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Quality of TCM Drugs and TCM Products

– current status in the European Union –

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1. INTRODUCTION

Traditional Chinese Medicine (TCM) has been the primary medicinal treatment for a large part of the Chinese, Korean, Taiwanese and Japanese (Kampo) population for more than 3000 years, but TCM has also achieved an increasing degree of popularity in Europe, e.g. in Germany, Austria, Switzerland, Belgium, the Netherlands or Great Britain. There, TCM is practiced in specific hospitals or by TCM practitioners in conjunction with, or as an alternative to Western medicine [1, 2].

Alongside TCM applications such as Qigong or acupuncture, treatment with herbal drugs (as decoction) plays an important role in the TCM system. To achieve the desired pharmacological effect a multitude of different herbal drugs and in some cases animal-derived products are mixed together [3]. Unfortunately, due to the complex mixture of these Chinese herbal medicines, the biological identification of its contents can be quite a challenging task [4], thus raising concerns about TCM quality, safety and efficacy [5].

Additionally the lack of regulations (wild harvesting) regarding cultivation of these medicinal herbs leads to considerable variation of pharmacological relevant compounds among batches of herbs since the chemical composition is dependent on source/climate, geographical/ geological origin, genotype, phenotype, seeds, part of plant, conditions during growth (e.g. minerals), time of harvest, use of pesticides or herbicides [6].

Undeclared or misidentified TCM ingredients and adulterations can pose serious health risks to consumers.

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The most well-known incident of misidentified ingredients in Europe happened in Belgium in the early 1990's, with similar cases in several other countries worldwide. The mix-up of the toxic herb *Aristolochia fangchi* with the anti-inflammatory agent *Stephania tetrandra* led more than a hundred women to suffer kidney failure, with many later developing cancer of the urinary system [7].

Furthermore several patients suffered from cardiac toxicity and atropine poisoning in Hong Kong around 2004, when *Tupistra chinensis* (root) was supplied instead of *Panax notoginseng* (root), and *Datura metel* (flower) instead of *Campsis grandiflora* (flower), respectively [8].

Another characteristic feature of TCM are the processing methods ('pao zhi'). While a unique and advantageous property, these processing methods can also generate confusion and may pose serious health risks to consumers, if the processing has not been conducted in an adequate way.

Basic processing includes washing, drying or slicing of the plant material, while more complex processing methods such as stir-frying, boiling or steaming are used to modify the therapeutic effects (e.g. detoxify, increase potency), alter bioavailability or preserve active ingredients [9]. A proposal for a new general chapter '5.18. Preparation of Drugs for Traditional Chinese Medicines' was published in Pharmeuropa 22.2 and then republished in Pharmeuropa 24.2 under a new title 'Processed drugs for traditional Chinese medicine: glossary', which gives a summary about the different processing methods; additionally, a method for preparation of decoctions was described [10].

Especially the role of processing in the detoxification of *Aconitum* species has been well investigated with over 70 analytical methods described in the literature [6, 11]. Therefore poisoning from *Aconitum* species is mainly due to incorrect use – either use of poorly processed roots or due to poor directions of use [12-14]. Because of its importance, processing of *Aconitum* species is only allowed in state-approved companies.

The toxic constituents in *Xanthium sibiricum* (Xanthii fructus), a herb also known to require processing, are identified as diterpenoid carboxyatractyloside. Incorrectly used, this herbal medicine can lead to severe adverse effects, including jaundice, hepatomegaly, oedema, oliguria, haematuria, tonic clonic seizures, coma, respiratory and circulatory failure [15]. Nevertheless it has been shown that specific roasting reduces the content of atractyloside and other derivatives with formation of less toxic aglycones [16].

While these incidents are quite disturbing, TCM appears to be relatively safe with comparatively few reports of adverse reactions (ADR) compared with overall drug reports (restricted to the use of raw herbs). A recent review over a 10-year period identified 3122 case reports involving 140 drugs. Of these, oral use accounted for 32 % or reports and 56 % from injected extracts. Allergies, e.g. skin itch, dermatitis and anaphylactic shock were the most common ADRs [17]. In Hong Kong around 77 adverse events related to herbal drugs have been reported to the Hong Kong Department of Health between January 2000 and June 2004 [18].

Nevertheless it should be of upmost importance to make TCM as safe as possible for the implementation of TCM into the western medicinal system. Most of the reported adverse effects could have been avoided either by an appropriate quality control system, reducing the number of erroneous substitutions and quality defects, as well as an appropriate education of TCM practitioners and traditional application of these Chinese herbs, reducing misuse and direct toxicity.

Unfortunately the wealth of the Chinese literature is not widely available. Notable in English language is the Materia medica: Chinese Herbal Medicine [19], the monograph proposals by Wagner *et al.* [20] and the official English issue of the Chinese Pharmacopoeia [21]. Further, the latest issue of the Japanese Pharmacopoeia [22] and the monographs of the Hong Kong

Chinese Materia Medica Standards [23] are freely available on the internet. Also notable is the German DAB, the British Pharmacopoeia as well as the French Pharmacopoeia.

Several official authorities have recognised the increasing importance of herbal medicinal products and of TCM in particular and therefore have concerned themselves with the establishment of guidelines and standardisation procedures. On international level an ISO standardisation procedure for TCM (TC 249) has been established in 2009, in which the German side (DIN) took on the world secretariat for the 'Quality and Safety of TCM Products' in May 2011 and provides its convener [24]. The European Directorate for the Quality of Medicines & HealthCare (EDQM) comprises 2 groups of experts on phytochemistry, who elaborate monographs for the European Pharmacopoeia (Ph. Eur.) on herbal drugs and herbal drug preparations (groups 13A and 13B). Since 2007 a special working group has been started with the elaboration of monographs on traditional Chinese plants and preparations (TCM group).

2. LEGAL STATUS OF TCM DRUGS AND DERIVED PRODUCTS

The legal status of herbs and phytomedicines in Western countries differs considerably. The U.S. market is characterised by relatively low legal requirements for herbals and herbal medicinal products (considered as dietary supplements) compared to the European market, which is characterised by considerably higher legal requirements.

TCM drugs (as in raw herbs) are not considered as pharmaceuticals in the EU at the time of import, but as pharmaceutical pre-products. Because of this status, pharmaceutical law limitations (e.g. import permit or GMP certification) do not apply for raw herbs. Nevertheless, raw herbs are only allowed to be sold in pharmacies because of their medicinal use.

After receiving a prescription and purposefully mixing these herbal drugs by a pharmacist, the legal status changes and these drugs are then classified as pharmaceuticals/remedy. Approval according to § 6 and § 11 of the German Pharmacy Operating Ordinance [25, 26] or any other corresponding legal framework in the respective member states of the EU is necessary. This includes the proof of identity by the responsible pharmacist as well as the reassessment of the corresponding Certificate of Analysis (CoA, containing proof of identity and absence of contaminants), issued by a European laboratory.

In contrast to raw herbs, there appears to be significant confusion about the regulation of derived products, e.g. formulas, granules, hydrophilic concentrates, capsules or tablets, in short also called herbal medicinal products/preparations.

In recent legislative texts, medicinal use of herbal medicinal products (HMP) has been harmonised by the EU [27]. Use as well established or as traditional herbal medicinal product has been defined in Directives 2004/27/EC and 2004/24/EC amending Directive 2001/83/EC [28-30]. Medicinal products are now defined by Directive 2004/27/EC as 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological, immunological or metabolic action, or to making a medical diagnosis' [29].

All medicinal products including HMP are only allowed to be marketed in the EU with a marketing authorisation or registration application by the competent authorities (e.g. EMA). A marketing authorisation requires the documentation of pharmaceutical safety, quality and efficacy as well as risk information, dosage, indication fields or pharmaceutical form. A registration application (e.g. as traditional herbal medicinal product) offers a more simplified application process, efficacy and safety is based on long standing use and experience (at least 30 years within the EU, products from outside the EU must prove at least 15 years within Europe and 15 years outside Europe) [31].

This legal framework has also been confirmed by the German Federal Administrative Court [32], stating that granules are considered as pharmaceuticals (harmonised with all corresponding EU laws).

As a direct result of this legal framework and the respective court decision, trading of granules, hydrophilic concentrates, capsules, tablets or any other derived products from TCM raw herbs without a marketing or registration application has to be considered as illegal. Furthermore, direct import of these products from the manufacturing countries (e.g. China, Korea) requires an official import permit and a third-country inspection for Germany according to § 72 resp. § 72a German Drugs Act [33] or any other corresponding legal framework in the respective member states in the EU. Additionally, marketing as a functional food without a registration (European Food Safety Agency, EFSA) is also not possible.

Several of these products, especially granules, claim to be phytoequivalent to herbal drugs and therefore may not require a registration. Yet, the phytoequivalence (see [34, 35] for definition) of these products has not been proven.

On the contrary, several incidents and publications indicate that the claimed phytoequivalence (e.g. extraction by water) is not fulfilled, that labeling requirements are ignored (e.g. wrong Drug/Extraction ratio), that TCM products have been (intentionally) adulterated with (synthetic) drugs (of known pharmacological effect) and that these products even pose serious health risks [36-44].

Because of these incidents, the authors are working on a further publication, evaluating the quality of TCM products, especially focusing on granules.

As mentioned in the Introduction, processing is an advantageous and unique feature of TCM. With regards to the above described legal framework, the status of 'processing' has to be reevaluated.

In principle, 'processing' of TCM herbal drugs in Europe is possible, but would require a GMP certification of the production site (e.g. pharmacies). Taking into consideration the economic and financial efforts required to obtain such a GMP certification, coupled with the lack of information on processing methods (most of the literature is still only available in Chinese), processing in Europe has to be regarded as economical unfeasible. 'Processing' of TCM drugs is a modification of active principles, therefore a new product (HMP) and requires a GMP certification. Production without GMP certification is illegal. A more sensible approach might be to import these products directly from the country of origin.

3. QUALITY REQUIREMENTS FOR TCM DRUGS AND PRODUCTS

While the EU provides the legal framework for TCM drugs and products, the Ph. Eur. supplemented by the Chinese Pharmacopoeia provide the specific parameters and monographs which are considered to be generally and commonly important for the assurance of quality of TCM raw herbs. Specific monographs for TCM products are defined in the respective registrations (HMP, THMP).

The authentication of TCM drugs both includes identifying its botanical origin and evaluating its pharmaceutical quality (proof of identity, determination of contents and assay) as well as the absence of contamination and falsification [45].

The identity, purity, content tests and tests for the lack of contaminations of raw herbs are well described in the respective Pharmacopoeias [46].

Nevertheless the identification of extracts, granules and ready-to-use TCM pharmaceuticals pose a considerable problem. Because of their manufactured character, identification via macro- and microscopical methods cannot be realised. Furthermore these products have to

be considered as pharmaceuticals, including the need for a registration (as described in the previous chapter). Thus, proofs of identity, purity tests and content tests have to be conducted according to the manufacturers requirements (e.g. loss on drying or possible ash content) and according to product-specific monographs, described in the corresponding registration.

4. IDENTITY TESTS

The aforementioned proof of identity, mostly characterisation of secondary compounds in herbal drugs, requires sophisticated techniques, which should provide good sensitivity and selectivity, should be time and cost efficient, easy to operate and accepted by the authorities.

Within the last decades a multitude of techniques and methods for the analysis of herbal drugs have been developed, starting with TLC, HPLC, GC, CE, coupled with UV/VIS-, DAD-, MS- or NMR-detectors.

Among these techniques, several are discussed for the identity check of TCM herbal drugs as well as TCM products.

A relatively new approach is the DNA analysis of plant material (e.g. DNA molecular marker, PCR, etc.). Techniques based on DNA analysis provide specific and accurate data with regard to various plant species and are especially useful to distinguish closely related herbal drugs [47, 48]. Unfortunately, identification methods based on DNA analysis require a complicated mode of operation and are characterised by high costs [45]. Another disadvantage of DNA analysis based methods is their lack of information on the expression pattern. The pharmacological effect of a therapeutic plant primarily depends on its ingredients (phenotype), not only on its genes/DNA (genotype). Additionally these methods are usually not stable enough for routine analysis and are not suitable for the analysis of derived products (e.g. granules or extracts) [45], therefore their acceptance by legal authorities is questionable.

In contrast, spectroscopic methods excel thanks to fast and non-destructive methodology, often combined with simple preparation of the samples [4]. During the last century a vast array of spectroscopic methods have been developed, e.g. UV/VIS-, IR-, Mass- or NMR-spectroscopy.

While these spectroscopic methods provide excellent information on pure, single substances, determination of several compounds in mixture is quite a difficult task. Therefore spectroscopic methods are usually coupled with chromatographic systems, resulting in a 2-step process: separation of compounds by chromatographic means and secondly, detection of the separated compounds by spectroscopic methods.

Nevertheless, detection of multiple compounds in mixture by means of spectroscopic methods is an important research field at universities, especially in the area of mass-, NMR- or NIR/MIR-spectroscopy.

NIR- or MIR-spectroscopy is already established for the determination of water in food or dietary supplements or for purity evaluation of synthetic compounds in the pharmaceutical industry (raw materials and pre-products) [49]. Quantitative determinations are also possible, but require external calibration with a conventional method (e.g. GC, HPLC) as well as validation according to ICH guidelines [50].

Few reports of NIR- or MIR-spectroscopy applications have been published in connection with TCM.

Basically, the NIR- and MIR-spectrum is comprised of a large set of interference and combination bands [51]. This leads, coupled with the complex composition of herbal drugs and natural plant products to extremely complicated spectra, additionally distorted by the lack of homogeneity of the sample, wavelength dependent scattering effects and other sources of variability [52]. Therefore it is very difficult to assign absorption bands to specific functional groups, not even mentioning chemical components [53].

In order to interpret NIR spectra, multivariate statistical techniques (chemometrics) are necessary to extract the information about the compositional properties hidden in the NIR spectrum [54].

Although the MIR or NIR technique has some advantages, it also has some distinct disadvantages. The most frequently cited benefit of no required sample preparation is only partly valid, because particle size, moisture level, temperature as well as physical effects (e.g. comparing whole, ground or powder samples) influence the NIR spectra. In order to achieve reproducible test readings and results, the above mentioned parameters, among others, have to be standardised according to the respective test specifications [55].

Additionally the high number of samples and batches, coupled with the biological diversity (see Introduction) of herbal drugs, complicate the development of suitable statistical models for the identification of TCM products and result in very high costs. Especially since the samples for the development require authentication by conventional analytical methods (TLC, GC or HPLC) [56].

Comparable to DNA analysis based methods, the validation of the NIR or MIR technique is considered a problem and therefore the EDQM as well as the ISO TC 249 group do not consider the NIR/MIR technique suitable for the identification of TCM [57].

Thus it must be concluded that at the present time that the current NIR-systems established in the market for the identification of TCM herbal drugs and derived products do not comply with the aforementioned requirements and therefore are not suitable for the authentification of TCM herbal drugs or derived products (e.g. granules).

In contrast to the already described, relatively new methods, planar chromatography, also called TLC (as well as HPTLC) has been used for the analysis of herbal drugs for over 70 years and still plays an important role in the identification and qualification of medicinal plants and dietary supplements. Furthermore, detection of adulteration is a widely used TLC application field and even quantitative determination of a marker substance is possible [58]. TLC tags at comparing many samples, when flexibility is important and rapid semi-quantitative data are needed at low cost per sample. With regards to TCM, even identification of derived products, e.g. granules, is possible by TLC.

TLC nowadays is not only a universally accepted technique, but also a standard method for the identification and qualification of medicinal plants and synthetic drugs in several pharmacopoeias. Because of its importance, the USP, the Ph. Eur. and the Chinese Pharmacopoeia are revising their general TLC method section to keep up the state of the art of the technique [46, 59, 60].

Typically, monographs described in the above mentioned pharmacopoeias provide a specific, optimised solvent system and a specific marker compound for identification. Yet, herbal drugs are complex mixtures of compounds and from a medicinal and also from a legal point of view, the drug in its entirety must be regarded as the active principle. The detection of a single marker substance may only give information on a small facet of the plants pharmaceutical effect. In many cases, the active principles are not fully known and above all reference compounds are quite expensive.

The question for the proof of identity can be much better answered by chromatographic fingerprinting, which represents the complete complexity of an herbal drug. For these reasons, the EDQM started with the establishment of so-called herbal reference extracts for selected herbal drugs [61].

Based on the concept of herbal reference extracts, coupled with simplified sample preparation and simplified TLC fingerprinting techniques, an identification system for TCM herbal drugs and derived products has already been developed.

5. CONCLUSION

TCM, with its huge treasure of pharmacological active herbal drugs, has many benefits to offer. But it is important to evaluate the balance between benefits and possible harms. While the traditional application of raw herbs seems relatively safe with a low number of adverse effect reports, the potential risk of adverse effects by derived products, e.g. granules, extracts or ready-to-use TCM, has to be considered significantly higher.

The recently introduced legal framework by the EMA (European Medicinal Agency, Herbal Medicinal Products) promotes a single market for these products by introducing consistent standards and procedures and by encouraging cross-border trade. Unfortunately, knowledge about the active constituents and their pharmacological effect of many herbal drugs still needs improvement.

In order to integrate TCM as an equal system into the western medicinal system, authentication of herbal drugs is a critical step for standardisation and finally for the quality control of TCM.

Because of their complex composition, fingerprinting techniques seem to be the method of choice for the identification and qualification of these drugs. And, although a multitude of highly sophisticated, very promising analytical techniques have been developed during the last decades, HPLC- and TLC- fingerprinting is still the method of choice for quality evaluation of herbal drugs.

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