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New Analytical Monographs on TCM Herbal Drugs for Quality Proof

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Summary
Regardless of specific national drug regulations there is an international consensus that all TCM drugs must meet stipulated high quality standards focusing on authentication, identification and chemical composition. In addition, safety of all TCM drugs prescribed by physicians has to be guaranteed. During the 25 years history of the TCM hospital Bad Kötzting, 171 TCM drugs underwent an analytical quality proof including thin layer as well as high pressure liquid chromatography. As from now mass spectroscopy will also be available as analytical tool. The findings are compiled and already published in three volumes of analytical monographs. One more volume will be published shortly, and a fifth volume is in preparation. The main issues of the analytical procedure in TCM drugs like authenticity, botanical nomenclature, variability of plant species and parts as well as processing are pointed out and possible ways to overcome them are sketched.

Zusammenfassung
Ungeachtet spezifischer nationaler Arzneimittelregulierungen gibt es einen internationalen Konsens darüber, dass sämtliche TCM-Präparate verbindlichen qualitative hochstehenden Standards entsprechen müssen, die an der Echtheitsprüfung, Identifizierung und chemischen Komposition orientiert sind. Zudem muss die Sicherheit der von Ärzten verschriebenen TCM-Arzneien gewährleistet sein. In der nunmehr 25-jährigen Geschichte der TCM-Klinik Bad Kötzting wurden 171 TCM-Präparate einer analytischen Qualitätsprüfung unterzogen, unter anderem mittels einer Dünnschichtchromatografie sowie einer Hochdruckflüssigkeitschromatografie. Zudem wird jüngst die Spektroskopie als analytisches Instrument eingesetzt. Die Ergebnisse dieser Testverfahren sind bereits zusammengefasst und in drei entsprechenden Bänden publiziert; weitere Publikationen sind derzeit in Vorbereitung. Hier werden die wichtigsten Herausforderungen der Analyse wie Echtheitsprüfung, botanische Nomenklatur, Variabilität der Pflanzenspezies und -teile sowie Aufbereitung hervorgehoben und potenzielle Lösungsmöglichkeiten skizziert.

Legislation

When we started this work 25 years ago, we noticed that the methods stipulated in the former Chinese Pharmacopoeias were not sufficient to meet the high standards of the official German and European drug regulatory authorities. Among the various prerequisites for a perfect quality proof of these herbal drugs, authentication and safety proof took precedence. Identification was at first primarily synonymous with the macroscopic and microscopic botanical authenticity. Since that time, however, chemical composi-

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tion and particularly the complex entities of the low molecular constituents have become of greater interest for oral medicinal application and thus in evaluating the pharmacological effects and therapeutic efficacy of the plant drug extracts obtained by decoction or other extraction processes.

Independent of the specific national drug regulations for countries around the world, there is also an international consensus that all TCM drugs must meet certain stipulated high quality standards. Additionally, it must be guaranteed that all TCM drugs prescribed by physicians are safe for patients. The safety proof aims mainly to exclude any kind of possible falsifications of the herbal drugs and to ensure a limited concentration of heavy metals, aflatoxins and defined microbial adulterations.

Fig. 1. Tu Youyou.

Applied Methods in Quality Proof

The main method used is the TLC (thin layer chromatography), which allows us to visualise the main characteristic constituents as coloured TLC photographs. The second, globally used method is HPLC (high-pressure liquid chromatography) in the form of a so-called fingerprint analysis. This technique allows us to detect the complex entities of all low-molecular constituents of a plant drug extract, with the advantage that the single constituents can be made visible in the form of peak profiles. Additionally, the single constituents can be quantified by using online-recordable UV spectra with the diode array. It is also possible to gain preliminary information as to which chemical structure type the single compounds may belong. From that year on, LC-MS (liquid chromatography-mass spectrometry) is also available for the analysis of plant extracts whose chemical compositions have previously been investigated only minimally.

Analytical Monographs of Investigated Herbal Chinese Drugs

The following volumes were / are going to be published by Springer, with financial support from the TCM hospital Bad Kötzting [1–3]:

- Vol. I and II (2011) containing 80 analytical monographs
- Vol. III (2015) containing 23 analytical monographs
- Vol. IV (2016) containing 22 analytical monographs (publication scheduled for July 2016)
- Volume V is currently in preparation; the publication is scheduled for February/March 2017.

A list of all completed analytical monographs of TCM drugs is presented in table 1 and table 2. (All single analytical monographs published can be purchased at *www.springer.com/de/book/9783709107621*). One example for an investigated herbal Chinese drug is *Artemisia annua* L. which recently gained attention in reference to the Nobel Prize in Medicine in 2015 awarded to the Chinese Professor Dr. Tu Youyou, Beijing (fig. 1) who isolated artemisinin as the main constituent of this plant. Today, artemisinin is applied in combination with various chemosynthetic drugs (e.g., mefloquin) in the treatment of malaria.

Prospects for Improvement of Quality Proof of Chinese Herbal Drugs

Authenticity of TCM Drugs Not Definitely Assessed

Some herbal drugs originated from wild collections are not yet cultivated under controlled conditions. If they are derived from cultivations it must be taken into account that they may originate from quite different climate zones and are harvested under different conditions. Therefore, their chemical authenticity and homogeneity within a defined plant species often cannot be guaranteed. We have thus investigated as many herbal drug samples as we were able to acquire from different districts, climate zones and markets in China, as well as reference drugs from some German herbal drug firms that also import herbal drugs from China.

Lacking Information on Plant Parts

In 5–10% of imported plant drugs from China, we do not receive any specific information about the plant part (flos, fructus, semen, folium, cortex or radix and rhizoma) from which they were derived. Such drugs are specified as 'herba' analogues in the Chinese Pharmacopoeia. For these drug samples, it cannot be expected that the TLC and HPLC chemical fingerprints are homogenous. Not all parts of a herbal drug contain the same chemical constituents. The documentation in the corresponding herbal analytical monographs confirms this assessment (e.g. Herba Leonuri, vol. II; Herba Lysimachiae, vol. III or Herba Violae, vol. IV). Therefore, it will be necessary to correct this discrepancy in one of the following Chinese Pharmacopoeia publications. Otherwise, it is unlikely to reproduce the results of clinical application.

Uncertain Botanical Nomenclature

The non-uniform nomenclature for the same plant from various regions of China can cause impermissible confusions or falsifications. This occurred some years ago when the root of *Stephania*

Table 1. Contents, alphabetically (Latin nomenclature)

Monograph	Volume
Acanthopanacis senticosi, Radix	I
Achyranthis, Radix	III
Aconiti kusnezofii, Radix	II
Aconiti lateralis, Radix	II
Acori calami, Rhizoma	II
Acori tatarinowii, Rhizoma	II
Albiziae, Cortex	IV
Alismatis, Rhizoma	II
Allii Tuberosi, Semen	V*
Alpiniae Katsumadai, Semen	V*
Amomi rotundus, Fructus	I
Ampelopsis, Radix	V*
Andrographis, Herba	I
Anemarrhenae, Rhizoma	I
Angelicae dahuricae, Radix	I
Angelicae pubescentis, Radix	I
Angelicae sinensis, Radix	I
Apocyni veneti, Folium	III
Arctii, Fructus	IV
Arecae, Pericarpium	V*
Armeniacae, Semen	V*
Arnebiae, Radix	V*
Artemisiae annuae, Herba	IV
Artemisiae argyi, Folium	IV
Artemisiae scoparia, Herba	II
Asari, Herba	I
Astragali, Radix	I
Atractylodes macrocephalae, Rhizoma	I
Atractylodis lanceae, Radix	II
Aucklandiae, Radix	III
Aurantii immaturus, Fructus	V*
Aurantii, Fructus	V*
Bambusae, Caulis	III
Belamcandae sinensis, Rhizoma	I
Bupleuri, Radix	I
Camelliae, Folium	II
Carthami, Flos	II
Cassiae, Semen	II
Celosiae, Semen	IV
Chaenomelis, Fructus	II
Chrysanthemi, Flos	V*
Cimicifugae, Rhizoma	II
Cinnamomi, Cortex	II
Citri reticulatae viride, Pericarpium	II
Citri reticulatae, Pericarpium	II
Clematidis, Radix	I
Cnidii, Fructus	II
Codonopsis pilosulae, Rhizoma	I
Coptidis, Rhizoma	I
Corni, Fructus	IV
Corydalis, Rhizoma	II
Crataegi, Fructus et Folium	III
Curcumae longae, Radix	II
Curcumae, Radix	II
Curcumae, Rhizoma	II
Cuscutae, Semen	V*
Cyperi, Rhizoma	III
Desmodii styracifolii, Herba	III
Dictamni, Cortex	V*
Dioscoreae hypoglaucae, Rhizoma	II
Dioscoreae nipponicae, Rhizoma	II
Dioscoreae oppositae, Rhizoma	II
Dioscoreae septemlobae, Rhizoma	II
Dipsaci, Radix	II
Drynariae, Rhizoma	I
Ecliptae, Herba	I
Ephedrae, Herba	IV
Epimedii, Herba	II
Equiseti hiemalis, Herba	V*
Eriocauli, Flos	III
Eucommiae, Cortex	II
Evodiae, Fructus	I
Forsythiae, Fructus	I
Fraxini, Cortex	IV
Frittilariae, Bulbus	I
Ganoderma	II
Gardeniae, Fructus	I
Gastrodiae, Rhizoma	I
Gentianae macrophyllae, Radix	IV
Ginkgo, Folium	V*
Ginseng, Radix et Rhizoma	II
Glehniae, Radix	V*
Glycyrrhizae, Radix et Rhizoma	III
Gynostemmatis, Herba	III
Houttuyniae cordatae, Herba	I
Isatidis, Radix	II
Kochiae, Fructus	IV
Leonuri, Herba	II
Ligustici chuanxiong, Radix	I
Ligustri lucidi, Fructus	III
Linderae, Radix	V*
Lonicerae japonicae, Caulis	II
Lonicerae japonicae, Flos	II
Lonicerae, Flos	II
Luffae, Fructus	III
Lycii radicis, Cortex	II
Lycii, Fructus	II
Lycopi lucidi, Herba	I
Lycopodii, Herba	III
Lysimachiae christinae, Herba	III
Magnoliae officinalis, Cortex	I
Magnoliae, Flos	II
Mori radicis, Cortex	II
Mori, Folium	II
Mori, Ramulus	IV
Morindae officinalis, Radix	III
Moutan, Cortex	III
Myrrha	V*
Notoginseng, Radix et Rhizoma	II
Notopterygii, Rhizoma seu Radix	I
Oldenlandiae, Herba	III
Olibanum	V*
Ophiopogonis, Radix	II
Paeoniae albae/rubrae, Radix	I
Persicae, Semen	V*
Peucedani, Radix	III
Phellodendri amurensis, Cortex	II
Phellodendri chinensis, Cortex	II
Picrorhizae, Rhizoma	V*
Pinelliae, Rhizoma	I
Piperis longi, Fructus	II
Plantaginis, Herba	IV
Plantaginis, Semen	IV
Platycodonis, Radix	III
Polygalae, Radix	V*
Polygoni avicularis, Herba	V*
Polygoni cuspidate, Rhizoma et Radix	V*
Polygoni multiflori, Radix	I
Poria	II
Prunellae, Spica	IV
Psoraleae, Fructus	IV
Puerariae, Radix	I
Quinquefolii, Radix	II
Rehmanniae, Radix	I
Rhei, Radix et Rhizoma	II
Rosae laevigatae, Fructus	V*
Salviae miltiorrhizae, Radix et Rhizoma	II
Sanguisorbae, Radix	V*
Saposhnikoviae, Radix	III
Sappan, Lignum	IV
Sarcandrae, Herba	III
Schisandrae, Fructus	I
Schizonepetae, Spica	V*
Scrophulariae, Radix	I
Scutellariae barbatae, Herba	V*
Scutellariae, Radix	II
Sesami nigrum, Semen	IV
Siegesbeckiae, Herba	II
Sinapis albae, Semen	IV
Sinomenii, Caulis	I
Siraitiae (Momordicae), Fructus	III
Solidaginis, Herba	V*
Sophorae flavescentis, Radix	II
Sophorae immaturus, Flos	I
Spatholobi, Caulis	III
Stephaniae tetrandrae, Radix	I
Trachelospermi, Caulis et Folium	V*
Tribuli, Fructus	II
Trichosanthis, Fructus	IV
Trichosanthis, Radix	IV
Trigonellae, Semen	V*
Uncariae cum Uncis, Ramulus	I
Vaccariae, Semen	IV
Verbenae, Herba	V*
Violae, Herba	IV
Viticis, Fructus	IV
Xanthii, Fructus	IV
Zanthoxyli, Pericarpium	I
Zingiberis, Rhizoma	V*
Ziziphi spinosae, Semen	I

*Currently in process.

Table 2. Contents, alphabetically (Chinese names)

Chinese name	Volume
Aiye	IV
Bai hua she she cao	III
Bailian	V*
Baishao	I
Baixianpi	V*
Baizhi	I
Baizhu	I
Bajitian	III
Banlangen	II
Banxia	I
Banzhilian	V*
Beimu	I
Beishashen	V*
Bianxu	V*
Bibo	II
Buguzhi	IV
Cang'erzi	IV
Cangzhu	II
Caodoukou	V*
Chaihu	I
Cha-yeh	II
Chenpi	II
Cheqiancao	IV
Cheqianzi	IV
Chishao	I
Chuanshanlong	II
Chuanxinlian	I
Chuanxiong	I
Ciwujia	I
Dafupi	V*
Dahuang	II
Danggui	I
Dangshen	I
Danshen	II
Difuzi	IV
Digupi	II
Dihuang	I
Diyu	V*
Duhuo	I
Duzhong	II
Ezhu	II
Fangfeng	III
Fangji	I
Fenbixie	II
Fuling	II
Fuzi	II
Gancao	III
Ganjiang	V*
Gegen	I
Gouqizi	II
Gouteng	I
Gualou	IV
Guangjinqiancao	III
Guanhuangbo	II
Gujincao	III
Gusuibu	I
Hehuanpi	IV
Heizhima	IV
Heshouwu	I
Honghua	II
Houpo	I
Huaihua	I
Huaimi	I
Huajiao	I
Huangbo	II
Huanglian	I
Huangqi	I
Huangqin	II
Huhuanglian	V*
Huluba	V*
Huzhang	V*
Jianghuang	II
Jiaogulan	III
Jiegeng	III
Jiezi	IV
Jili	II
Jingjiesui	V*
Jinqiancao	III
Jinyingzi	V*
Jinyinhua	II
Jiucaizi	V*
Jixueteng	III
Juemingzi	II
Juhua	V*
Kushen	II
Kuxingren	V*
Lianqiao	I
Lingzhi	II
Luobumaya	III
Luohanguo	III
Luoshiteng	V*
Mabiancao	V*
Mahuang	IV
Maidong	II
Manjingzi	IV
Mianbixie	II
Mohanlian	I
Moyao	V*
Mudanpi	III
Mugua	II
Muxiang	III
Muzei	V*
Niubangzi	IV
Niuxi	III
Nüzhenzi	III
Qianghuo	I
Qianhu	III
Qingfengteng	I
Qinghao	IV
Qingpi	II
Qingxiangzi	IV
Qinjiao	IV
Qinpi	IV
Rendongteng	II
Renshen	II
Rougui	II
Ruxiang	V*
Sangbaipi	II
Sangye	II
Sangzhi	IV
Sanqi	II
Shanyao	II
Shanyinhua	II
Shanzhaye	III
Shanzhaye	III
Shanzhuyu	IV
Sharen	I
Shechuangzi	II
Shegan	I
Shengma	II
Shenjincao	III
Sichangpu	II
Sigualuo	III
Suanzaoren	I
Sumu	IV
Taoren	V*
Tianhuafen	IV
Tianma	I
Tusizi	V*
Wangbuliuxing	IV
Weilingxian	I
Wuweizi	I
Wuyao	V*
Wuzhuyu	I
Xiakucao	IV
Xiangfu	III
Xinyi	II
Xixiancao	II
Xixin	I
Xiyangshen	II
Xuanshen	I
Xuduan	II
Yanhusuo	II
Yimucao	II
Yinchen	II
Yinxingye	V*
Yinyanghuo	II
Yizhihuanghua	V*
Yuanzhi	V*
Yujin	II
Yuxingxao	I
Zangchangpu	II
Zelan	I
Zexie	II
Zhicaowu	II
Zhimu	I
Zhiqiao	V*
Zhishi	V*
Zhizi	I
Zhongjiefeng	III
Zhuru	III
Zicao	V*
Zihuadiding	IV

*Currently in process.

tetrandra (Hanfangji) was mistaken for the root of *Aristolochia fangji* (Guanfangji). The latter contains the carcinogenic aristolochic acid which can produce severe nephrotoxic side effects. A similar Chinese drug is the tetraploid Acorus tatarinowii with a high content of carcinogenic β-asarone in contrast to the diploid *Acorus calamus* L., known officially in most Western countries. This must also be corrected in one of the next Chinese Pharmacopoeias. Meanwhile, special chromatographic methods were developed and described in the analytical monographs to avoid such falsifications.

Great Variability of Plant Species

Several herbal drug monographs of the Chinese Pharmacopoeia list more than 2 species or subspecies, and sometimes up to 8 species labelled as synonyms, subspecies or subvarieties. It is assumed that all species contain the same constituents in the same amount. In 20 years of TLC and HPLC fingerprint investigations, we have shown that in many cases considerable differences were detectable between the single species and the main official drugs. Correspondingly, it may be suggested that a great number of the 'subspecies' do not possess the same pharmacological and therapeutic efficacy. This fact must be taken into consideration.

Processing of TCM Drugs

Apart from simply cutting and cleaning of the raw drugs, the Chinese Pharmacopoeia describes many other types of pretreatment or processing that is not considered in Western pharmacopoeias. In the Pharmacopoeia of the People's Republic of China, the processing is defined as 'a unique pharmaceutical technology that processes crude drugs according to their individual nature, and the requirements of drug dispensing, pharmaceutical preparation, and clinical use, following the Traditional Chinese Medicine theory'. However, in none of the monographs the necessity of specific processing is substantiated. According to the Chinese Pharmacopoeia, processing can be achieved primarily through the following methods: roasting and broiling, scalding, calcining, carbonising, steaming, boiling, stewing with wine, vinegar or salt water and different kinds of stir baking. In one example, the alkaloid-containing herbal drugs of Aconitum spp., *Aconitum carmichaelii* and *Aconitum kusnezoffii*, are treated with salt water, liquorice root, black beans and water after scalding by heating at high temperature with sand. The TLC and HPLC fingerprint analysis shows that in the processed roots, the alkaloids aconitine and mesaconitine are significantly degraded. Here, the necessity to reduce the aconitine content is clear because of its toxicity in higher doses (i.e. in an unprocessed form). Therefore, in Western countries such as Germany, aconitine preparations are acceptable only in homeopathic dilution form (e.g., as aconitum D6 or D12). This means that it is mandatory to limit the proportion of aconitine to a stipulated level.

As far as the processing methods of the Chinese Pharmacopoeia are concerned, they must be replaced by the modern phytochemical methods demanded by the German and by most European drug regulation authorities.

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Disclosure Statement

H.W. is chief of the drug control centre for TCM drugs, located at the University of Munich and member of the hospital's scientific advisory board. R.B. is member and D.M. is chair of this board.

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