 33 were related to anthroposophical and 45 to allopathic medicines, 3 to phytopharmaceuticals and 1 to a homeopathic medicine.

Conclusion: The described system for the collection and documentation of ADRs has proved effective for the evaluation of reported ADRs in close cooperation between prescribing physicians and the study center. General standards for the collection, transfer and evaluation of data can be used in any other environment. They also may contribute to an effective Pharmacovigilance system within the European Union.

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Regulatory Approach to Herbal Medicine Safety in Canada

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Herbal medicines require pre-market authorization from the Natural Health Products Directorate by means of a Product Licence issued under the authority of the Canadian Natural Health Products Regulations. Product safety, efficacy, and quality evidence is assessed according to standards of evidence similar to those of the Australian Therapeutic Goods Administration and the U.S. Department of Health and Human Services. Unique is our mandate to ensure that Canadians have ready access to herbal medicines that are safe, effective, and of high quality, while respecting freedom of choice and philosophical and cultural diversity. This is realized by assessing benefits versus risks not only from the pharmacological perspective but also with respect to health claims and risk information from other paradigms such as Traditional Chinese Medicine, Ayurveda, or homeopathy. The mandatory Site Licence for an importer, manufacturer, packager or labeller is granted on the basis of compliance to Good Manufacturing Practices developed specifically for herbal medicines that take into account their distinctive differences compared to conventional pharmaceuticals, and the capacity of the NHP industry in Canada. Clinical Trial Authorizations involve assessment of study products and protocols according to Good Clinical Practices and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Allowances are made for the possible substitution of data from previous (e.g. traditional) use in humans in place of preclinical data that may be limited or unavailable for certain herbal medicines. Research Ethics Boards approving the conduct of herbal medicine trials must have expertise in Complementary and Alternative Medicine. For products already on the market prior to the new Regulations (January 2004), a Compliance Policy based on levels of risk sets priorities to bring unlicensed products into compliance by 2008. The Adverse Reaction Reporting system has been improved for including data on herbal medicines. When an herbal medicine safety issue is identified, a Health Hazard Evaluation, prepared in collaboration with our pharmacovigilance agency, the Marketed Health Products Directorate, provides recommendations for the appropriate level of action by health inspectors and customs agents.

Pharmacogenomics and Herbal Medicines

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There is a great deal of inter-individual variability in how different individuals respond when challenged with chemicals (drugs, herbals, environmental chemicals, and those contained in foods). Part of this variability is genetically determined, and study of this area has acquired various "-omics" terms. Pharmacogenomics is the term used when referring to variability in responses to medicinal products. This has largely been applied to pharmaceutical products, with little work so far on herbal medicines. Research with pharmaceutical compounds has clearly shown that variability in response (efficacy or toxicity) is dependent on a number of genes (i.e. it is multi-genic), and their interaction with the environment (i.e. it is multifactorial). Use of strategies where patients have been inadequately phenotyped, and/or where a superficial genotyping approach has been employed, has led to conflicting data in the literature. This has in turn has led to difficulties in clinical implementation of pharmacogenomics. Nevertheless, there have been some striking successes in the field of cancer, HIV and anticoagulation, which will be used as examples. Since many of the active components in herbal medicines have pharmacokinetic and pharmacodynamic characteristics that are similar to pharmaceutical compounds, it should be possible to conduct pharmacogenomic studies in patients on herbal medicines. However, such studies will need to be standardised in terms of the pharmacological phenotype (dose and proportions of active components) of the herbal medicine being studied, which may be problematical given that the studies will need to have large sample sizes.

Communication of Herbal Safety Concerns

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The communication of herbal safety concerns provides a profound and complex challenge for all those committed to preventing harm to consumers and patients. It is considerably more problematic than even the communication of safety issues in modern medicines.

Across the world, herbals are the subject of a variety of deeply embedded – sometimes magical – beliefs and practices. In developed countries, they occupy a protected place in consciousness, often on the basis of faith rather than evidence. Their ancient credentials, alongside the assumed benign quality of natural ingredients, put them largely beyond question.

The current state of scientific knowledge makes development of reliable messages very difficult: there is little good data about safety and efficacy; identification of ingredients is problematic; contamination and/or poor manufacturing practices are not uncommon; interactions with other herbals, modern medicines and diet are little understood; much herbal use is invisible to science (self-medication, in particular).

The communication of these and other concerns faces the challenge of influencing deeply held beliefs and long established practices, on the basis of partial knowledge and a large measure of uncertainty. Pitched against scientific communication are the forces of sales and marketing by traditional practitioners and by industry. The commercial issues (and the markets) are enormous and growing, and investment in promotion is substantial – whether at village or community level, or in national and international marketing.

The failures of conventional communications in medicine, based on the bureaucratic, distributive model, demonstrate that changing attitudes and behaviour is extremely difficult. In the field of herbals, as in all high level medical, social and public health concerns, a dynamic, reciprocal, interactive, user-focused model of communications must be adopted if citizens are to be reached and protected from harm. The energy, creativity and persistence of the commercial sector's communications have to be the standards against which activities are planned and measured.

The communications model proposed includes: knowledge of audiences through direct contact and collaborative research; clarity of messages and tailoring to audience segments; sophisticated, creative planning, writing, design, production, campaigning and interaction; using all available channels and media; frequency and repetition; monitoring of effects.

The competition for attention is so great, that only if our messages and concerns stand out from the crowd shall we be noticed and have some chance of making a positive difference. The specialist skills of effective, modern communications need to be recognised and employed by those whose primary expertise is in science, medicine, research and regulation.

Submitted Abstracts

1. A Pilot Study of Community-Pharmacy-Based Pharmacovigilance of an Over-the-Counter Herbal Medicine Ginkgo (*Ginkgo biloba*): Methodological Issues from Work in Progress

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Background: At present, the identification of herbal safety concerns relies on spontaneous reporting systems such as the UK's 'yellow card' scheme. Such schemes have limitations, particularly under-reporting.[1] Other pharmacovigilance methods include collection of adverse event data using observational methods. While the feasibility of using observational studies for pharmacovigilance of conventional over-the-counter (OTC) medicines has been previously assessed,[2,3] the aim of this study is to assess the feasibility of a community pharmacy based pharmacovigilance method for an OTC herbal medicine.

Method: This was an observational cohort study based in community pharmacy. Contact details for all pharmacies in Hertfordshire were obtained from the Royal Pharmaceutical Society of Great Britain (RPSGB). The owner/superintendent pharmacist of each pharmacy/pharmacy multiple was sent information about the study and invited to participate. Non-responders were followed up twice at 3-week intervals. Staff in participating pharmacies were trained in the study procedures and were given study packs.

The consumer recruitment period was set at 12-weeks. During this period, pharmacy staff were instructed to give a consumer recruitment pack to purchasers of ginkgo-containing products. Consumers who wish to participate are required to complete a consent and recruitment form, and return these directly to a study investigator (AMA). Eligible participants are then sent follow-up questionnaires at 1, 4, 12 and 26 weeks after the index purchase. Questionnaires will collect data on the use of the purchased product and other medicines, details of any adverse events experienced, and contact with healthcare providers (HCPs). Where consent is given, HCPs will be contacted to confirm details and any action taken by them.

Results: So far the pharmacy recruitment phase of the study has been completed and the consumer recruitment phase is ongoing. In total, 67/240 (28%) pharmacies responded to the initial invitation to participate. Of these, 5 (7%) agreed to participate, 18 (27%) were excluded (7 did not sell herbal medicines and 11 others did not stock ginkgo products) and 44 (66%) declined the invitation to participate. To date, 6 ginkgo purchases have been made and 6 recruitment packs given out.

Conclusion: Both the low numbers of participating pharmacies and low sales volume of the specific herbal medicine used in this model, suggest that it is unlikely that sufficient numbers of consumer purchasers will be recruited. Further work is planned to explore the barriers to participation in such research.

Keywords: community pharmacy, herbal medicines, pharmacovigilance

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2. Drug-Drug Interaction Studies with *Harpagophytum procumbens* (Devil's Claw)

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Drug-drug interactions can lead to severe side-effects and have resulted in (1) early termination of drug development, (2) refusal of drug approval, (3) severe prescribing restrictions, (4) withdrawal of drugs from the market. Regulators (FDA, BfArM) have, therefore, issued guidelines for studies of in vitro drug interaction that should be conducted during drug development. Recent studies revealed potentially fatal interactions between herbal remedies and traditional drugs.

No such interactions have been associated with the herbal drug *Harpagophytum procumbens* (Devil's Claw). However, since extracts of Devil's Claw are becoming increasingly popular in treating chronic inflammatory diseases such as osteoarthritis, it was decided to investigate systematically its potential for drug interactions.

Traditional indications of Devil's Claw extracts in herbal medicine are complaints of the GI-tract, functional insufficiencies of the liver, gall-bladder, renal and urinary systems. Preparations made from the secondary tubers of Devil's claw are successfully used in patients with rheumatic diseases (arthrosis and low back pain).

In vitro tests with human cells have become an effective and highly predictive tool for investigating the drug interaction profile of herbal products. In this study a proprietary extract (Allya®) of Devil's Claw was investigated.

The extract had no effect on the viability of human hepatocytes. At the highest concentration (2500 µg/mL) the calculated vitality is higher than 100%. Possibly, this effect is due to coloration (interaction with the MTT dye). However, the data suggest that this observation did not interfere with the validity of the data.

The inhibitory effect upon catalytic activity of three cytochrome P450 isoforms using pooled human liver microsomes was investigated. Diclofenac 4′-hydroxylation (marker reaction CYP2C9) and testosterone 6β-hydroxylation (marker reaction CYP3A4) was not inhibited by 0.5 mg/ml of Devil's Claw extract. Minor inhibition was observed with bufuralol hydroxylation (marker reaction CYP2D6). In general an inhibition of CYP2D6 could be considered critically, as CYP2D6 is polymorphically expressed in humans. So-called "poor metabolizers" (human individuals which show low CYP2D6-specific enzyme activities) are more prone to adverse drug effects or toxic side effects related to CYP2D6 inhibition due to their inborn low level of enzyme activity. The clinically relevant concentration of Devil's Claw is expected to be at least 10 times lower than the concentration tested in this study. Therefore, a clinically relevant drug-drug interaction with respect to CYP inhibition regarding CYP2C9, CYP2D6 and CYP3A4 is unlikely.

At the highest concentration tested (0.5 mg/ml) the Devil's Claw extract showed an induction of CYP1A2 and CYP3A4 enzyme activity whereas CYP3A4 was already induced at 0.05 mg/ml. The induction potential at 0.5 mg/ml represents 4 % (CYP1A2) and 21 % (CYP3A4) of what is elicited by the model inducers. Therefore, a clinically relevant drug-drug interaction with respect to CYP induction regarding CYP1A2 is unlikely. The inductive effect on CYP3A4 should be further investigated.

3. Is the Appearance of Mycotoxins in Herbal Medicinal Drugs a Relevant Health Risk?

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Mycotoxins are acute and chronic toxic products of moulds that can be found in a big variety of natural products. The UN Food and Agriculture Organization (FAO) estimates that 25% of the world production of foodstuff is contaminated with mycotoxins and therefore there are several regulations in Germany and the EU that provide limits for mycotoxins in food.

For herbal medicinal products however, only aflatoxin is mentioned in the European Pharmacopoeia, but no limits are given. The German "Aflatoxin Verbots-Verordnung" provides limits for pharmaceutical ingredients that are used for the production of pharmaceutical products, but again other mycotoxins like ochratoxin A, patulin and fusarium toxins as fumonisins, zearalenone and trichothecenes are not mentioned.

This might be partly due to a lack of information about the amounts of mycotoxins in herbal medicinal drugs. One exception is liquorice root where contaminations with ochratoxin A are well known since several years and therefore the German regulatory body for the market authorisation of finished medicinal products set a limit for ochratoxin A in liquorice root that is used in pharmaceutical products.

LC and LC-MS methods[1,2] can be used to analyse mycotoxins in herbal drugs and screenings with LC methods have shown that there are several herbal drugs with positive results for mycotoxins.

Herbal drugs with sporadic positive results on aflatoxins are for example fennel, bitter orange peels, mistletoe and liquorice root while a significant higher number of positive results on aflatoxin could be found in e.g. Senna fruit tinn., nux vomica seeds or ginger root.

Ochratoxin A was sporadically found in fennel, orange peels and rooibos while many positive results were found for example in liquorice root.

Screenings of herbs on other mycotoxins like patulin, zearalenon or fumonisin showed that positive results can be found for these mycotoxins as well.[3]

The results show that there are several herbal medicinal drugs that can be contaminated with mycotoxins and that therefore a consequential analysis of these toxins in herbal medicinal drugs can reduce the involved potential health risks.

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4. Spontaneous Reporting of ADRs Associated with Herbal Medicines: Final Results of a Cross-Sectional Survey of National Pharmacovigilance Centres

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Objective: To explore and describe the current practices of national pharmacovigilance centres (NPCs) with regard to spontaneous reporting of adverse drug reactions (ADRs) associated with herbal medicines.

Method: A structured questionnaire for data collection was designed and developed. The final sampling frame comprised the NPCs of 71 official and 13 associate member countries of the WHO Uppsala Monitoring Centre (UMC) programme. Seven follow-up mailings were sent to non-responders at 4-week intervals after the initial mailing. Data were entered into Microsoft Excel version 10 for storage and analysed using SPSS version 13. Preliminary results have been presented previously.[1]

Results: Responses from 62 countries (74%) were received. In total, 54 (87%) respondents accept spontaneous ADR reports for herbal medicines. Of these, 17 (31%) specifically encourage certain reporter groups to report suspected ADRs associated with herbal medicines and 2 (4%) said they have a separate spontaneous ADR reporting form for herbal medicines. In response to statements regarding herbal ADR reporting, 61% of respondents agreed/strongly agreed that their current ADR reporting form needs modifying in order to effectively collect data on suspected herbal ADRs, 27% agreed/strongly agreed that there should be a separate ADR reporting form for herbal medicines, and 61% disagreed/strongly disagreed with the statement that there should be a separate ADR reporting scheme for herbal medicines. Of the 59 spontaneous ADR reporting forms and 45 sets of guidelines obtained, 5 (8%) forms and 14 (31%) guidelines specifically mentioned the term herbal medicines.

Conclusion: Current practices of NPCs for spontaneous reporting of ADRs associated with herbal medicines vary. Few NPCs undertake activities specifically to encourage reporting of suspected ADRs associated with herbal medicines. However, there is support from NPCs for modifying existing spontaneous ADR reporting forms to improve the collection of information on herbal medicines.

Keywords: Pharmacovigilance, adverse drug reaction reporting, herbal medicines

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5. Herbal Medicine Usage In New Zealand: a Pilot Study Focusing on Customers of Community Pharmacies

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Background: A number of studies have shown that the use of herbal medicine is increasing in many western countries but very few have looked specifically at New Zealanders' usage of these remedies.[1]

Aims: The aims of this study were to investigate the usage of herbal medicines in New Zealand by customers of community pharmacies and to identify the potential for interactions between herbal medicines used by pharmacy customers and other medicines they might also be taking.

Methods: General information about the usage of herbal medicines throughout New Zealand was obtained by surveying a randomized selection of community pharmacy customers who were asked to complete a written questionnaire that asked for details of herbal medicines used, why and how used, together with general demographic data. Specific information about the potential for interactions between herbal and other medicines being taken concurrently by pharmacy customers was obtained by means of structured face-to-face interviews with 50 people, conducted in three pharmacies in different suburbs of a single city by one researcher.

Results: Over 70% of those surveyed had used one or more herbal medicines in the previous twelve months, mainly to promote well-being and prevent illness (particularly upper respiratory tract infections). Few had informed their pharmacist (45%) or doctor (37%), or had consulted their health practitioner even when they were taking other medicines concurrently (42% consulted pharmacists, 15% consulted doctors). Of those using herbal and other medicines concurrently, 24% were using combinations that could, potentially, interact adversely.

Discussion: Despite the limitations of sample size, the results of these studies indicate that the general pattern of usage of herbal medicines in New Zealand is similar to that in other western countries, as is the potential for harmful interactions between the various medicines being used.[2,3] A larger study is now planned, one that will take into account the potential for sampling and other biases, and that will also attempt to clarify the clinical as well as the potential significance of any herb-drug combination identified.

Conclusion: This pilot study has indicated that many pharmacy customers are currently using herbal products and that at least some of these products have the potential to interact adversely with other medicines they might also be using. Pharmacists are thus ideally placed to provide their customers with accurate, informed and unbiased information about herbal products, provided that they are willing and able to undertake the necessary training to do so.

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6. Rongoa Maori: New Zealand's Medicinal Plants: Creation and Use of a Database

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Background: New Zealand is thought to be home to about 1970 plant species, of which about 1600 are considered indigenous.[1] At least some of these plants may have been used for generations by the indigenous people, Maori, although the identification and specific usage of these has been hampered by the lack of a written Maori language, prior to European settlement in the 19th century.[2,3]

Aims: The overall aim of this study (which is on-going) was to glean information from both published and other sources about the folklore of Rongoa Maori (plant medicine usage by Maori) and compare this traditional usage with what is known of the chemical composition of these plants. The secondary aim was then to carry out more detailed investigations of selected groups of plants to determine whether an identified traditional use could be supported by their pharmacological activity.

Methods: Literature cited by those involved in the debate about medicinal plant usage was sourced from historical and other records; more recent publications were identified through conversations with representatives of local Maori, some of whom were also useful sources of additional information that had been handed down from one generation to the next. The more conventional, scientific literature was then searched for information about the chemical constituents of plants highlighted by traditional usage as being of medicinal importance. Some plants had also been investigated pharmacologically; information about these was sourced from databases such as Medline.

Results: The New Zealand Medicinal Plants database thus created, although still far from complete, has been used to identify groups of plants that might be effective against certain conditions so that these might be tested to determine whether the cited usage and known chemical constituents were in accord with the results obtained from pharmacological and other investigations. This has involved a certain degree of intuitive guesswork because the terminology used to describe disease in the 19th century is not necessarily that used in the 20th and 21st. One such study involved the investigation of plants that might stimulate uterine muscle. Three of ten plants identified via folklore and chemical constituents demonstrated significant pharmacological activity.

Conclusion: As herbal medicine usage becomes more popular in New Zealand as elsewhere, it is increasingly important that accurate information, based on scientific investigations as well as traditional usage is readily available to the general public. The New Zealand Medicinal Plants database is one such tool.

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7. Changing With Herbs: Analysis of Prescribing by Herbal Practitioners in a Pilot Randomised Controlled Trial of Treatment During the Menopause

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Introduction: In most traditions, herbal practitioners prescribe and dispense mixtures of several herbs which are formulated for the individual patient. This can make analysis of prescriptions complicated if safety concerns arise. In addition, there is a lack of data on current prescribing practice in western herbal medicine.

A pilot randomised controlled trial of treatment by herbal practitioners of women with menopausal symptoms has recently been completed. This provided the opportunity to analyse a series of individual prescriptions. In the light of current safety concerns about the usage of products containing *Cimicifuga racemosa*, Black Cohosh,[1] it was considered useful to estimate current dosage in herbal practice. A Review of Herbal Practice showed that *Cimicifuga racemosa*, Black Cohosh is used by some herbalists in menopausal complaints.[2]

Aim: The aim of this part of the study is to describe and analyse the prescribing practice of the three herbal practitioners

Method: The participants were post-menopausal women aged 46–59, not taking hormone replacement therapy or any other treatment for menopausal symptoms, who were recruited by letter from a general practice list. After entry into the trial, women were block randomised into treatment (15) and control (30) groups. Treatment consisted of 6 consultations over 5 months and the control group were offered treatment after 4 months. The three herbalists were Members of the National Institute of Medical Herbalists. Change in menopausal symptoms was measured using the validated Greene Climacteric Scale.[3] Prescriptions were analysed for 14 women in the treatment group and 20 women in the control group. A series of 6 prescriptions for each of 34 women were available for analysis.

Prescriptions were entered on a database to record the number of herbs, combinations, dosage and rationale. For *Cimicifuga racemosa*, sources of tinctures were noted and daily dosage was estimated. Data on *Cimicifuga racemosa* collected during a Review of Herbal Practice was included.

Results: A substantial number of herbs were used in a range of combinations and the dosage of *Cimicifuga racemosa* is reviewed.

Conclusion: The study shows that it is possible to analyse herbal prescriptions and that the information can add to the safety profile of medicinal plants.

Discussion: Data from clinical trials does not, in itself, demonstrate safe practice as the number of participants is small but can contribute to evaluation of the safety of current practice in herbal medicine.

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8. Polyintoxication due to Plants and Drugs: Essay of Method of Analysis of Clinical Features to Assess Causal Relation ADRs

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Background: Polymedication and self medication are public health issue in Africa. To assess ADRs in Cote d'Ivoire we used French imputation method. The causality assessment of evens occurred in polymedication and self medication is difficult The aim of this study was to apply simple method to assess drug causality by compared analysis of clinical features.

Material and methods: In 2002 we recorded six cases related to the use of plants and drugs in intensive care of two teaching hospitals in Abidjan (Cote d'Ivoire - West Africa). The clinical features related to the plants or drugs of our study were compared with those from a database.

Results: All of them were young and female sex. Their age varied from 16 to 44 years. Plants were associated with chloroquine or paracetamol or diclofenac or amoxicilline or ascorbic acid. The clinical features observed were mainly abdominal pain syndrome which was mostly associated with either drunkenness or neurosensorial troubles (buzzing in the ears, blurring). A surgical abdominal and a neurological syndrome with state of shock were also observed. In four cases there are an agreement with French imputation method for drug associated. One case was related to plant and then in one the conclusion of responsibility of plant and drug was impossible.

Conclusion: Theses preliminary results should be improved by others studies. This clinical approach could provide an opportunity in developing countries.

Keywords: Herbal medicine, Intoxication, Imputation

9. Effective and Cost-Efficient Pharmacovigilance Activities for Herbal Medicinal Products

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Introduction/Background: There is an interest on innovative and cost-efficient operational procedures for routine pharmacovigilance activities for generic herbal medicinal products, allowing identification of case reports of serious ADRs in literature databases and preparation of PSURs. Methods: The pharmacovigilance activities are based on a differentiated and cost-efficient system for the retrieval of potential cases for expedited ADR reporting to regulatory authorities and the development of two IT-assisted PSUR templates which implement the current international and national requirements. Despite these regulatory specifications it is possible to generate a basic version covering the minimal requirements as well as a complex version addressing all topics required in the current ICH guidelines. Results: For the identified case reports, electronic ICSR/ADR reports are generated and a causality assessment based on the primary publication and/or follow-up information is performed. Synergy effects will be outlined when performing this search for generic medicinal products. Conclusions: This system of pharmacovigilance activities should be common to many different pharmaceutical companies with respect to the medical and scientific literature and could be easily used by third party service providers as well as by pharmacovigilance departments of marketing authorisation holders.

10. Pharmacovigilance of Herbal Medicines in Australia

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Background: In Australia, herbal, vitamin, and mineral products with therapeutic claims are classified as 'complementary medicines' (CM) and regulated by the Therapeutic Goods Administration (TGA). Exempt from regulation are extemporaneously-compounded preparations, and those imported for personal use.

The vast majority of CMs regulated by the TGA are considered 'low risk' and may only contain active ingredients from a specified list, are restricted in the claims they can make, and are required to be manufactured at licensed premises under conditions of GMP. Spontaneous reports of suspected adverse reactions (ADR) to complementary medicines are monitored at TGA by the Adverse Drug Reactions Unit (ADRU).

Objective: To present an analysis of ADR reports mentioning herbal medicines, received by ADRU during 2004–2005.

Results: In the 2 years 2004–2005, ADRU received 19,279 ADR reports, including 500 reports (2.6%) implicating at least one CM, of which 263 reports (1.4%) mentioned at least one herbal medicine. 123 of these 263 reports (47%) also implicated non-herbal CM ingredients, mainly vitamins and minerals. These 263 reports represent about 21% of all herbal medicine ADR reports in the Australian database, which dates back to 1971.

Reporting patterns for herbal medicines for 2004/2005 show, as expected, relative underreporting from hospitals (21% of CM reports were from hospitals versus 32% of all reports) and overreporting from consumers (8% for CMs versus 2% of all reports). However, the bulk of CM reports were received from industry (31%), hospitals (21%), general practitioners (20%), and community pharmacists (11%).

The reports in 2004–2005 mentioned 273 individual herbs, appearing 1069 times (average 4.1 herbs per report), of which 132 herbs appeared in only a single report. The most commonly-reported herbs in ADR reports in 2004-2005 were: ginkgo (37 reports); ginger (27); milk thistle (26); siberian ginseng (23); garlic (21); and echinacea purpurea (21).

During this time, there were 5 reports of interactions between herbal medicines and warfarin; herbs implicated were cranberry (2 reports), garlic (1), celery (1 report; glucosamine with chondroitin also involved), and multiple herbs (1 report).

Discussion: Herbal medicines are used widely in Australia, with 21% of the adult population estimated to use at least one herbal medicine per year.[1] Australia has a well-developed spontaneous reporting system, however, the low volume of reporting for herbal medicines, combined with the use of multi-ingredient preparations, mean that it is often difficult to draw significant conclusions from an analysis of spontaneous reporting data. Consideration is being given to means for improving pharmacovigilance of herbal medicines.[2]

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11. Side Effects of *Thymus vulgaris* L. Reported to Iranian Pharmacovigilance Center

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The genus *Thymus*, which belongs to the Lamiaceae family, consists of about 350 species widespread around the world. In Iran, 14 species exist, among which 4 are endemic.[1] *Thymus vulgaris* cultivated with a common use as medicinal herb and food additive.

The major components of the essential oil of *T.vulgaris* are thymol, carvacrol, flavonoids and phenolic acids.

Some species of *Thymus* are used in Persian folk medicine as an expectorant, carminative, anti spasmodic and for control of diarrhoea and enuresis in children.

Many studies with these geneses especially T.vulgaris has shown various activities such as bronchoantispasmodic, expectorant and antibacterial effects.[2] These effects have been principally attributed to the volatile oil and flavonoid constituents. However the adverse effects of this plant include dermal and mucous membrane irritation.

With this manuscript we report the cases collected in Iranian Pharmacovigilance center via spontaneous reporting about the side effects of *Thymus vulgaris* as an herbal medicinal product. *Thymus vulgaris* used as an expectorant in Iran.

There were four cases of *Thymus vulgaris* induced adverse reactions reported to Iranian Pharmacovigilance Center. The reported reactions involved urticaria, rash, face oedema and pruritus. The indication for using the product was cough in all four cases. The causality assessment based on WHO criteria revealed that 3 reports were probable and one case identified as certain with positive rechallenge. Although allergic reaction to this product is unlikely to happen, immediate medical attention is needed if it occurred. Regarding the low reporting frequency of adverse events induced by herbal products in comparison with those induced by chemical agents in Iran, these reports are of high importance both quantitatively and qualitatively, indicating that the safety of herbal products need more attention. According to the findings related to cases reported, designing a detailed program by Pharmacovigilance centers to detect, assess, report and prevent herbals-induced-adverse events is highly recommended.

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12. Surveillance of Adverse Events to Herbal Preparations: The Italian Experience.

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Introduction: In Italy phytotherapy is used by 4.8% of the adult population and 2.5% of children (data from a year 2000 survey). Adverse reactions to herbal medicine and possible interactions between herbal preparations and synthetic drugs have been pointed out in the recent years. Objectives of this study were: to collect adverse events to herbal medicine, to sensitize health personnel on use of herbal preparations by their patients and users on a correct utilization of these products.

Methods: Since April 2002 a surveillance of adverse events to herbal preparations, based on spontaneous reporting, has been set up. Forms can be downloaded from the web from selected sites and then sent to the Istituto Superiore di Sanità, where they are analyzed by a scientific committee of experts. Periodical reports focused on problems of particular interest are forwarded to the Italian Medicines Agency.

Results: From April 2002 to October 2005 we received 154 spontaneous reports. The male to female ratio was 0.4, and the mean age was 40 years (44 in women and 32 in men). Twenty nine percent were related to adverse reactions followed by hospitalization, 6% to life-threatening reactions. Dermatological, cardio-vascular, neurological and gastrointestinal were the most frequent reactions. Among the latter 10 hepatitis were reported. The main indications for use of herbal preparations were upper respiratory tract infections; weight loss, psychological distress (insomnia, depression, anxiety); gastrointestinal problems. Ten reports (6%) were related to allergic reactions to propolis containing products.

Conclusions: Products containing herbs are often used in italy for therapeutic purposes as self-medication. Our surveillance pointed out that reactions to herbs are often serious and they involve children, pregnant women and the elderly, groups of population particularly sensitive to the wrong belief that “natural” means “safe”. It is important to provide correct information to patients and health personnel on safety of herbal preparations.

13. Herbal Safety: Toxicological Evaluation and Reports from the Poison Control Centre of Milan, Italy

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Introduction: The Poison Control Centre of Milan is the leading toxicologic center in Italy, receiving about 58 000 requests of consulence every year for suspected acute poisonings. These calls come from physicians or directly from patients at home: so the PCC is an important observatory of toxic effects due to every kind of substance used (correctly or uncorrectly) by people.

Methods: A review of 1378 calls concerned to alternative medicine remedies and collected from January 2001-June 2005 was analysed to assess the magnitude of toxic and adverse effects due to herbal (795 calls) or homeopatic (538 calls) preparations in Italy.

Results: The most severe clinical cases were related to adverse reactions during normal therapeutic use (i.e. rhabdomyolysis, several hepatic damage) or to acute poisonings due to contamination or adulteration with toxic substances.

Among these cases there are two lead poisonings from ayurvedic preparations, at least four atropine-like poisonings due to an indian batch of Coleus Forskolii contaminated with tropane alkaloids and a life-threating gastric haemorrhage in a child treated with an herbal syrup containing salicylates.

Several poisonings are due to herbal sold in health food stores or over the internet for recreational use, as Salvia Divinorum or Argyreia Nervosa.

Conclusions: In spite of the supposed safety of herbal and homeopatic remedies, it's really difficult to make a correct toxicological evaluation of these products.

It's hard or impossible to find information about pharmacological action, kinetics, therapeutic and toxic dose of botanical principles, expecially if they are not included into the European Pharmacopea (i.e. guggul).

Moreover, botanical preparations sold by herbalists are often extemporaneous mixtures of herbs, lacking a label, while the labels of many packed products are unclear or incomplete and we know that these preparations may be adultered and real composition may be quite different from that declared.

The surveillance of herbal medicines appears to be more difficult than pharmacovigilance of conventional drugs, and the laboratory assessment of active contents is necessary to ascribe clinical effects to a toxic or adverse action from these medicines.

The identification of dangerous products by Poison Control Centres and the quick alert of Authorities allows to take urgent actions to protect public health.

14. Perspectives on Adverse Drug Reactions and Pharmacovigilance of Herbal Medicines in Nigeria.

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Herbal medicines are widely used in Nigeria for maintenance of health, prevention and treatment of diseases. There is an increase by the general public in the use of herbal medicinal products. One of the reasons for this increasing use is the belief that these medicines are inherently safe and non toxic.

NAFDAC, the country's drug regulating body has created awareness on the need for pharmacovigilance of synthetic drugs and adequate reporting of adverse drug reactions (ADR) with the setting up or a national pharmacovigilance centre. Applying current pharmacovigilance tools for synthetic drugs on herbal medicinal products possess a lot of challenges especially adequate reporting systems. There are several problems associated with sourcing, identification, naming, formulation and utilization of herbal medicinal products. NAFDAC is enlisting herbal medicinal products to ensure good manufacturing practices.

Random interviews/Focus group discussions were conducted with 320 users of herbal remedies in different locations within the northern and southern regions of Nigeria by means of questionnaires. These focused on frequency in use of herbal medicines, whether they seek professional advice on use of products, awareness of ADR on synthetics and herbal medicinal products and action taken after experiencing ADR. 192 respondents (61.2%) are aware of ADR on synthetics. Only 72 respondents (22.5%) will consult the medical practitioner for serious ADR to conventional medicines because of public enlightenment and awareness but not for a similar ADR to a herbal remedy as herbal medicines are considered 'safe' due to their inherent properties and any ADR is not scientific but rather spiritual.

It is concluded that consumers of herbal medicines do not associate ADR with herbal medicinal products. This has a lot of implications and challenges for pharmacovigilance of herbal medicinal products. There is need for public enlightenment as currently done for synthetics and development of schemes linked with both the practitioners and patients to optimize safety and spontaneous reporting of ADR.

15. Toxicological Studies on the Purified Protoberberine Alkaloidal Fraction of *Enantia chlorantha* Oliv (Annonaceae)

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We have examined the cumulative effects of the protoberberine alkaloid fraction (AF) of the stem bark ethanolic extracts of *Enantia chlorantha* on some body tissues and organs as well as on certain biochemical and metabolic parameters in mice. Acute and sub chronic toxicity studies were carried out in 120 mice using oral and intraperitoneal administrations.

Fatality was not recorded in mice injected intraperitonealy with 100 mg kg−1 and 150 mg kg−1 dose level but larger doses resulted in death and the mean lethal dose (LD50) of 200 mg/kg was recorded. Daily monitoring of the mice subjected to sub-chronic toxicity studies showed neither behavioral/untoward reactions or death in any of the animals.

The histopathological examination of the test animals when compared with the control revealed that, the sub-chronic use of the alkaloidal fractions does not have any pathological effects (lesion) on the organs examined (the stomach, the kidney, the oesophagus and the liver) except the lungs which showed mild and moderate oedema. The biochemical and metabolic analysis of the mice plasma did not show any significant difference when the corresponding values for the test mice were compared with the control mice ($P>0.05$) at the end of the 14 days treatment using both 20 mg kg−1 and 2 mg kg−1 dose levels

The results obtained in this study suggest the relative safety of short-term use of preparations containing *E chlorantha*, a very popular antimalarial herbal remedy in Southern Nigeria.[1]

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16. Trends in the Use of Herbal Medicines by Traditional Birth Attendants (TBAs) in South-Western Nigeria.

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Medicinal plants are the primary source of medicines used by Traditional Birth Attendants in Nigeria (Sofowora, 1982). Several medicinal plants of global importance originate in the country. For example, Calabar bean (Physiostigmone venenosum) was traditionally used in Nigeria.

The purpose of the study the trends of Traditional Birth Attendants in South--Western Nigeria.

Three hundred questionnaires were distributed to TBAs in the South Western geographical zones of Nigeria comprising Oyo, Ondo and Lagos States. Sixty-eight percent of the respondents were women while 32% were men.

Fifty-nine percent of the respondents refer cases to orthodox doctors while 41% don't refer cases. The later group may not want to refer their cases because of the unhealthy working condition that exist between them and the orthodox doctors. (Wirth, 1995).

Majority (73%) of the respondents document their cases. There is relatively high level of literacy amongst the respondents (68%). This probably influenced the result on collaboration as 77% of them are willing to collaborate with orthodox doctors. Eighty-four percent use only manual manipulation for their diagnosis. This is related to the symptoms observed. (Carpenter et al., 1995). The long duration of recovery for 75% of the respondents reveals one of the deficiencies of Traditional Birth attendants although they enjoy unwaning popularity.

Key Words: Trends, TBAs, Herbal Medicines, South-Western Nigeria.

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17. Expert Reports on THMPs and Pharmacovigilance Planning

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Introduction/Background: There is a need of an analysis and a proposal how to do the bibliographic review of the safety data together with an expert report with respect to the different body of evidence for the various THMPs. Based on the assumption that a uniform format with the aim to cover all evidence derived from the research will not be adequate for a substantial number of traditional used herbal substances, simply because there is no data to report, another concept should be favoured.
Methods: In view of the information statements given for a THMP regarding benefit and risk there should be a justification for each single statement which is based on the practical experience and/or on scientific data in a tabulated format. The expert report may independently go in detail and present the relevant data on safety issues.
Results: Obviously the amount of data with relevance to the safety differs between herbal medicinal substances used and for a significant part of them – especially for THMPs – there might be only the patients' and physicians' experiences made in the past which contribute substantially to the general safety assessment of the drug. On the other hand there are phytotherapeutics with a huge background of preclinical and clinical research mainly from recent investigations.
Conclusions: The pharmacovigilance planning issue is primarily not related to THMPs because often no evidence for safety related findings is available. However, a profound assessment of the safety situation is obligatory and has to be the reference for the plans on the pharmacovigilance activities even though no specific safety studies have to be planned.

18. Five Cases of Hepatitis Associated with a Chinese Herbal Product

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Background: We report a series of five cases of hepatitis with jaundice associated with the use of 'Shen Min' a medicinal herbal product from the USA. This product contains a single herb extract of *Polygonum multiflorum* (He Shou Wu) and is marketed for self-medication as a hair tonic in capsule form. The processed form of He Shou Wu is traditionally used in Chinese medicine as a tonic, for weakness of the lower back, nocturnal emissions, insomnia and premature greying of the hair.[1] Previously reported adverse effects include nausea, abdominal distension and loose bowel movements.

Table II. Summaries of case reports

Patient	Age/sex	Duration of use	Co-medication	Liver function tests		
				ALT	AST	GG
1	40y/male	2 mo	Chitosan	2467	3000	198
2	39y/female	4–6 mo	Melatonin		751	140
3	69y/female	3 mo	None	2122		
4	50y/female	4 mo	Thyroxine oestrogen patch HRT	1174	1026	
5	38y/female	5 mo	Calcium multivitamins	1698	1487	Normal

Discussion: In previous reports of hepatitis associated with *Polygonum multiflorum*[2,3] the anthraquinone glycosides were thought to be the causative constituents as they can form highly reactive anthrones in the liver. However, when used as a hair tonic, Polygonum is normally processed to reduce the anthraquinones and the laxative properties of the herb. Analysis of the product used by these patients showed that the anthraquinones were below detection level, so it is unlikely that these are the causative agents. No other hepatotoxic ingredients could be identified, and these five cases appear to be idiosyncratic reactions.

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19. Plants Toxicology Databases

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Introduction: study of plants toxicity and adverse reactions is essential to avoid harm associated with their use. Ensuring that correct nomenclature is used for implicated plants is the first and the main step in identifying them.

Goals: to summarize standard botanical names with their vernacular ones (French common names, Arabic common names and Moroccan common names) for 'Botanicus': the first database and relevant toxic plants data in monographs form named 'Phytotox' via a searchable electronic second database.

Methods: plants included in this project were those which were associated with poisonings and adverse reactions notified to Moroccan Poison Control Centre and Pharmacovigilance (1980–2004) and mainly those which are reputed to be toxic via the literature. Electronic databases are based on Access system.

Results: Botanicus includes 290 botanical names and their 2314 common names, as well as their plant family. The second database or Phytotox includes photographs, lists of toxic plant parts, toxic active principles or toxic chemical constituents, signs related to acute poisoning for each plant studied (92 plants), toxic dose if available and management of poisoning.

Conclusion: The two databases will provide emergency physicians, clinical toxicologists, all health professionals and scientists with information on the toxicity of plants, including a full toxicity profile to assist in providing fast and appropriate answers to questions concerning adverse effects associated with plant use.

20. Isolation and Investigation of Surface Activity, Membrane Toxicity and Absorption Enhancing Effects of the Total Saponins from *Acanthophyllum korshinskyi*

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Introduction: Saponins are plant originated glycosides with surface activity and hemolytic effects. In recent years some plant saponins have been evaluated as absorption enhancers of poorly absorbable drugs such as peptides and proteins.

Objectives: In this research total saponin (KTS) was extracted from the roots of *Acanthophyllum korshinskyi* and its surface tension lowering, membrane disrupting and absorption enhancing effects were studied.

Methods: The plant was collected from North-east khorassan and its roots were dried under appropriate conditions. The dried roots were grinded, defatted by petroleum ether followed by several extraction steps and finally the extracted saponin was freeze dried. Membrane disrupting effects of the total saponin was investigated using human red blood cells by determination of percentage hemolysis using spectrophotometer at 540 nm. Surface tension lowering effects of saponin was determined by capillary rise method. Also a Franz diffusion cell with rabbit duodenum as a model membrane was designed to study the enhancing effects of total saponin on drug transport through rabbit intestine using phenol red (PR) as a water soluble model drug.

Results: KTS at a concentration of 25 μg/ml induced complete hemolysis at 25°C. Also KTS decreased the surface tension of water in a concentration dependent manner and its cmc occurred at around 6–8 μg/ml. KTS solutions at concentrations of 0.1–0.5% w/v were used as penetration enhancer and induced significant increase in the permeability of mouse skin to phenol red as a model drug.

Conclusion: It can be concluded that KTS could possibly be used as an absorption enhancer in the formulation of poorly absorbable drugs. However potential membrane toxicity of this compound should be taken into account.

Keywords: Acanthophyllum, Saponin, absorption enhancer, Surface tension, Haemolysis

21. Views on Effectiveness and Safety of Traditional Chinese Herbal Medicines (TCHMs): Preliminary Analysis of Semi-Structured Interviews with TCHM Shop Employees

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Background: In the UK, unlicensed Traditional Chinese Herbal Medicines (TCHMs) and TCHM consultations are available in high-street TCHM shops without the involvement of a statutory regulated healthcare professional. Several high-profile safety concerns have occurred associated with TCHMs provided by TCHM outlets,[1] yet there is a lack of research into aspects of TCHM practice that are relevant for pharmacovigilance.[2]

Aims: To explore TCHM outlet employees' views on and experiences with safety and effectiveness, and to identify their risk management strategies, with respect to TCHMs.

Methods: Face-to-face semi-structured interviews using a questionnaire designed for this purpose. TCHM retail outlets (n=12) were systematically identified in one London postcode area and staff were invited to participate. Six interviews were carried out in English/Chinese with 2 TCHM practitioners, 1 shop manager and 3 shop assistants in 4 participating outlets. Interviews were transcribed verbatim (and translated into English where necessary). Data are summarized and categorized manually using a framework approach comprising key themes identified *a priori* and emerging from the data.

Results: Participants described several conditions, including skin conditions (e.g. psoriasis, eczema), stress/anxiety, and for boosting energy and the immune system, for which they believed treatment with TCHMs is most effective. Compared with 'Western' medicines, interviewees considered TCHM to be more effective for chronic conditions, and most considered "acute" conditions (e.g. "broken limbs", as "painkiller", acute appendicitis and other "emergency situations") to be difficult or inappropriate to treat with TCHM. Interviewees also identified specific patient groups ("babies", pregnant women and individuals with diabetes) for whom they would not recommend TCHMs. Interviewees typically considered TCHMs to be "safer" than Western medicine, and believed that TCHMs were "always safe", "did no harm to your body" and "had no side effects", although some acknowledged that, for example, "with any medicine, too much is not good". Adverse effects occurring during TCHM treatment were considered part of the normal response to treatment. Other "complaints" described included (unpleasant) taste, lack of effectiveness and difficult preparation methods for TCHMs. In response to customers reporting ADRs, staff's actions included asking customers to stop taking the TCHMs, consulting colleagues, and telling patients to continue treatment as the effect (e.g. diarrhoea) is "expected".

Conclusions: TCHM outlet employees in London use several strategies to reduce the risk of harm from use of TCHMs. However, there are areas where interviewees described behaviours or expressed opinions suggesting a lack of awareness of safety issues.

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22. Can Traditional Chinese Herbal Medicine Retail Outlets in London, UK, be Identified Using Public-Access On-line Sources?

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Background: Several high-profile safety concerns are associated with unlicensed traditional Chinese herbal medicines (TCHMs) sold/supplied by TCHM retailers and practitioners.[1] Rapid communication of information on safety concerns to stakeholders is important to protect public health. However, there is currently no statutory regulation in the UK for TCHM retailers or practitioners, and a comprehensive list of premises and individuals involved with the sale/supply of TCHMs is not available. This information could help in developing efficient herbal safety communication systems.

Aims: To explore the feasibility of using the Yellow Pages online telephone/address directory (http://www.yell.com; YP) and two TCHM organisations' (Register of Chinese Herbal Medicine, Association of Traditional Chinese Medicine; RCHM/ATCM) members lists to identify TCHM retailers in London.

Methods: YP does not include a specific category for TCHM (or similar term). Searches for potential TCHM outlets used the words "Chinese medicine" combined with the 118 London postcode areas (e.g. NW1). This strategy retrieved addresses listed under the categories "Alternative Health" (AH) and "Clinics". Those listed under AH were entered into Excel; exclusion criteria were applied for non-TCHM complementary/alternative medicine providers/organisations. Inclusion criteria (appearance of oriental-type words/characters in their names possibly associated with TCHMs) were applied to remaining names/addresses. TCHM practitioners with London addresses were obtained from the RCHM/ATCM lists. Data from YP and RCHM/ATCM were combined to achieve a final list of potential TCHM retailers. Data from YP and RCHM/ATCM were collected during May and December 2005, respectively.

Results: After excluding duplicates, 904 AH providers (AHPs) were identified from three AH subcategories ('*Herbalists*', '*Acupuncture Practitioners*', '*Complementary Therapies*') in YP. Of these, 451/904 (49.9%) AHPs were excluded; 208 (23%) were classified as potential TCHM retailers, 103 of which used oriental-type words in their business names (e.g. 'Chinese'); 245 (27.1%) were unclassifiable. In total, 261 London addresses were identified from RCHM/ATCM. In total, 86/208 (41.3%) potential TCHM retailers found in YP were identifiable from RCHM/ATCM; 20/245 (8.2%) unclassifiable AHPs were found in RCHM/ATCM. Overall, 383 potential TCHM retailers were identified from YP and RCHM/ATCM combined, although another 225 AHPs could not be definitively excluded.

Conclusions: A substantial number of premises in London potentially is associated with TCHM retailing. Ongoing work aims to establish their involvement, if any, with the sale/supply of TCHMs. Use of multiple sources is necessary to identify potential TCHM outlets. On-line sources can identify obvious TCHM providers, but do not yield a definitive list of all TCHM retailers. This may be impossible to achieve without statutory regulation of TCHM practitioners and retailers.

Reference

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23. Reporting Adverse Events and Drug Interactions Associated with Natural Health Products: Development of a Theoretical Framework

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Introduction: In Canada, adverse events including drug interactions are voluntarily and spontaneously reported through the Canadian Adverse Drug Reaction Monitoring Program. Under-reporting is a major limitation with any spontaneous reporting system but especially with adverse events and drug interactions associated with natural health products (NHPs).
Purpose: To develop a conceptual framework for active surveillance of adverse events and drug interactions associated with NHPs. The objectives of the framework are to: 1. Identify major factors that influence adverse event incidence in users of NHPs. 2. Highlight important factors affecting a patient's decision to report an adverse event. 3. Hypothesize inter-relationships between the factors identified.
Methods: A framework was developed from a literature review on active reporting systems for over-the-counter and prescription drugs. Risk factors for adverse drug reactions and drug-herb interactions were determined from previous studies. Concepts uniquely pertinent to NHP study were extrapolated from previous literature on NHP users.
Results: An adequate theoretical framework for actively studying NHP adverse event and drug interaction reporting has not been previously established. Adverse event/drug interaction reporting for NHPs is divided into two phases: (ii) The occurrence of an adverse event/drug interaction and (ii) The decision to report. The first phase is influenced by several factors such as the individual patient's characteristics, their beliefs and perceptions about NHPs, characteristics of the NHP itself, as well as the method of use of the product. The second phase is influenced by the characteristics of the adverse event/drug interaction itself as well as knowledge of and access to reporting resources. Information sources are important for both phases
Conclusion: This framework will be used to develop an active surveillance model that will be pilot tested as part of R. Walji's PhD requirements. The project will attempt to test the feasibility of using active consumer surveillance to gather adverse event and drug interaction information on natural health products.
Keywords: natural health product; CAM (complementary alternative medicine); active surveillance; post-marketing; adverse event; adverse effect; ADR (adverse drug reaction); side effect; herb-drug interaction; SAR (suspected adverse reaction); pharmacovigilance.

24. Systems Biology: Scientific Evidence and a Novel Quality Control for Traditional Chinese Medicine (TCM)

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Key for worldwide registration and acceptance of Traditional Chinese Medicine (TCM) is the ability to provide scientific evidence in combination with a quality control system based on the bioactive ingredients. A Plant-to-Patient platform is described that is comprised of varies novel approaches based on Systems Biology to tackle these issues

The use of indigenous herbs is a very important concept for TCM materials medica production and specific areas are known to produce the highest quality herbs especially when Good Agricultural Practice (GAP) is practiced. In relation to the QC aspect a number of factors need to be considered besides the geographical source, such as variation in climate and soil factors which can influence the growth of herbal plants and consequently the composition patterns. In addition, the processing of TCM materials medica is also a very important part which has a history as long as traditional Chinese herbal medicine itself but needs to meet modern Good Manufacturing Practice. It underlines the importance of tools to accurately measure the composition of TCM products in order to guarantee the quality of herbs.

Modern scientific technology tools are now available to accomplish standardization of TCM products in order to achieve a high level of efficacy and safety, enhancing the introduction into the international markets. The complexity of ingredients and the aspect of synergistic bioactivities in TCM, limited the analysis for quality control so far only on major components for each herb and had no evidence for a direct relation with bioactive components. The systems Biology approach, a multi dimensional chemical and pharmacological approach enables linking of the complex metabolic profile of herbs with biological effects and is therefore a key for quality control of TCM materia medica, while providing simultaneous scientific evidence for the underlying efficacy. This is crucial for registration of herbal medicinal products such as under the new EU Herbal Medical Products guideline.

The approach is highlighted by a study using *Rehmannia glutinosa* (Di Huang), demonstrating how under controlled conditions variations can be induced and detected using herbal metabolite fingerprinting of herbs and extracts. Plants were grown under different temperature conditions in a green house to investigate the influence of climate and subsequent processing in different ways to study the effects for material medica of *R. glutinosa* post-harvest. GC-MS combined with principle component analysis (PCA) was used as analytical model for this demonstration model. In addition, the concept of linking biological activity to constituents in herbal products, using a systems biology approach, has been demonstrated in a cell based assay related to inflammation.

25. Pharmacovigilance: Quality and Assessment of Published Suspected Adverse Drug Reactions (ADR) of Herbal Medicines

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Background: According to the pharmacovigilance (PV) guidelines, each marketing authorisation holder (MAH) has to set up an appropriate system in order to collect, collate and evaluate informations about suspected ADRs. Concerning the scientific literature, the MAH is expected to screen and report to the authorities promptly published suspected (serious) ADR associated with the use of the active substances of its medicinal product(s). The screening of literature has to be done periodically in widely used systematic literature databases.

Objective: For to support a qualified risk management system and for to assess published ADRs of herbal products.

Methods: Two databases (Medline, Embase) are screened in monthly intervals since 2003 for almost 200 main herbal substances, used for herbal medicinal and homeopathic products. Database retrievals are performed by predefined search strings, combining i) a specific herbal substance search string, consisting of botanical, pharmaceutical and common name(s) and safety-relevant constituents (e.g.: hypericum, hypericum extract, hypericum perforatum, St. Johns wort, hypericin); and ii) a PV relevant search string: such as adverse/side effects, adverse reactions, case reports, interaction (as freetext or database specific descriptors and qualifiers). The reporting and assessment of the retrieved suspected ADRs is done according to the suggestions of the CIOMS working group V.

Table III. Results of database screening

Herbal Substance	Total number of suspected case reports in 3 years	Registered HMPs	Other herbal products	Product characteristic deficient	Patient's medicinal and drug history deficient
Gingko	12	11	1	8	7
Hypercium	9	8	1	8	5
Cimicifuga	4	3	1	3	1
Eucalyptus	4		4	3	1
Camphora	3	3			
Chamomilla	2		2	2	

Conclusion: Many papers reporting suspected ADRs of herbals have flaws. Very often not substantiated suspicions were found, which are not based on a thorough scientific procedure of assessment. External contractors and MAHs should precisely assess published suspected reactions before defining them as true ADRs.

26. Advances in Study of Nephropathy Caused by Chinese Herbs Containing Aristolochic Acid

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This is a summary of the research advances on the Chinese herbs containing aristolochic acid and the nephropathy caused by aristolochic acid. At present, more and more attention has been given to the Chinese herbs such as manchurian dutchmanspipe stem and tetrandra root and their preparations, which induced the impairment of renal function and other adverse reactions. This article makes a general view of the progresses in studying clinically and pathologically the Chinese herb preparations containing aristolochic acid and its acute toxicity, carcinogenesis, genic toxicity and the toxicity occurring beyond kidney, especially, the aristolochic acid nephropathy (AAN) in order that those Chinese herbs are used properly and standardizingly and the traditional Chinese medicine benefits the humans more efficiently. In China there are over 40 kinds of medicinal herbs and preparations that contain aristolochic acid, including aristolochia, dutchmanspipe root, tetrandra root and manchurian dutchmanspipe, etc. Observation shows aristolochic acid is incident to accumulation in vivo, which is the basis for chronic toxicity. When given orally to rats, aristolochic acid was mostly metabolized to aristolochic lactam. Drenched three months consecutively, it induced severe papilloma at the sinus of cardiac stomach and malignant pathological changes also occurred. Clinical observation shows, by taking extended lowdose of medicines containing aristolochic acid, the human can contract not only aristolochic acid nephropathy, acute or chronic, but also carcinoma, especially the cancer in urinary system. An adduct of deoxyadenosine aristolactam was found in the kidney tissues of patients with aristolochic acid nephropathy and this adduct was deemed to hold an activity of incurring mutation and carcinoma. Some researchers think the toxication mechanism of aristolochic acid is that the DNA mutagenesis in kidney tissue accelerates damnification and the fibrosis process, consequently leading to urethra epidermic cancer. The pathogenesis of AAN is still unknown, but two major hypotheses exist: cell toxicity hypothesis and kidney ischemia hypothesis. The author thinks the three major causes for aristolochic acid nephropathy are: unqualified Chinese herbal medicine prescribers, the discrepancy of medicament variety and dose amount and individual variation. Modern scientific experiments have validated, although strong evidence has indicated that akebia stem, especially manchurian dutchmanspipe stem, possesses kidney toxicity, manchurian dutchmanspipe stem in the amount stipulated by pharmacopoeia does not bring about pathological changes of kidney stroma fibrosis in rat, and manchurian dutchmanspipe stem will not cause kidney lesion if it is used within legal amounts. So we must attach great importance to the toxicity and side effects of Chinese herbal medicine, establish the dosage norms of aristolochic acid toxication and apply such medicines appropriately and reasonably.

Keywords: Chinese herbs containing aristolochic acid, aristolochic acid nephropathy (AAN), manchurian dutchmanspipe stem, toxicity, carcinoma in urinary system.

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