

SAFETY OF TRADITIONAL REMEDIES

Michael Heinrich

Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London, UK.

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Summary

Local and traditional systems of medicine have a great potential for improving health care at the local level. This review examines safety issues surrounding botanicals used in medical systems all over the world and discusses examples of safety issues associated with traditional remedies. Acute and chronic toxicity, drug interactions, adulterations, the quality of botanical products used and measures for quality control are at the centre of the discussion. The data is largely drawn from Europe and North America, but shows the overall need for proper monitoring systems for botanicals. Examples discussed in greater detail are pyrrolizidine alkaloid containing drugs, *Aristolochia* species (used in many regions of the world) as well as kava-kava (*Piper methysticum* G. Forst.). A user-oriented approach is needed resulting in applied research for the further development of such autochthonous resources (ethnopharmacy).

1. Introduction—safety of phytotherapeutic preparations

Local and traditional systems of medicine constitute a prime example of a 'life support system'. Normally traditional medicine is seen as a system of knowledge passed on orally and many of the features of traditional medical systems are similar in different cultures of the world. Medicinal plants are an important element of such traditional or indigenous medical systems. On the other hand Europe, and to a lesser degree China,

Japan and India, have seen development of *written* traditions on medicinal plants and their therapeutic potential. Some of these are specifically called 'traditional' (e.g. Traditional Chinese Medicine, TCM) and thus circumscribing what to include under the heading of 'traditional medicine' and what not is problematic. Practically all plant-based medications/formularies are based on local or regional traditions and with the writing down of such medications they simply became a *formally recognised* tradition and one which for later generations often became an established school of thought (or even a dogma, as in the case of Medieval interpretations of ancient Greek medicine). A variety of labels are used for these resources (botanical medicines, herbal medicines, medicinal herbs, traditional medicinal plants) and the remedies derived from such a resource (phytomedicines, phytotherapeutic preparations). Often these two groups are lumped together.

Overall there is good empirical evidence regarding isolated bioscientific aspects of such botanicals like data on the local or traditional use of many of these products (ethnobotany), for small molecule (bioactive) constituents (natural product biology) of such species and for certain types of *in vitro* or *ex vivo* effects (pharmacological data). On the other hand, few of the locally used medicinal plants are sufficiently well known to allow an assessment of their efficacy, pharmacological effects and safety. Specifically regarding European phytotherapy, there is a significant body of clinical evidence on the potential benefits and potential risks associated with the use of such products. The vast majority of this information relates to the use of specific botanical medicines formulated as phytopharmaceuticals often used in the same manner as conventional pharmaceuticals, usually under the supervision of a health care professional (often a physician and sometimes an alternative practitioners). While in some cases a huge body of evidence exists for the efficacy and safety of certain phytotherapeutic preparations (e.g. St. John's Wort – *Hypericum perforatum* L., Valerian – *Valeriana officinalis* agg. L.), there has been very little investigation of the clinical efficacy and safety of most botanical medicines and combinations of phytomedicines used throughout the Western world. The situation is even more difficult if one considers botanical preparations derived from African, American, Australian, or and to a lesser degree many Asian traditions, where the most significant gaps in our knowledge exist. One important aspect of many European health care systems is a close network of monitoring for adverse drug effects and interactions. In many cases this has resulted in the detection of such adverse effects—a field of research commonly termed 'pharmacovigilance'. In this review the focus is not on such relatively well monitored health care systems, but on local and traditional medical systems which normally are self-regulated or often not regulated at all. The examples are drawn from several medical systems, but most are in fact based on research conducted on the use of such preparations in Europe and North America, two regions with a long tradition in monitoring adverse effects of drugs. The general safety of commonly used European phytomedicines and drug interactions of such preparations is beyond the scope of this review and is covered in a recently published review.

An ethnopharmacological discussion on the 'Safety of Traditional Remedies' needs to look at the topic from a variety of angles. However, I argue that in each case the prime concern regarding the safety of traditional remedies has to be the patients' safety. Safety is, of course, not an absolute category. No treatment is without risk and an assessment

will always be based on the current knowledge about a botanical drug's or extract's pharmacological effect and clinical effectiveness, as is the case for licensed medicines. As a consequence and also since many botanical medical products are used by many different cultures throughout the world, I will discuss the matter focusing on individual plants and their safety profile, i.e. I will adopt an *ethnopharmacological* approach.

The meaning of the term 'toxicon' (Greek – 'of or for a bow') as such already points to other aspect of toxic substances: their use in hunting and warfare. Harmful effects of chemically defined drugs are well known. Since in this discussion the main interest is in the role of toxic medical substances in popular medicine, in indigenous societies or other systems of self health-care, a field based observational research and not a clinico-toxicological approach is the best basis for a discussion of these issues. From this perspective, we can heuristically distinguish three main groups meriting discussion: *acute and chronic toxicity* (including teratotoxicity, genotoxicity) as well as *interactions of the botanical with other* (botanical) *drugs or foods*.

In our case, acute toxicity relates to those toxic effects which can be observed immediately and where it will be possible to ascertain such effects through direct observation of toxic effects. Symptoms the patients will directly experience after taking the medicine allow her/him to directly link the medicine with the effects observed. Acute and chronic toxicity are biomedically defined on the basis of the experimental procedures used in order to detect such effects. Other effects commonly studied are teratogenic and genotoxic effects. Since little is known about the effects of traditional and local remedies, a pragmatic approach is used here in order not to overcomplicate the discussion.

Chronic effects are those which can normally not be observed directly, but which will only become apparent in epidemiological studies or using other biomedical tools long after the use of such a medicine (or after it has been taken for a prolonged period of time). In both cases toxic effects are included which are—according to the patients' or healer's perspective—in fact the desired effects, but which are due to a toxic action of the medicine as exemplified in case of azarcon and greta discussed below.

While chronic and acute toxicity of traditional and local medicines are reported occasionally, the last of the three categories relates to direct or indirect interactions between the medicine taken and any other medicine—a topic which has received practically no attention in ethnopharmacological research (see part 2.3). In this case the focus is on the effect the use of one remedy has on the pharmacological effects as well as the metabolism and clearance of other (plant derived or synthetic) medications. It is not only an issue with medicines, but also of relevance for example with certain foods.

The examples in the following are drawn from different cultures and are used to illustrate the general problem. Importantly, there is no clear distinction possible between a traditional medical system and other health care systems (see above), like the many systems of Complementary and Alternative Medicine (CAM). To complicate things further, what is a CAM remedy in one country, may in fact be an element of the established medicine in another. Thus none of these categories is fixed. Instead they are culturally constructed and consequently in this MS, the term traditional medicine is

used in its broadest sense, but in no way do I want to imply that this terminology fully covers all meanings of the concept 'traditional medicine'.

2. Examples of safety issue with traditional remedies

My very first personal encounter with issues relating to the toxicity of traditional botanical medical products dates back to the first weeks of my field work for a PhD with the Lowland Mixe of Oaxaca, México. One of the first plants documented ethnopharmacologically was a member of the Asclepiadaceae, *Asclepias curassavica* L. or blood flower. This plant is called 13 Equal (Majk Tekëk Tsom) in Mixe—a rather enigmatic name. The plant attracted one's attention not only because of the strange name, but also because it clearly was a species which the healers looked at with great respect. The general use of the white latex from the leaves and stems was in the treatment of constipation and as a general purgative. From a bioscientific perspective, it is well known to contain cardiotoxic cardenolides, a class of compounds widely distributed in the family. The healers' most notable and for me unforgettable comment about the plant was '*Tres gotas te curan, nueve te matan*' (three drops [of the white latex] cure you, nine kill you). As a consequence of this toxicity the plant had become less and less popular for this purpose and had been replaced with, for example, sodium bicarbonate or other milder acting purgative plants. The toxicity (and presumably also the desired pharmacological effect) is due to these highly active cardenolides.

This example highlights some crucial points:

- ◆ Clearly a small but significant part of traditional pharmacopoeias has very serious acute toxic effects and in this example, the healers were fully aware of it.
- ◆ In this case the direct observation of acute effects were presumably passed along over the generations.
- ◆ The example also shows the healers' keen interest to search for less toxic alternatives.

Another illuminating example of a botanical remedy's toxic effects was reported from Austria (Southern Tyrol)—one which looks at the general question from a medico-pharmaceutical perspective. Venous-occlusive disease was diagnosed in an 18-month-old boy who had regularly consumed a botanical tea mixture since the third month of life. The boy developed portal hypertension with severe ascites. Histology of the liver showed typical symptoms of serious hepatic deterioration. The tea contained peppermint and what the mother thought was coltsfoot (*Tussilago farfara* L.), a species commonly used in Europe in the treatment of respiratory symptoms. The parents believed the tea aided the healthy development of their child. Phytochemical analysis indicated high amounts of pyrrolizidine alkaloids (especially seneciphylline and the corresponding N-oxide). The authors calculated that the child had consumed at least 60 µg/kg bodyweight per day of the toxic pyrrolizidine alkaloid mixture over 15 months. Detailed macroscopic and microscopic analysis of the leaf material indicated that the child had actually been given another member of the Asteraceae, *Adenostyles alliariae* (Gouan) Kern. (an alpine butterbur), a species which looks superficially similar to coltsfoot (especially in the sterile state). This species had been erroneously gathered by the parents in place of coltsfoot. The child recovered completely within 2 months. A

similar, however, lethal case is known from Switzerland. In this case a pregnant women regularly consumed a tea presumably containing *Petasites hybridus* (L.) G., butterbur (instead of coltsfoot *Tussilago farfara* L., as the mother had assumed) resulting in the death of the newly born baby.

Of course, such examples are known from many regions of the world. For example, similar hepatotoxic pyrrolizidine alkaloids are present in the Mexican medicinal plant *Packera candidissima* (Greene) Weber.

Especially in northern Mexico and the Hispanic population in south-western USA, this plant is used for the treatment of kidney ailments and noted for its antiseptic properties. Phytochemical analysis showed the presence of high levels of pyrrolizidine alkaloids and their *N*-oxides in the root (0.76% dry weight) and the aerial parts (0.36% dry weight). Senecionine, integerrimine, retrorsine, and usaramine were identified in the aerial parts, while senkirine is the main PA in the roots.

The latter three examples illustrate two other crucial aspects:

- ◆ There is a need to monitor for chronic effects of botanical medical products popularly used.
- ◆ Adulterations, whether accidentally as in this case or in order to substitute one drug for another are a frequently overlooked risk if the botanical material is not assessed pharmacognostically.

Commenting on an early draft of this paper, Dan Moerman (U. Michigan) raised the question of how relevant such isolated cases are. Certainly, these cases are rare, but—especially for countries where no monitoring of adverse effects of botanical remedies is common and where health authorities have no or little power to regulate the use of certain phytomedical preparations—the overall number of cases is completely unknown and we can only speculate how many cases exist in any given country, region or community.

In countries or regions where the state does not provide adequate health care systems, the role and presence of local and traditional medical systems is likely to assume a much greater influence than in areas where (normal state-controlled) systems of pharmacovigilance have been implemented. These are, of course, also regions where private or state-run health care is in place and where these services are accessible to the majority of the population.

Consequently, raising the awareness of healers regarding the toxicity of their locally used botanicals and other medicines is a crucial step of developing a local health care system. While healers are—based on their experience (see above) —aware of these issues, there are no mechanisms in place to inform healers or other representatives of the local populations about the results of bioscientific and other academic or commercial studies. These three case studies illustrate ways to detect and study individual cases using observational single-case approaches; the following chapter looks at the problem from an epidemiological, anthropological and toxicological perspective.

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Biographical Sketch

Prof Dr Michael Heinrich, Head of Centre, Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London. Pharmacognosist, biologist (Dr. rer nat.habil, Univ. Freiburg 1989, 1997, Dipl. Biol, 1985) and anthropologist (M.A., Wayne State University 1982). He has many years of research experience in a multitude of aspects of medicinal and food plants, as well as at the interface of cultural and natural sciences and with a particular interest in the cultural basis of medicinal plant use in lowland Mexico and other countries. His current research interests include: medicinal and food plants of the Mediterranean basin, Mexico and adjacent countries; anti-inflammatory natural products focusing on transcription factors as molecular targets; quality, safety and standardisation of herbal medical products used in Europe; cognitive aspects of medicinal plant usage, and the history of (European) plant derived medicines.