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Why is Research on Herbal Medicinal Products Important and How Can We Improve Its Quality?

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ABSTRACT

Research on herbal medicinal products is increasingly published in "Western" scientific journals dedicated primarily to conventional medicines. Publications are concerned mainly not only on the issues of safety and interactions, but also on efficacy. In reviews, a recurring complaint has been a lack of quality studies. In this opinion article, we present the case of Chinese herbal medicines as an example, as they have been extensively used in the global market and increasingly studied worldwide. We analyze the potential reasons for problems and propose some ways forward. As in the case of any drug, clinical trials for safety, efficacy, and/or effectiveness are the ultimate demonstration of therapeutic usefulness of herbal products. These will only make scientific sense when the tested herbal products are authentic, standardized, and quality controlled, if good practice guidelines of evidence-based medicine are followed, and if relevant controls and outcome measures are scientifically defined. Herbal products are complex mixtures, and for such complexity, an obvious approach for mechanistic studies is network pharmacology based on omic tools and approaches, which has already begun to revolutionize the study of conventional drugs, emphasizing networks, interactions, and polypharmacological features behind the action of many drugs.

Key words: Herbal medicinal products, Network pharmacology, Omic tools, Polypharmacology, Traditional chinese herbal medicines

INTRODUCTION

A recent PubMed search (done in September 2013) using the key word *herbal medicinal products* (HMPs) gave rise to 30,917 hits, with about 2700 of them published in 2013. The first (most recent) 10 papers deal with type II diabetes or diabetic nephropathy, comparison between Europe and China on the safety of materials, the European Union (EU) herbals directive, plant metabolomics in quality assessment, various activities of selected herbs, and integrative nanomedicine.[1-10] Examples of typical articles published in a Western medical journal are either original papers on interaction potential,[11,12] or systemic and general reviews on the use of herbal medicines in various conditions,[13,14] on the quality, efficacy, and safety,[15] on herb–drug interactions[16,17] or herbal side effects, especially in hepatotoxicity.[18] A recurring theme in conclusions of these reviews was the lack of adequate scientific data to judge efficacy and/or safety and the less-than-desirable quality of the published data. At least in the Western scientific establishment, there is a rather strong impression that research

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on herbals has been rather haphazard and sporadic, when compared with conventional medicines, and often also outdated and wanting of quality.

CURRENT CONDITION OF HERBAL RESEARCH

What is behind the current condition of herbal research?

There are some obvious, although not thoroughly surveyed, reasons for the current condition of research on herbals. The first is lack of sustainable funding in this area. In the USA, the situation is probably improving. Since 1999, National Center for Complementary and Alternative Medicine (NCCAM) at National Institutes of Health (NIH) has been funded US$ 50-128.8 million per annum, which has been dedicated to complementary and alternative medicines including herbal medicines. The above-mentioned "less-than-desirable quality" is also due to lack of funding and functional mechanisms for interregional, intersectoral, and interdisciplinary collaborations on training and sustaining people to do high-quality herbal research and on dissemination, implementation, and further refinement of good practices, resulting in the sporadic feature of research and various expertise needed for high-quality herbal medicine research scattered around different parts of the world.

Changing research and market for herbal medicines – Chinese herbal medicines as an example

There are a number of reasons to think that HMPs have a potential to become a significant part of efforts to advance drug discovery and development. In particular, pharmacologists shuffling through recent issues of international journals have certainly become aware of an increasing contribution of research from China, often dealing with traditional Chinese herbal medicines or their components. This mere observation testifies the emphasis of the Chinese scientific establishments on the research of their 2000-year medicinal heritage.

It has been estimated that total value of the world market for herbal products stands at around $83 billion and Europe accounts for over 50% of the total.[19] Also, the use of Chinese herbal products is a worldwide phenomenon and Europe has a long history of their use and research.[20] For instance, in 2008, China announced a major economic stimulus package, including an investment of US$ 124 billion in healthcare. Due to the deep cultural roots of herbal products in China with its 1.3 billion people and the strong commitment of the State to further develop their use in both domestic and global settings, it is anticipated that in the coming years, a larger global market for herbal products will be created.[21] Chinese herbal products are important for Europe because after Asia, Europe is the second largest import/export market of these products,[20] and in China alone, approximately 100,000 herbal formulae and over 11,000 individual medicinal plants have been documented, which are generally hailed as rich natural resources for developing new drugs, including new lead compounds and new types of multi-component drugs.[22,23]

Changing attitudes of regulators in the EU and the USA toward HMPs

In the EU, HMPs have been granted an official medicine status by the European Medicines Agency through legislation in 2001 and its Committee on Herbal Medicinal Products was established in 2004. Since then, more than 100 HMPs have undergone scientific assessment, which in most cases have resulted in a regulatory status either as a well-established use or a traditional use. These classifications relate to the time a product has been on the market in the EU and elsewhere and also to the nature and adequacy of scientific evidence.

In the USA, most HMPs still fall under the legislation of botanical products, i.e. they are under food legislation. Historically, the US Food and Drug Administration (FDA) has been reluctant to approve herbal products as prescription drugs due to their complexity, but this has now changed since Veregen (sinecatechins), the first herbal product derived from green tea (綠茶 Lǜ Chá; Camellia sinensis), was approved by the FDA in late 2008 for certain types of external genital or perianal warts,[24,25] followed by Crofelemer approved in December 2012 for the relief of diarrhea in HIV/AIDS patients taking antiretrovirals.[23] In 2010, it was estimated that approximately 25% of botanical investigational new drug (IND) applications submitted to the FDA were derived from Chinese herbal medicines.[26] Indeed, as a group of specialist FDA officials have concluded, although new botanical drugs pose many challenges for both industry and the FDA, these challenges can be successfully met.[25] Currently, a number of standardized Chinese herbal products have been under clinical trials in the USA, including PHY906 (黃芩湯 Huáng Qín Tāng) for cancer patients, which has passed a multicenter, open-label, dose escalation phase I/II trial,[27] and Dantonic® (丹參滴丸 Dān Shēn Dī Wán), which is undergoing phase III trial for the prevention and treatment of stable angina.[28] In addition, after a multicenter trial and a liver re-biopsy study in Asia demonstrating good safety and efficacy profiles,[29,30] Fuzheng Huayu is now in a phase II clinical trial for patients with hepatitis C–induced liver fibrosis in America.[31] In keeping with the positive attitude of the FDA, the NIH also emphasizes the importance of traditional and alternative medicines through establishing NCCAM, with a budget of US$ 120.7 million for 2013.[32] The industrial sector also reacted to the promising prospects of Chinese herbal products. For example, Pfizer and GlaxoSmithKline have greatly increased their investments into further developments based on Chinese herbal medicines.[33,34]

Why are new approaches needed?

There are several reasons why new approaches are needed to tackle challenges in drug development and clinical treatment. Possibly the most important reason is the emergence of chronic diseases as major causes of morbidity and mortality in developed countries and increasingly also in developing countries. Most chronic diseases are not single entities. Instead, there are usually several etiological factors and multiple mechanisms within numerous molecular pathways and networks behind various manifestations of the disease.[35,36] Preventing and treating these major chronic diseases have led to the use of multiple drugs to tackle different targets and various symptoms, which furthermore

have been associated with an increasing frequency of adverse interactions and side effects.[37] While drug development has generated novel drugs (albeit rather slowly), the outcome of drug treatment has not improved to an expected extent, judged on the basis of risks and benefits. It seems that one of the reasons for the less-than-satisfactory success of drug development during the recent decades has been the single-target–single-compound or one-disease–one-drug paradigm based on the emphasis of molecular biological approaches and tools.[38] Molecular biology has been extremely successful in finding and pinpointing potential drug targets, but the consequent development of exceedingly potent and selective compounds has not fulfilled expectations in clinical reality. Consequently, it seems desirable to cover multiple targets at the same time with multiple active principles, but at a balanced and personalized manner.

HERBAL MEDICINES AS MULTI-TARGET DRUGS FOR COMPLEX DISEASES

Herbal medicines are complex drugs with multiple potential targets and actions

To treat a complex chronic disease would require covering multiple targets, and in conventional drug therapy, this leads to polypharmacy. In this light, it has to be stressed that herbal medicines, just for the sake of them being based on plant-derived products, are chemically complex mixtures containing multiple major and minor constituents with multiple potential targets and mechanisms. European tradition has been slow in recognizing these new possibilities perhaps because of the currently ongoing consolidation of the EU legislation concerning well-established and traditional medicines. Meanwhile, some other traditional medicines, such as those used in Asia,[39] not only provide invaluable knowledge resulting in new Western drugs and drug leads,[40] but also highlight different approaches characterized by personalized medicine and the use of complex herbal products.[25] Accumulating evidence suggests that using omic methods, including genomics, transcriptomics, epigenomics, proteomics, metabolomics, etc., to revisit traditional medicines will lead to new insights and offer opportunities for new types of medicine.[41,42]

What is an appropriate conceptual background?

For complex medicines, the current reductionist approach (which has worked admirably with conventional single drugs) is ill suited for analyzing the actions and interactions of multiple chemicals with multiple targets at different levels of an organism. Instead, a systems approach is required, be it called systems or network biology, medicine or pharmacology, whose "goal is to understand in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology."[43] Development of drug–target and drug–ligand networks to reveal an essentially polypharmacological nature of conventional drugs and the application of the ensuing polypharmacology to disease networks have resulted in a new, more comprehensive view of drugs as multitarget molecules, with often overlapping on-target and off-target actions.[44-46] For this concept to be applicable to complex herbal products, one has to replace only a multitude of conventional drugs (which is usually derived from the database of FDA-approved drugs) with HMPs with multiple components. There are already a few examples of the application of network pharmacology in the analysis of multiple targets and actions of a specific HMP.[47]

What kind of scientific tools are needed?

The above conceptual background for drugs is still based to a large extent on *in silico* exercises, even if some of its predictions have been studied and often successfully proven by experiments.[45,46] Models and networks need to be populated by experimental data, which come from studies using various omic techniques, and naturally by bioinformatics for retrieving, storing, and handling of the huge amount of data.

As a legacy of the multibillion dollar human genome sequencing projects, technological innovations have exponentially increased affordability of genomic and transcriptomic studies. Meanwhile, shotgun proteomics,[48] targeted proteomics,[49,50] and multiplexed quantitative proteomics using isobaric tags[51] have made the proteomics technology faster, more sensitive, and much more affordable than ever before. To illustrate the affordability of the metabolomic technology, an international company specialized in metabolomic service charges US$ 350 per sample, including sample processing, high-performance liquid chromatography/mass spectrometry (HPLC/MS), gas chromatography/mass spectrometry (GC/MS) analysis, statistical analysis, pathway mapping, and data interpretation. Finally, analysis of omic data or integrated data from different omic levels can now be addressed using a systems biology approach.[52]

The omic techniques are increasingly being used in connection with functional screening assays, which are able to measure phenotypes, i.e., complex physiological and pathological traits and perturbations.[53] A recent analysis suggested that the majority of recent first-in-class drugs are actually developed with the help of phenotypic screening assays.[54] It is envisaged that in the long run, it is possible to build a screening scheme in which various subcellular and cellular assays are used in conjunction with most modern analytical data-rich techniques, e.g. omics, imaging, and chemical analytical tools, to enable a comprehensive screening paradigm. One such example is the suggestion to screen complex herbal products with respect to absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic characteristics in a stepwise manner, envisaged to lead to the prediction of pharmacokinetic behavior of a product before actual clinical trials.[55]

THE WAY FORWARD

The way forward – GP-TCM as an example

To promote good practice in the research of traditional Chinese medicine (TCM), with a particular focus on Chinese herbal medicines, the *Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era* consortium, widely known as GP-TCM, was launched by the European Commission under its Seventh Framework Programme (FP7) on 1 May 2009.[56] With two of us (QX, TPF) as coordinator and deputy coordinator, re-

spectively, this 3.5-year FP7 coordination action project discussed state of the art and produced guidelines for studies of Chinese herbal medicines, with an emphasis on using an omic approach. The consortium voted confidence in the omic and network pharmacology technologies in the research of complex herbal products and had their main findings published in the open-access GP-TCM *Journal of Ethnopharmacology* special issue.[57,58] For example, the consortium noted that an omic approach was granted a patent for quality control of complex herbal products in 2003 (Patent Cooperation Treaty No.: GB00/00428), was successfully applied to control the quality and investigate the mechanisms of action of Huangqin Tang (黃芩湯 Huáng Qín Tāng), a Chinese herbal medicine formula of four herbs,[27,59,60] and was also explored in personalized diagnosis and for rescuing drug discovery.[41,42] To ensure sustainable collaborations in the development and refinement of good practices beyond the lifespan of GP-TCM (May 2009-October 2012), the FP7 consortium also led the establishment of a new not-for-profit organization, known as the GP-TCM Research Association.[61] Launched in April 2012, this association has officially succeeded the missions and legacies of the FP7 GP-TCM project since November 2012. It will remain a devoted link between Europe, China, and other parts of the world, especially dedicated to dissemination, validation, and further development of good practice guidelines through interregional, interdisciplinary, and intersectoral collaborations.

Search for promising leads and useful assays

As pharmacologists/toxicologists (OP, TPF) and nephrologist (QX), we became interested in Chinese herbal medicines for different reasons, but all based on evidence. For example, in a UK–China collaboration led by King's College London, anti- and pro-fibrotic activities of herbs used in TCM were studied systematically using objective, quantitative, and novel assays, based on reports in the literature[62] and also guided by the theories and practice of TCM.[63] Extracts of 17 herbal formulae and 11 individual herbs as well as 5 herbal compounds were found to be anti-fibrotic and extracts of 3 herbs were found to be pro-fibrotic.[62,63] Thus, there are real activities in herbal entities. The question is how to improve the quality of research on herbals, especially complex herbal mixtures, so that they can be used more efficaciously and more safely.

Another interesting example is our observation on herbal regulation of angiogenesis. Ginseng (人參 Rén Shēn) is a commonly used nutraceutical. Intriguingly, existing literature reports both wound-healing and anti-tumor effects of ginseng extract through opposing activities on the vascular system. To elucidate this apparently contradictory perplexity, the University of Cambridge led an international team and merged a chemical fingerprinting approach with a deconstructional study of the effects of pure molecules from ginseng extract on angiogenesis.[64,65] A mass spectrometric compositional analysis of American, Chinese, and Korean ginseng, and Sanqi (notoginseng) revealed distinct "sterol ginsenoside" fingerprints, especially in the ratio between a triol, Rg_1, and a diol, Rb_1, the two most prevalent constituents, with the dominance of Rg_1 leading to angiogenesis, but Rb_1 exerting an opposing effect. This study explained, for the first time, the ambiguity about the effects of ginseng in vascular pathophysiology based on the existence of opposing active principles in the extract. Differential gene expression profile of human endothelial cells revealed Rg_1 promotes angiogenesis via the modulation of genes that are involved in cytoskeletal dynamics, cell–cell adhesion, and migration. Further work demonstrates that Rg_1 stimulates angiogenesis via endothelial nitric oxide synthase (eNOS)[66] and vascular endothelial growth factor through the glucocorticoid receptor,[67] while Rb_1 and Rg_3 inhibit angiogenesis by up-regulating pigment epithelium-derived factor through the β estrogen receptor.[68] It is noteworthy that some metabolites of ginsenosides are novel inhibitors of breast cancer resistance protein.[69]

Another angiogenesis modulator is *Angelica sinensis* (當歸 Dāng Guī), which contains alkylphthalides, ferulic acid, and polysaccharides. Previous reports showed that *n*-butylidenephthalide (BP), an alkylphthalide derived from the volatile oil of Radix *A. sinensis* (VOAS), exhibited anti-platelet, anti-anginal, and anti-cancer activities. We have recently reported that BP and VOAS are anti-angiogenic.[70,71] In contrast, Lam *et al.,*[72] showed that an aqueous extract of Radix *A. sinensis* (AQAS), which contained 60% polysaccharide, was pro-angiogenic. These studies clearly highlight the fact that a single medicinal plant contains a variety of bioactive compounds, sometimes with opposite pharmacological activities.

Research at University of Oulu has been especially focused on pharmaco/toxicokinetic and safety assessment of HMPs, which poses great challenges due to their complex nature. The chemogenomic approach could provide important predictions also for potential harmful effects, as recently demonstrated for some TCM and Ayurvedic medicines by Mohd Fauzi *et al*.[73] However, these essentially *in silico* predictions have to be confirmed and eventually validated by experimental and/or clinical studies, in which omic approaches might be invaluable in surveying and delineating various toxicities and underlying mechanisms of actions.[74] The *in vitro* metabolism, transport, and interaction assays used for conventional drugs under development have been successfully applied and modified for the study of HMPs.[75-77] However, currently, it is possible to predict the behavior or responses of the complete HMPs on the basis of their individual components only to a limited extent. It is obvious that the presence of multiple components will give rise to interactions at all levels of kinetics and dynamics of HMPs, for good or bad.

Good practices and a paradigm change in complex herbal medicine research are necessary

Based on the above analysis, we are convinced that HMPs are both interesting and important. Looking forward, good practices and a paradigm change are necessary to study HMPs in a productive way. Examples have been set regarding traditional herbal medicines by some pioneering groups, and in particular, by the GP-TCM project funded by the EU, establishing the necessary framework to facilitate the change. The GP-TCM Research Association is expected to play a major role in moving forward good practices in this increasingly important area. To further facilitate this, European funding like those provided by the NCCAM in the USA will be needed. Admittedly, the one-disease–one-drug

concept will still benefit by the new approach in that promising leading compounds will be identified and used for further development. However, this is not enough because complex chronic diseases need complex therapeutic solutions, and complex herbal medicines may play a significant role in supplying such solutions and lead to efficient and safe prevention and treatment. At least they are worthy of a fair trial.

What are the implications of the above perspectives and arguments to clinical pharmacology? Thus far, clinical trials on HMPs have provided a rather indefinite and even bleak view about their therapeutic benefits. However, it is quite possible that the current gold standard, a placebo-controlled randomized double-blinded trial, is unable to provide a relevant outcome about medicines that are primarily intended for personalized and holistic use, as is the case with Chinese herbal medicines. Nonetheless, the FP7 GP-TCM project has agreed on a guideline on randomized controlled clinical trials of Chinese herbal medicines,[78] which should serve as a plausible starting point for further development. In any case, whatever the form of the clinical trial is, at least the major results emanating from omic experiments and systems analyses should be considered and incorporated into the design of clinical trials, especially regarding relevant surrogate markers as clinical endpoint measures and for mechanisms.

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