

An overview on adverse drug reactions to traditional Chinese medicines

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The safe use of Chinese materia medica (CMM) and products in traditional Chinese medicine (TCM) practice conventionally relies on correct pharmacognostic identification, good agricultural and manufacturing practices based on pharmacopoeia standards and rational/correct CMM combinations with TCM-guided clinical prescribing. These experience-based principles may not absolutely ensure safety without careful toxicological investigations when compared with development of new pharmaceutical drugs. Clinically observed toxicity reports remain as guidance for gathering toxicological evidence, though essential as pharmacovigilance, but are considered as late events for ensuring safety. The overview focuses on the following factors: global development of TCM that has affected conventional healthcare; examples of key toxic substances in CMM; reported adverse drug reactions (ADRs) consequential to taking CMM and TCM products; and proposals on rational approaches to integrate the knowledge of biomedical science and the principles of TCM practice for detecting early ADRs if both TCM products and orthodox drugs are involved. It is envisaged that good control of the quality and standards of CMM and proprietary Chinese medicines can certainly reduce the incidence of ADRs in TCM practice when these medications are used.

Introduction

Background information on traditional Chinese medicine

Traditional Chinese medicine (TCM) is a medical practice with its own diagnostic system and treatment principles that originated in ancient China. It considers the body's well-being in relationship to its functional balances within the physical and social environments, with different principles from those of conventional orthodox medical (OM) practice [1]. To understand the principles of TCM, one may need to recognize the hypothesis of balanced functioning of the body, mind and spirit with healthy flow of activity and energy (collectively known as *Qi*) along the whole person via specific meridians. But if the circulating *Qi* is blocked for any reason or becomes excessive or deficient, pathological symptoms/disease patterns may result. The flow of *Qi* may be disrupted by an imbalanced diet or lifestyle, overwork,

stress, repressed or excessive emotions or lack of exercise. Diagnosis in TCM emphasizes the importance of determining the internal disturbance of the individual person by observing external signs of the body as a whole system. It involves the collection of clinical information from the patient via the four cardinal TCM diagnosis procedures: (i) inspection/observation (features in complexion, eyes, face and tongue); (ii) auscultation (listening) and olfaction (smelling); (iii) questioning/history taking; and (iv) palpation diagnosis (wrist-pulse detection). These four procedures are essential to determine the cause and origin of the problem from which the patient suffers. Some diagnostic steps are similar to questioning/observation procedures in OM diagnosis. The TCM practitioner's accumulated experience in 'palpation diagnosis' to detect the imbalanced flow of *Qi* within the body system, together inspection, listening/smelling and questioning are essential TCM diagnostic procedures. Such procedures allow the practitioner to

decide what treatment is employed under the ‘treatment based on syndrome differentiation’ (or *Bian Zheng Lun Zhi* in Chinese) principles [1–3].

Traditional Chinese medicine treatment often includes the use of acupuncture or medical massage (*Tuina*) to clear stagnant energy along meridians, *Qigong* to balance the state of mind, a Chinese materia medica (CMM) mixture as a drug or as a functional diet/food and *Taichi* for exercising the body [1, 2, 4]. In today’s TCM practice in many countries and regions, some TCM practitioners often prescribe preparations of Chinese medicines, including those which are manufactured as decocted granules from aqueous CMM extracts, proprietary Chinese medicines (PCM) and other over-the-counter (OTC) products [4]. A proprietary Chinese medicine refers to any proprietary product composed of Chinese herbal medicines, formulated in a finished dose form and known or claimed to be used for the treatment of any disease or for the regulation of the functional states of the human body.

These experience-based health/illness observations and treatment methods as recorded in the ancient texts over 3000 years may not be understood readily from OM viewpoints or interpreted in terms of biomedical science. Although TCM never stopped being used for healthcare in the community at large, it is notable that since 1949, when TCM was officially re-introduced, integrative approaches have been adopted in China by the government to provide both OM and TCM healthcare for the public. This integration made it possible to investigate the biomedical scientific aspects of the experience-based TCM principles [3, 4]. Owing to the advancement of science and technology in the postgenomic era [4], since the early 2000s several groups of biomedical researchers have worked on the concept that the complexity of TCM principles can be interpreted in terms of modern biomedical science with systems biology as holistic *in vivo* approaches, with aims to determine the efficacy of TCM [5, 6] and to obtain evidence on how TCM works as well as to assess the quality and toxicity of CMM/PCM [7].

Purpose of the overview

The description above is an oversimplified introduction to the principles of TCM diagnosis and treatment. The purpose of this overview is to provide a current account on the scientific reasons underlying how and why adverse reactions may occur due to improper management and use of TCM products. Special focus is given to the CMM/TCM products; how the recent global development of TCM has affected public acceptance of its contribution to healthcare; key toxic chemicals in CMM; reported adverse drug reactions (ADRs) consequential to taking CMM and TCM products; and an attempt to propose a rational approach to integrate the knowledge of

biomedical science and TCM practice principles for detecting early ADRs if both OM and TCM medications are involved.

Global view on the use of traditional Chinese medicine

Although TCM has played an indispensable role in maintaining the health of people in China and several Asian regions, its biomedical/scientific value remains largely not understood according to the biomedical and OM concept. Many existing reports are often inconclusive due to the often less stringent research design according to the general OM norm of clinical trials. This deficiency has led to criticism domestically in China and worldwide. Many reasons can be given for underdeveloped TCM research compared with the vigorous advances, over a short period of 300 years, in OM development. These reasons may include the following: subjective and individualized TCM diagnosis, which is often incompatible with the conventional methodology for clinical research; the complexity and wide diversity of CMM for treatment of diseases; and the difficulty of choosing correct controls for complex acupuncture, physical therapy and CMM remedies. The lack of research funding and a worldwide shortage of qualified researchers who understand both TCM principles and modern medical knowledge in practice and biomedical technologies should never be underestimated [3, 4].

Despite such limitations in the academic circle, the popularity of TCM is growing fast, not only in Asia but also in the Western world. Traditional Chinese medicine and related complementary medicine have been fully integrated into the health systems of China, North and South Korea, Thailand and Vietnam. It has been reported that ~75% of the population used complementary medicine at least once a year in France, 77% of pain clinics provide acupuncture in Germany, and 90% of respondents in a survey will accept TCM treatment for managing their health and disease [2, 8].

Increasing appreciation and scepticism regarding traditional Chinese medicine

In developed regions worldwide, increasing use of CMM remedies and PCM products has created both scepticism and support of TCM practice, which has been the major debate since the publication in 1992 of a successful randomized clinical trial on the use of a herbal mixture containing 10 Chinese materia medica (CMM) as one prescription for atopic eczema [9]. Unfortunately, sometimes available on the market are CMM products adulterated with pharmaceutical drugs and made of incorrectly identified crude CMM, some of which even result in liver and kidney toxicity. These unprofessional practices, such as adulteration, inappropriate processing

and preparation of CMM products from commercial organizations do not give TCM the right reputation and recognition [10]. It is emphasized that government regulatory agencies should set up harmonized monographic standards for CMM and regulatory control over the import and export of natural or medicinal products to ensure public safety [11].

The requirement for expertise to implement improvement

Specific risks exist with the use of TCM in a conventional OM environment by persons often unfamiliar with the underlying principles of TCM. In Europe, the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) carried out a survey on the status of TCM in 2008/2009. The key points of the findings are summarized in Box 1.

Box 1

Summary of 2008/2009 survey from the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care, Strasbourg (<https://www.edqm.eu/en/CD-P-PC-Committee-of-Experts-on-quality-and-safety-standards-in-pharmaceutical-practices-1329.html>)

- Unlicensed medicines manufactured outside Europe often do not comply with international or European quality standards
- Natural products/remedies used in TCM range from medicines, foodstuffs, food supplements and cosmetics to borderline products
- Major differences exist in the legal status of TCM in Australia, China, Europe, North America and regions with different regulatory approaches
- There is a lack of harmonized requirements for the qualification, training and professional regulation of persons practising TCM
- There is a lack of or insufficient knowledge about the impact of TCM in medical and pharmaceutical practices and public health;
- There is a need for harmonized policies on the products and practices for consumers and patients and for surveillance of the safety of practices and products
- There is a need for specific training for TCM prescribers, dispensers, practitioners and therapists

The resources of professional experts and requirements for quality TCM medications and nonpharmacological interventions are prerequisites before one can assess the

quality, safety and efficacy of TCM treatment and prevention of disease in regions outside China. Traditional Chinese medicine practitioners generally need to have formal university-level education and pass a national/regional qualification examination before being granted a licence to practise, and the commercial TCM products are under national or regional surveillance in China, including Hong Kong and Macau. Global collaboration is believed to be a good way to look at evidence-based practice of TCM and enable it to be integrated into healthcare systems worldwide, as shown in the following section.

Good practices of TCM research in the postgenomic era (GPTCM)

Good practices in research are the basis for evidence-based medicine [12]. The European funded project on GPTCM [13] has amassed over 100 scientists from 15 European and nine non-European countries, who have been actively involved in various disciplines in TCM research and TCM practitioners who have been active in clinical research. They took part in the project during the period from May 2009 to October 2012 to meet and discuss how best to review the published research data available from reliable journals, texts and reports on the good practice of TCM research in 10 categories covering quality, safety and toxicology, *in vitro* and *in vivo* laboratory methods, clinical research in TCM including acupuncture, and regulatory aspects of TCM and herbal products. The consortium of GPTCM has provided a comprehensive review report submitted to the European Commission and published 20 peer-reviewed papers in the 2012 issue of the *Journal of Ethnopharmacology*, volume 140, which are fully accessible to the public as an information dissemination process [14–34]. A continuation of the effort of the consortium has been set up to co-ordinate global development and networking tasks, with the foundation of the GPTCM Research Association (GPTCMRA) in 2012. There are five interest groups in the GPTCMRA, covering quality control and standardization, pharmacology and toxicology, clinical and *in vivo* studies, acupuncture and regulatory affairs [35].

Chemical ingredients in Chinese materia medica and related products

The supply of source materials and manufactured products has not been keeping pace with the ever-increasing global demand for CMM and PCM and related products [8]. Poor-quality products on the market may escape regulatory surveillance in certain regions due to a lack of agreed regulatory control [11]. The commercially available herbal products may be contaminated with

excessive or banned pesticides, microbial contaminants, heavy metals, chemical toxins and pharmaceutical drugs [10]. Excessive toxic substances and microbial contaminants may be traced to the sources and storage of these herbal materials, while the presence of pharmaceutical drugs can be related to unprofessional practice of the manufacturers [10]. Problems arise when herbal materials with confusing ethnic/local naming [36] are available as substitutes, which was the case in the supply of the wrong CMM in a slimming regimen used in Belgium that created several bad headlines on TCM in the West [36, 37]. It is therefore essential to gain knowledge of the chemical constituents or general contents of herbal medicines in order to understand how toxic substances come to be present in these medicinal materials that are supposed to be safe. Examples of traditional CMM will be used to illustrate some of these issues.

The Pharmacopoeia of the People's Republic of China (Generally referred as the Chinese Pharmacopoeia) [38] provides the list of CMMs with upper limits of contaminants described above and other monographic standards. Those which are considered poison/toxic contain extra warnings and guidance for usage. The European Directorate for Quality Medicines and Healthcare (EDQM) has also commissioned a Working Party on TCM to provide drafts of CMM monographs since 2008 [39] for inclusion in the European Pharmacopoeia.

The major chemical constituents in Chinese materia medica

Each CMM may contain hundreds of chemical compounds, some of which are still unknown, mainly as a result of the small amounts that cannot be isolated or detected by existing analytical technology. Those described for analysis in the pharmacopoeias often contain not less than 0.1% w/w of the dried CMM. Some of these compounds may not be the active constituents, but are used only as marker compounds for quality assessment and may fall into the following major categories as summarized in Box 2.

Box 2

Key chemical classes identified in Chinese materia medica as described in pharmacopoeia monographs [38]

- **Alkaloids.** Several alkaloids derived from plant sources have significant adverse effects when they interact with the nervous system. The CMMs that contain alkaloids possess mild activity, and most have antibacterial, fever-reducing and sedative effects, but they produce adverse effects if the dosage is too high and on a prolonged high-dose regimen. In proper TCM practice, the practitioners should be knowledgeable about the use of CMM

formulary of mixtures to avoid excess usage of CMM containing alkaloids. Generally, these compounds are often consumed in quantities of several hundreds of milligrams per day without adverse reactions. Some CMMs contain pyrrolizidine alkaloids that are hepatotoxic [40] (See 3rd bullet point under Box 3.)

- **Flavonoids.** These can be subdivided into flavans, flavanones, flavanols, anthoxanthins and anthocyanidins. Virtually all of these are safe compounds, often present in health supplements and nutraceuticals, which may have antioxidant effects, promote circulation and alleviate allergic reactions. The flavonoids (myricetin and quercetin) in ginkgo leaf [41] and puerarin in *Pueraria Lobata Radix* [42] possess these effects and are used in doses of several hundred milligrams. They are considered safe, apart from interactions with anticoagulant treatment.
- **Pyrones, quinones and other oxygenated compounds.** Virtually all of these are safe compounds that promote circulation and alleviate spasms and pain. For example, the benzopyrones of *Angelica sinensis Radix* (Danggui) and the quinones of *Salvia miltiorrhiza Radix et Rhizoma* (Danshen) are used to aid circulation and relieve pain and are used in doses of several hundred milligrams. However, both are contraindicated with warfarin treatment [43–45]. Some quinones form active oxygen radicals *in vivo* after biotransformation, which are toxic to the body after prolonged usage with high dose, similar to paracetamol overdose poisoning.
- **Terpenes.** They can be subdivided into mono-, di-, tri- and sesqui-terpenes. Virtually all of these are safe compounds that may have effects of promoting circulation and calming agitation. The triterpenes of Asia ginseng (*Ginseng Radix* from *Panax ginseng*), American ginseng (from *Panax queqifolius*), Sanqi (*Notoginseng Radix* from *Panax notoginseng* Burk F.H. Chen), Dazao (from *Ziziphus jujube* Mill.) and Chaihu (*Bupleuri Radix* from *Bupleurum chinense* DC) are consumed in quantities of several hundreds of milligrams to provide circulation-promoting and sedative effects safely.

Key intrinsic toxic substances in Chinese materia medica

Poisonous and potent CMMs are documented in the Chinese Pharmacopoeia [38], which provides processing details, extra warnings and guidance for usage. These CMMs contain intrinsically toxic chemicals that can harm the body with high doses and on prolonged usage. They are considered as special scheduled drug/substances [11] in some regions and can be prescribed only by

experienced TCM practitioners. Examples of these key CMMs containing toxic chemicals are shown in Box 3.

Box 3

Intrinsic toxic chemicals found in certain restricted Chinese materia medica

- Aconitines. *Aconiti kusnezoffii* Radix Preparata (Zhicaoowu), *Aconiti* Radix Preparata (Zhichuanwu) and *Aconiti lateralis* Preparata (Fuzi) contain the toxin aconitine and related alkaloids. Although they have been processed by hydrolysis from source materials to less poisonous alkaloids, such as hyaconine and mesaconitine, their monographs emphasize that the total content of the three alkaloids should not be >0.02%. They can be prescribed only by experienced TCM practitioners according to formulary principles of composite CMM prescriptions. These CMMs are seldom used as single herbal drugs.
- Strychnine and brucine. Processed *Strychni semen* (Maqianzi) contains 1.2–2.2% of strychnine and 0.8% brucine calculated with reference to the dried drug, and this CMM can be prescribed only by experienced TCM practitioners.
- Pyrrolizidine alkaloids. These can be found as natural constituents in 12 plant families. The edible sources, including milk, honey, wheat, herbal medicines, herbal tea, dietary supplements and functional foods, have been found to be contaminated with pyrrolizidine alkaloids [40], which may potentially cause human health problems, such as veno-occlusive liver disease, when ingested with foods or herbal medicines. Chinese materia medica containing pyrrolizidine alkaloids include *Arnebiae seu Lithospermi* Radix (Zicao), *Senecio scandens* (Qianliguang) and *Tussilago farfara* Flos (Kuandonghua).
- Aristolochic acid. There has been a reduction in the number of CMMs containing this lethal toxin for inclusion in the 2010 CP since the early records in the Chinese Compendium of Materia Medica (Ben Cao Gang Mu) compiled by the venerated physician Li Shizhen (1518–1593) of the Ming Dynasty [46]. This is due to an episode of unprofessional use of a wrongly named CMM, *Aristolochia fangchi* Radix (Guangfanhchi), in a commercial product consisting of pharmaceutical drugs and herbal medicaments as a regimen for weight reduction [35, 36], resulting a series of end-stage renal disease cases [47] in Belgium. This CMM toxicity episode has opened up a worldwide investigation on the toxicity of aristolochic acids in medicinal plants used in other ethnic medicines and weeds that are found growing among food crops in the Balkan regions [48].

Reports of adverse drug reactions related to Chinese materia medica and proprietary Chinese medicinal products

Pharmacovigilance systems remain the best source of ADRs for herbal medicines in general, but are not as well developed as the pharmaceutical reporting systems. For this reason, it is likely that the true incidence of ADR events may be under-reported.

Official channel

China's National Center for Adverse Drug Reaction Monitoring (CNCADRM) was established in 1989 by the State Food and Drug Administration (SFDA, which has now been renamed the China Food and Drug Administration, CFDA), well before China joined the World Health Organization's Programme for International Drug Monitoring in 1998. In March 2004, China formally promulgated the final version of the Regulations on Adverse Drug Reaction Reporting and Monitoring. This modern system supplements an informal reporting system in scholarly publications [49]. The CFDA oversees an extensive network of drug safety 'watchdogs', including the CNCADRM and 32 regional centres throughout China for both pharmaceuticals and TCM products. While postmarketing surveillance guidelines are not yet available in China, it was pointed out in the review by Du and co-workers [49] that eventual issuance may include adaptation to particular cultural and clinical practices.

The review by Du and co-workers [49] reported that the system for ensuring drug safety has faced several big, unique tests in recent years. The first challenge came from a TCM product:

Houttuynia Herba (Yuxingcao) is used traditionally in composite formulae in aqueous decoction form. In the 1980s, injectable formulations of Houttuynia Herba were approved by the then SFDA; as the product was available in cheaper prices resulting with rapid effect that it became widely used in clinical practice for infections. From 1988 to 2003, the CNCADRM received 272 adverse drug reactions/adverse drug events (ADR/ADE) reports, 52 of which were for severe ADRs/ADEs, related to its injection [50]. In August 2003, the National Center issued a warning letter to health professionals [51]. Then, on June 1, 2006, the SFDA temporarily withdrew all seven injectable forms of the Houttuynia Herba from the market [52]. After a three-month evaluation, the SFDA decided to let the injection return to the market step by step with risk management (e.g., collecting ADR/ADE reports and alerting clinicians about appropriate use) [53] with instructions for production of the herbal injection.

The authors of the present overview do not consider that the 'Houttuynia Herba Injection' is a traditionally

recognized TCM medicine. It is a new class of medicine approved by SFDA and permitted to be prescribed in China.

Academic publications

Meanwhile, academic publications on ADRs remain the key published data that can be collected for information, as reviewed in a series of annual reports from the 'Side Effects of Drugs Annual' (SEDA) edited by J.K. Aaron and published by Elsevier [54]. Of particular interest in terms of ADRs resulting from treatment with TCM, the annual accounts from 2010 to 2012 can be located in Chapter 48, 'Treatments used in complementary and alternative medicine', of the series of SEDA. Details of the 2012 version are included in the reference list [55].

Depending on the data available in the literature, most of the reported ADRs are either case reports or case series. The topics reported in the Annual for TCM treatment include the following: oral formulations in ready-made PCM products; injectable formulations of CMM; nutritional supplements; specific medicinal plants; acupuncture treatment; massage therapy; and interactions between pharmaceuticals and TCM products.

Global overview of factors responsible for adverse drug reactions from traditional Chinese medicinal products

Concern regarding ADRs from TCM treatment exists in developed regions where increasing TCM practice is being observed. Despite the limited scope, a recent survey of practitioners in Europe and China provides some reassurance that the vast majority of CMMs and PCMs in regular use are known to be relatively safe [56]. This can be interpreted by considering key factors that are responsible for the reported ADRs.

Those CMM that contain identifiable intrinsic toxic ingredients, as summarized in Box 3, will receive particular attention in regions outside China, where most of them are banned from usage due to regulatory control. Yet some of these toxic CMM are useful for treating difficult diseases [57] when used by experienced TCM practitioners even though they are banned by some regional regulatory bodies [58]. It is important to distinguish good practice and malpractice in the integrity of the TCM industry and practice whether within or outside China. Adverse events have been found to be mainly the result of using contaminated products and lack of competence of practitioners in Europe (see Box 1), rather than because CMM/PCM medicines are inherently risky. The Medicines and Healthcare Regulatory Agency in UK has warned against herbal products that

may be manufactured to low quality standards and be deliberately adulterated or accidentally contaminated with toxic or illegal ingredients [59, 60].

Box 4 summarizes the key factors that are involved in the outcomes of ADRs when CMM/TCM products are used. Pharmacovigilance systems have only been established recently for CMM medicines in China and not in other regions, thus the true incidence of adverse events may be under-reported or inaccurate; nevertheless, the available data indicate that their overall safety is better than would be suggested by the widely publicized incidents involving adulterated products and herbs known to be toxic [56].

Box 4

Some key factors responsible for adverse drug reactions to Chinese materia medica/proprietary Chinese medicinal products

1. Pharmacopoeia standards of CMM/PCM

- Variability of control assurance on the qualitative and quantitative composition of CMM/PCM
- Accidental supply of incorrect species, adulterants, pharmaceutical additives
- Uncontrolled contaminants from origin (pesticides, heavy metals) during storage (microbial and mycotoxins) and inadequate processing (excessive toxic chemicals)

2. Patients' conditions

- Ethnic/regional variability in drug response; patients' constitutions according to TCM diagnosis
- OM pathological conditions (hepatic and renal function; immunological compromise)
- Compatibility of OM/TCM diagnosis

3. Treatment complications

- TCM injectable products require extra pharmacovigilance
- Incorrect OM/TCM diagnosis
- Irrational withdrawal of medications
- Co-administration of OM and TCM medicines/potential drug-CMM interactions
- Acute and chronic treatment with OM and TCM

Future monitoring steps for adverse drug reactions in traditional Chinese medicine industry and practice

The regulatory role of pharmacopoeia standard

The community's impression, often incorrect, that herbal and natural products, including CMM/TCM products, are

safer than synthetic pharmaceutical medicines can only be assured via reasonable regulatory controls on these products. The present official and unofficial pharmacopoeias provide different standards in their monographs of herbal/natural materials [11], and it is also worth mentioning that global regulatory bodies have widely different view over registration of herbal products [25]. These regulatory bodies should co-ordinate a global agreement on monographic standards as suggested [11], which demand that the suppliers should provide traceability of their sources for TCM practitioners' prescribing and manufacturers' good manufacturing practice.

The challenge for future development of high-quality and safe traditional Chinese medicinal products

It is well known that no single chemical marker component is responsible for the total efficacy of TCM prescriptions [32, 33]. Pragmatic comprehensive fingerprinting analysis using modern combinations of instrumental technology, such as gas chromatography–mass spectroscopy, high-performance liquid chromatography–mass spectroscopy, high-performance thin layer chromatography–mass spectroscopy and ultra-performance liquid chromatography–mass spectroscopy, can disclose the composition and concentration of detectable ingredients in quantifiable operational conditions and therefore provide real-time quality information. Tilton and co-workers [34], using fingerprinting technology and gene-expression monitoring, worked on the quality assessment of a TCM composite formula called Huang Qin Tang, which was developed as a product with intellectual property protection known as PHY906. This composite formula, consisting of four distinct CMMs [*Scutellaria baicalensis* Radix (Huangqin), *Glycyrrhiza uralensis* Radix (Gancao), *Paeonia lactiflora* Radix (Baishao) and *Ziziphus jujuba* Fructus (Dazao)] has been documented for nearly 1800 years for treatment of common gastrointestinal distress, including diarrhoea, abdominal spasms, fever, headache, vomiting, nausea, extreme thirst and subcardiac distension. In addition to the requirement for conventional limit tests, such as tests for heavy metals, microbes and pesticide residues, with a multifaceted approach, the software technology PhytomicsQC was used to integrate the high-resolution chemical fingerprint, focusing on high-performance liquid chromatography–mass spectroscopy, the bioresponse fingerprint with genomics technology on differential cellular gene expression, the pharmacological *in vivo* validation in an animal model and a sensitive, quantitative comparison method. Such systems approaches using multifaceted technology (a combination of biological and chemical analyses) are not only good for the quality assurance of complex CMM mixtures, but also useful for the discovery of new indications or the development of new combinational formulae and new single-chemical compounds for drug development from phytochemical sources [Scheme 1 of reference 2].

PHY906 has eventually been approved by the US Food and Drug Administration (FDA) for Stage II clinical trials as an adjuvant therapeutic for several cancers [29]. Box 5 provides a summary of the steps involved.

Box 5

A summary on the future development of safe Chinese materia medica products

- Global harmonization of pharmacopoeia standards on CMM/PCM products [11]
- Future development of global regulations of PCM products [25]
- Chemical fingerprints as minimal quality control tools for CMM/PCM [32, 33]
- Application of comprehensive quality control for herbal products [34]
- Clinical trial of PCM with omics-based and TCM stratification [17, 26, 31]

Concluding remarks

It can be estimated that from monographs of CMM that ~5% of one non-toxic group of chemical constituents will probably provide some 50 to 100s mg of those compounds. Thus, a dose of several grams of the CMM in composite formula can usually be taken up orally, while the amounts of active components consumed would be in the region of hundreds of milligrams without any significant adverse effects from experience-based observation. Chinese material medica that have significantly toxic compounds (aconitines, aristolochic acids, pyrrolidines and strychnines) and those specifically depicted in the CP are not normally incorporated into the ready-made PCM and should not be available for use in the Western practice of TCM because of regulatory control on the import and export of these products [11, 58]. These potent CMM are only used professionally by experienced TCM practitioners in prescribed composite formulae (taken as decoctions) for appropriate disorders and for short period of treatment.

Properly trained TCM practitioners should have awareness and a good grasp of the therapeutic use of CMMs. A thorough knowledge is needed to recognize the types of activities to be expected from the dosages involved. From this information, one can analyse the reports of potential adverse reactions and draw certain tentative conclusions on the reported ADRs. Frequently, patients, medical personnel and practitioners who have had limited training in the use of CMM/PCM products may conclude that CMMs are the cause of producing a certain ADR. Information on chemical constituents in CMMs, their pharmacology, clinical effects, potential

ADRs and other valuable data are available in many Chinese language texts and some but not plentiful English language books and journals. If the reported ADR is observed outside China where the information is not available, adequate training is required for professionals and practitioners to study and be aware of the source of such materials before patient complaints are received and analysed. It is conceivable and possible to provide a rational response promptly and initiate a proper investigation. A good understanding of the mechanisms and timing of various types of reactions (such as allergies and toxic responses), interactions between CMM and pharmaceutical drugs, as well as the traditional Chinese medicine concepts and related interpretation of CMM effects (such as mutual contraindications in CMM combinations) will make it possible to use CMM as prescribed treatments with confidence and respond to concerns accurately and authoritatively. To establish such approaches, there is an urgent need to produce an updated and user-friendly database based on 'TCM-ADR and Interactions' and on the previous published text on 'Interactions between Chinese Herbal Medicinal Products and Orthodox Drugs' [61].

To avoid incidents of ADRs to TCM in the good practice environment, quality assurance of CMM and PCM and other TCM products remains one of the key factors for global acceptance of their evidence-based usefulness in healthcare. Only when this assurance is in place under regulatory control will safe products be available for practitioners to prescribe. As indicated in previous sections, basic and applied research towards mechanistic investigation, modes of action and development of combinational herbal medicines will produce meaningful directions for evidence-based or clinical studies [4]. Full control on the quality and standards of CMM/PCM can certainly reduce the incidence of ADRs in TCM when these medications are used.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; KC was appointed as the Joint Chair Professor under The Joint Chair in Traditional Chinese Medicine Program, by Office of Science Research in NSW, the University of Sydney and University of Western Sydney, Australia.

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