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Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chains

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Herbal medicines and products derived from them are a diverse group of products for which different (and often limited) levels of evidence are available. As importantly, such products generally vary in their composition and are at the end of an often poorly understood value chain, which often links producers in biodiversity rich countries with the large markets in the North. This paper discusses the current regulatory framework of such herbal medical products (with a focus on the UK) and using examples from our own metabolomic research on *Curcumal longa* L. (turmeric, Zingiberaceae) how value chains impact on the composition and quality (and thus the safety) of such products.
Overall, our recent research demonstrates the need for studying the links between producers and consumers of commodities produced in provider countries and that plant metabolomics offer a novel way of assessing the chemical variability along a value chain.

The importance of herbal medicines and potential risks of their use

Benefits and risks of herbal medicines have been discussed widely and very often the debate is marked by strong opinions in favour or against their use. Despite of this debate health care professionals need to recognize that patients commonly use such products and that the general public considers them to be a safe and relevant source of health care products [1] . This debate not only has resulted in general calls for health care professionals' awareness but also, more specifically, in the development of strategies for developing clinical risk management [2] and a range of other proposals to reduce risks associated with their use. All this requires an understanding of some unique pharmaceutical, pharmacological, toxicological and chemical properties of such products. Not only are they, of course, complex mixtures, but the composition of these mixtures will also vary based on the way they are gathered or grown, processed and formulated. Based on the existing scientific evidence and stringent quality regulations, registered/licensed herbal medicinal products (HMPs) are not part of Complementary and Alternative Medicine (CAM). They are pharmacologically active medicines and need to be treated similarly to conventional medicines, requiring a paradigm shift by health professionals [3].

In the context of clinical pharmacology, it is essential to understand that there are in fact very different challenges that need to be resolved:

- An ongoing debate focuses on the quality of the products on the market. As shown here this is closely linked to the regulatory framework for such preparations. A product which marketed without any medical, pharmaceutical or other regulation is bound to be very different from one which is regulated, for example, in the context of a licensing or registration scheme.
- Even in a regulated context, the composition of products derived from the same botanical drug will differ unless very similar extraction and processing steps are followed.
- Potential acute toxicity remains a potentially serious risk in case of unregulated products (as exemplified by aristolochic acid derivatives and urothelial malignancies [4])

- A common concern, which first arose out of the interaction potential of St John's Wort [5] (*Hypericum perforatum* L.) relates to potential interaction risks of herbal medical products or food supplements with other medical products, a problem which is augmented by the lack of reporting of such use by the patients to the medical and pharmaceutical practitioners.
- In clinical practice there is an ongoing debate on how to engage with traditional use / health benefit and efficacy of preparations used by patients and the boundaries with SmPC-type indications and regulated uses.

Each of these challenges results in unique questions which in regulatory contexts are addressed in diverse ways. This overview offers a critical appraisal of current needs for quality assurance and safety monitoring based on the existing regulatory frameworks and highlights the need for classical quality assurance and modern metabolomics approaches in order to ascertain a safe supply with herbal medical products.

In this paper I argue that we need to look at these complex and biologically active mixtures in a new way. Understanding the quality of a product along the value chain from the primary producers to the end users could make an important contribution to understanding what constitutes a high quality product and in which cases on the other hand, there may be quality problems that need to be resolved. Such a debate is also linked to the livelihoods of the primary producers of such products (see below).

The regulatory maze

The regulation of herbal medicines varies greatly between countries and global regions. It is complex and constantly developing. For example, in the UK, until about 2008 *Ginkgo biloba* L. was considered a food while in Germany it has consistently been a medical product and in the USA it is a food supplement (Table 1). In the UK it now is, as in many other European countries, generally regulated as a traditional herbal medical product. Many established herbal medical products are commonly sold in the UK and other European countries and these are often derived from products which historically were used more in a local and traditional context (for example by a group of healers). Popular demand and industrial interests have created a market for such products and their much wider use requires a regulatory framework which allows a more stringent control of a product's quality and safety, and which ultimately should also result in evidence based uses (Figure 1).

In the UK and the rest of the European Union the Traditional Herbal Medicinal Products Directive (THMPD) 2004/24/EC (see - http://www.mhra.gov.uk) provides a mechanism whereby manufacturers of good quality herbal medicines can register these as medicinal products based on a tradition of use, i.e. while the evidence for efficacy may be limited the product is considered to be safe and will only be used for minor, self-limiting conditions. Restricted medicinal claims on the packaging and the patient information leaflet (PIL) are allowed (e.g. 'a traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including the common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only'). The tradition of use is based on evidence that a corresponding herbal product (i.e. one derived from the same botanical drug and prepared in a similar way) has been used traditionally for at least 30 years (15 years 'non-EU' and 15 years in the EU, or more than 30 years in the EU). Importantly, a full expert report on safety and a quality dossier specifying how the company complies with the regulator's quality requirements needs to be provided. Also good practice along the entire supply chain has to be guaranteed by the manufacturer (the pharmaceutical producer). Each package must contain detailed information approved by the MHRA and an approved patient information leaflet. Overall, the scheme provides an assurance that the patient is receiving not only a good quality product, but also more reliable advice on its use. Pharmacovigilance of HMPs must be ascertained by the producer and, consequently, HMPs are fully covered under the UK's Yellow Card scheme. In case of any adverse event or reports on interaction only products which are either registered under this scheme or fully licensed

Table 1

Regulatory status of five exemplary plant based herbal (medical) products in five representative systems. The data are based on the authors own census and on data from colleagues in the respective countries

	UK	Australia	Russia	USA	Germany
Ginkgo	Food supplement/traditional medicine	Listed medicine*	Food supplement	Dietary supplement	Medicine
Echinacea	Medicine/traditional medicine/food supplement	Listed medicine*	Medicine	Dietary supplement	Medicine
Cimicifuga	Traditional medicine	Listed medicine*	Medicine/food supplement	Dietary supplement	Medicine
Siberian ginseng	Food supplement	Listed medicine*	Medicine	Dietary supplement	Medicine/food supplement
Mangosteen	Food	Food	Food	Food/dietary supplement	Food

*A medicine with generally lower claims and a good safety record (see text).

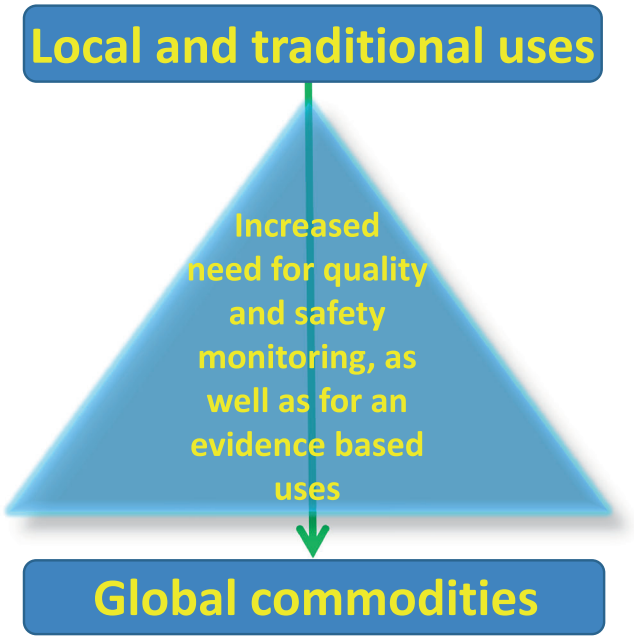

Figure 1

The development of local and traditional herbal medicines into global commodities poses key challenges in order to ascertain quality and safety and needs to be accompanied by studies in order to develop an adequate evidence – level of such products

can actually be identified at the level of the botanical drug used. Traditional herbal regulation (THR) products are clearly marked as such and carry a registration number. In the UK it also may display the certification mark (Figure 2), which, however, is not compulsory [6].

In the UK some herbal medicines are still exempt from licensing, most importantly those 'compounded and supplied by herbalists on their own recommendation' [specified under Section 12(1) of the UK's Medicines Act 1968] and those consisting solely of dried, crushed or comminuted (fragmented) plants. They must not contain any non-herbal 'active' ingredients and are sold under their botanical name and there are no written recommendations for use [specified under Section 12(2) of the Medicines Act]. The exemptions were initially intended to give herbalists the flexibility to prepare remedies for their patients and today include traditional medicines used by ethnic groups including traditional Chinese medicines (TCHM) and Ayurvedic medicines.

Another large group are food supplements, which are generally sold with no specific health claim, but with patients frequently expecting therapeutic effects. Their quality requirements are generally based on food legislation, which is less stringent than the medical legislation. In recent years some products have become available which are regulated as a medical device, like preparations derived from *Opuntia ficus-indica* (L.) Mill. -cladodes of prickly pear used for weight loss and in the management of diabetes or *Euphrasia* spp. eyebright used for disorders of the eye. This, however, has important disadvantages especially in terms of their safety monitoring. In addition, with the consumption of supplements rising, the incidence of side effects and drug interactions are increasing. Supplements are also not well covered under the pharmacovigilance schemes. Food supplements will generally not be regulated in such a stringent way in terms of their composition and quality. As exemplified for chemically defined supplements [7] problems associated with poor quality of commercially available nutraceuticals are widespread. Crucially, in most cases it is the manufacturer who decides whether a product is a food or a supplement or a HMP, and the number of regulatory actions taken by, for example, the MHRA, for lack of THR compliance is vanishingly small, and dependent upon consumer complaints.

Another example, Australia uses a two-tiered, risk-based approach for regulating all medicines. Low risk medicines, including most herbal and complementary medicines, are *listed* medicines included in the Australian Register of Therapeutic Goods (ARTG) and identified by a unique AUST L number on the label. Medicines deemed to be of higher risk are *registered* medicines and identified by an AUST R number. While registered medicines undergo full pre-market safety and efficacy evaluation, listed medicines are not evaluated for efficacy, but product sponsors must hold evidence to support the claims they make about the product. In Canada, Health Canada classifies herbal medicines as 'natural health products' which require a product license before they can be marketed. In the USA, herbal medicines are generally regulated as 'dietary supplements' by the U.S. Food and Drug Administration (FDA, www.fda.gov/Food/DietarySupplements/). It is a loose regulation (http://nccam.nih.gov/health/supplements/wiseuse.htm) which does not require that dietary supplements be assessed for safety and effectiveness prior to marketing. [8]

Figure 2

THR certification mark granted by the British MHRA

The analytical maze

A large share of the HMPs currently on the market are used as an extract, i.e. a processed and concentrated preparation of liquid or intermediate or solid consistency

normally produced from a drug (dried botanical material) resulting in a complex mixture of compounds, which will vary depending on:

- The composition of the raw material (which in turn depends on the growing conditions, initial processing, purity of the material)
- The processing of this raw material (i.e. the type of extraction used and the way it is then further processed)
- The formulation of this extract (or a crude drug) into a herbal medical product

Routine analytical procedures are well developed for those botanical drugs and the extracts derived from them which are widely used in Europe and more than 200 specific monographs for botanical drugs exist in the European Pharmacopoeia [9], which defines clear quality parameters for these products. Of course, unscrupulous operators and/or human error negatively impact on the quality of the raw material and the products derived from them (e.g. [10]). Unregistered products are not assayed for contaminants, unreported adjuvants, or other adulterants. Key problems include the intentional adulteration with conventional drugs (e.g. corticosteroids) as well as accidental or intentional botanical substitution or contamination with microorganisms and pesticides, problems which can now be controlled under the THMPD.

Ways forward

The above parts highlight some important needs in the context of the general and clinical use of medicinal plants and products derived from them

- For example, in the UK, regulation has resulted in ascertaining that over the counter products are generally of a good and reproducible quality and that the over the counter use of such products is limited to minor self-limiting disorders. However, products without quality assurance and with, in many cases, fraudulent or misleading claims are still available, for example, via the internet.
- Food supplements are also commonly available on the market and here therapeutic claims are less well defined. In general terms quality assurance of food supplements is much more limited.
- Quality assurance based on existing schemes very heavily relies on controls at the final stages of production and, at least for those products for which monographs exist, on robust analytical procedures.

In recent years and in order to secure high quality products a wider debate about the interface of agriculture and health has begun. This debate focuses on the quality of a product along the value chain from the primary producers to the end users and on the impact of such value chains on the livelihoods of the primary producers of such products (collectors, farm workers and farmers, peasants). There are numerous other stakeholders who contribute to how these value chains develop (e.g. interest groups, advertising agencies) and clearly they are embedded in a complex political maze which determines the regulatory framework. Recently, we suggested the combined use of the concept of value chains and of a phytochemical-analytical or metabolomics approach in order to understand these interdependencies and to assure the supply with consistent, high quality products [11]. Value chain research focuses on the nature of the relationships among the various participants involved in the chain, and on their implications for development. At any point in the chain, some degree of governance or co-ordination is necessary in order to take decisions on how the chain should be managed effectively [12]. The concept has been used widely in the food sector and also has been important in the context of Fairtrade® products (like tea, bananas and coffee) as well as in the debate about the sustainable supply with products from species which are rare or endangered. There is only a small body of literature focusing on value chains of herbal medical products [13].

Our research in recent years has used a mixed methods approach combining a value chain analysis with a study of the chemical composition of the starting materials sourced from diverse regions of India with a metabolomic analysis [14]. Metabolomics [15] is the comprehensive, non-biased, high throughput analyses of complex metabolite mixtures such as those typically seen in plant extracts. Achieving a broad overview of metabolic composition requires the establishment of a fully integrated approach for the optimization of sample extraction, metabolite separation/detection/identification, automated data gathering, processing and analysis, and quantification. Using turmeric (*Curcumal longa* L., Zingiberaceae) as an example and using a combination of analytical tools, 1H-NMR spectroscopy and high performance thin layer chromatography (HPTLC), we studied the composition and quality of herbal medicinal products along value chains.

While in this case we did not identify any major adulterations (e.g. with synthetic drugs) product samples obtained from within a vertically integrated value chain (i.e. ones with direct contracts between the local producers and the manufacturer abroad) show a close resemblance to fresh samples of turmeric rhizome with respect to their metabolite content [14]. Samples obtained from a non-integrated chain (also used as supplements, or as a spice) were contaminated with different other *Curcuma* species. Most of the products sold as aqueous extracts contained little trace of compounds that were present in the powder and that would

generally be regarded as quality indicators, some contained polysaccharides but others only simple sugars. In addition to this analytical part, detailed studies on the impact of these value chains on the livelihood of the producers were conducted [14].

Conclusions

Overall, this indicates that a more stringent regulatory framework guarantees better access to safe HMPs and that these have a place in treating minor self-limiting conditions. The approach suggested here offers a new strategy for using analytical techniques in the context of value chains of herbal medicines and food supplements. Clearly, in the context of clinical and applied pharmacology, a sharp distinction needs to be made between regulated and non-regulated products.

Competing Interests

The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares no support from any organization for the submitted work. MH had a specified relationship] with Fa. Schwabe Pharmaceuticals (Germany), Fa. Bionorica, Fa. Bioforce (Switzerland), Fa. Phytolab (Germany) and Fa. Pandalis (Germany) who funded research projects at the centre in the previous 3 years and there are no other relationships or activities that could appear to have influenced the submitted work

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