The Art and Science of Traditional Medicine

Part 2: Multidisciplinary Approaches for Studying Traditional Medicine
Herbal genomics: Examining the biology of traditional medicines

Traditionally herbal medicines, such as plant- and fungi-based remedies, have been used for more than 5,000 years. However, the genetic background, the agricultural traits, and the medicinal quality of most traditional herbs are poorly understood. With rapid advances in high throughput sequencing technologies and greatly reduced costs, a new discipline called “herbal genomics” has emerged. Researchers are now systematically categorizing medicinal herbs by sequencing, assembling, and annotating their genomes, and by analyzing their genes’ functions. The genomes of some commonly used herbs have already been sequenced, such as Ginseng (Ginseng radix or “mushroom of immortality”). This species has provided an effective model system that has facilitated the study of the biosynthetic pathways of secondary metabolites in medicinal fungal species (1). Genomic information, together with transcriptomic, proteomic, and metabolomic data, can therefore be used to predict secondary metabolism biosynthetic pathways and their regulation, triggering a revolution in discovery-based research aiming to understand the genetics and biology of herbs. Herbal genomics provides an effective platform to support the chemical and biological analyses of complex herbal products that may contain more than one active component. Therefore, it is now being applied to many areas of herb-related biological research to help understand the quality of traditional medicines and for molecular herb identification through the establishment of an herbal gene bank. Moreover, functional herbal genomics can contribute to model herb research platforms, herbal research, genomics-assisted herb discovery, and herb biology. All of these are important for securing the sourcing of the medicinal plants and their active compounds in the future.

Creating model herbs

With the recent developments in biotechnology and genomics, several species including Ginseng, Salvia miltiorrhiza, Ganoderma lucidum, Catharanthus roseus, and Aristolochia clematitis have emerged and have emerged as valuable models for studying the genetics and metabolic activities of herbs. These species have been shown to synthesize active pharmaceutical components, including iridoids, diterpenoids, and indole alkaloids. Although the core biosynthetic pathways of secondary metabolites in herbs are conserved, downstream pathways have evolved by adaptation and drift (2). Therefore genes from different cultivars of medicinal herbs or evolutionarily related species can be evaluated using these herbal models to understand the mechanisms underlying natural variation. These model systems can also be used to identify novel biosynthetic pathways for convergent secondary metabolites in closely related herb species. Recent advances in genome editing have provided feasible approaches by introducing or altering specific alleles; hence, genetic control over metabolites can be investigated (3). Although the elucidation of biosynthetic pathways is one of their most appealing features, model herbs can also provide information on perennial habits, development patterns, cultivation requirements, and resistance to environmental or biological stress (4).

Biological basis of geoherbalism

The Chinese concept of geoherbalism encompasses the use of “authentic” or “superior” herbs, which are produced in a specific location under optimal growth conditions of medicinal products and specific herb genotypes, allowing both genetic and environmental factors to be taken into account when considering herbal growth. ‘Omics provide novel and powerful tools to elucidate the molecular basis underlying geoherbalism and to select elite varieties. Creating herb pangenomes—the entire genetic code for all of the strains within a given species—can provide insights into identifying the “core genomes” and “dispensable genomes” of the species as well as the individual genetic variations that exist in different regions or ecological circumstances. Environmental stressors, such as pest control, can trigger epigenetic modifications; techniques such as DNA methylome analysis, chromatin immunoprecipitation (CHIP) sequencing, and small RNA sequencing are useful for identifying the influence of epigenetic factors. In addition, soil microbes can affect an herb’s environment, and metagenomic analysis of soil microbial populations can point to important interactions between microbes and herbs that may alter growth conditions (5).

Targeted herb breeding

Molecular breeding requires the availability of polymorphic markers and/or information about the associated genes. Since they are considered minor crops, herbs have been limited in genomics-assisted improvements due to the high cost of high-throughput sequencing and its increasing affordability have dramatically accelerated marker selection breeding programs through the sequencing of wild and domesticated varieties to identify gene pools for cultivation. 4. Geoherbalism Research

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accelerated the identification of many functional genes in model species and has also allowed the development of functional markers specific to the production of desired compounds, information that can be used for targeted molecular breeding (5).

Researching herbal synthetic biology

Although herbs are sources of novel and known therapeutic compounds, problems in sourcing are common. Biotechnology and genetic engineering offer approaches to alternative production methods. Metabolic engineering of medicinal plants has been studied extensively, resulting in, for example, Atropa belladonna plants producing scopoline instead of atropine. However, it is clear that current technologies need to improve the overall production of a plant compound, the overexpression of the primary gene leading to overproduction or even regulatory genes in the pathway are not sufficient, since compartmentalization, transport, storage, and co-factor availability may be important rate limiting factors. A better understanding of pathways involved would build a foundation for a more comprehensive approach to metabolic engineering. This is the goal of herbal synthetic biology, which involves the alteration or de novo synthesis of genomes, with the potential to address resource and purity issues. Furthermore, natural products for drug discovery can be structurally diversified by combining and introducing plant metabolic pathways into alternative organisms, such as bacteria or yeast (6). The conventional practice in herbal synthetic biology is to introduce the heterologous biosynthetic genes into an expression system to produce the products. However, a different approach for the large-scale production of a pure compound could be the engineering of an entirely new synthetic genome, as described for Mycoplasma (7).

Defining a molecular identity

DNA barcoding is revolutionizing the practice of herbal identification, utilizing the concept of "one herb, one species." Standardized DNA barcoding identification systems are available, but the process can be tedious. Analysis of a plastid genome as a superbarcode is a promising alternative for closely related species or cultivars that cannot be unambiguously distinguished by traditional DNA barcoding (8, 9). With the increasing availability of DNA barcodes, current market issues with herbal medicines that result from issues of inferior substitutes, adulterants, and counterfeits could be resolved. Overall, a standardized identification system based on DNA barcoding can play an important role in controlling the quality of traditional medicines through the accurate identification of herbal materials.

Constructing a herbal gene bank

Herbal genetic information is being accumulated with increasing speed, making the need for a common platform for integrated and consolidated access to all omics data paramount. Several herb-related databases have been developed to categorize and understand pathways of secondary metabolites leading to the design of more efficient and targeted searches for plant- and fungi-based remedies (2).

Despite its success thus far, herbal genomics still faces significant technological and ethical challenges. For instance, there have been only a few well-assembled herbal genomes released to date, partly because of their complexity. High heterozygosity, repetition-rich DNA sequences, and polyplody are factors that impede data assembly from short-read, whole-genome shotgun sequencing. Furthermore, the lack of high-throughput methods reduces the efficiency of identifying enzymes and pathways involved in the biosynthesis of secondary metabolites. There have also been ethical and biosecurity concerns regarding synthetic biology expressed by the scientific community and the public. Nevertheless, herbal genomics provides an unprecedented opportunity to revolutionize the use and acceptance of traditional herbal medicines, while contributing to the knowledge base essential for further proteomic and metabolomic studies.

References


FIGURE 1. Model herb systems and their applications.
effects will be consistent, irrespective of the geographic origin of the plant, the plant part used, or the method of plant preparation; that older or cultivated plant material is less effective than fresh, wild plants; that complex plant mixtures are necessary for effectiveness, but cannot be standardized; and that the traditional knowledge and the particular medicinal plant will always be available. The application of contemporary information, together with botanical, chemical, biological, and clinical research, provides an evidence-based research agenda for traditional medicine that serves both the practitioner and the patient (4). The next step, standardization (5), includes proper planting through DNA barcoding (6, 7), and the chemical profiling and quantification of all bioactive constituents in the material (6, 9).

Traditional Chinese medicine (TCM) is an ancient, holistic treatment system established through empirical evaluation, and exists in many related forms in Greater China, Japan, Korea, Vietnam, Malaysia, and Singapore. It seeks to restore energy (qi) and balance (yin and yang) through the use of medicinal plants, fungi, animal products, and minerals, and, superficially, appears quite different from the reductionist approach of Western medicine. However, modern biomedical science is now embracing the concept of systems biology, which views human diseases as the result of imbalance in homeostasis (10). Treatment of cancer or HIV/AIDS now involves a cocktail of drugs targeting different mechanisms of action. TCM is embracing network pharmacology, which investigates how the major constituents in a plant (or plants) act on various biological pathways to produce multiple, synergetic actions (11, 12).

The quality control (QC) of TCMs should begin in the field and continue throughout the production process. Developing a QC system for a TCM preparation is a critical, foundational step for the manufacture of a standardized product suitable for biological and clinical studies. A typical TCM preparation, often consisting of an admixture of multiple plants, represents a vast array of chemical constituents that are synergistically brought to bring about the observed therapeutic effects. Establishing a chemical and biological quality standard for such a complex TCM preparation represents a daunting analytical challenge. A comprehensive analytical approach, integrating chemical, metabolic, and biological analysis, was therefore developed to serve as a paradigm for establishing quality standards for TCMs.

Development of systemic analytical methods
A comprehensive analytical assay that can provide the chemical fingerprint component of a complex preparation is necessary to monitor quality and biological consistency of TCMs (Figure 1)(13, 14).

FIGURE 1. A systemic traditional Chinese medicine (TCM) quality research approach: from comprehensive research to simplified standard.

In our laboratory, liquid chromatography/mass spectrometry (LC-MS) techniques have been employed in order to explore the chemical profiles of various TCM plant materials. Ginseng, notoginseng, and American ginseng (Panax species, Araliaceae) are commonly used in TCM formulae and contain ginsenosides like triterpen and steroid saponins as their active ingredients. These three similar plants have differing clinical efficacies and are easily confused, particularly in their post-processing forms. A total of 623 ginsenosides, including 437 potential new ginsenosides, were characterized from the three plants, allowing specific biomarkers to be developed that can unequivocally differentiate between them (15). This technique was similarly applied to a number of TCM herbs, including Salvia miltiorrhiza, Ganoderma lucidum, Glycyrrhiza uralensis, and Rhodiola palustrum. In one case, a metabolic fingerprinting technique identified metabolites of the major tanshinones and salvianolic acids of S. miltiorrhiza in rats after oral administration of the plant, enabling the determination of metabolic pathways and excretion routes (16, 17). Combining both chemical and biological analyses provides an effective strategy for revealing active components. Given the complex metabolic matrix of S. miltiorrhiza, a three-tier strategy involving analysis of single compounds, extracted fractions, and the whole herb was adopted. A multi-level biological approach was used that integrated pharmacology, molecular biology, and systems biology. The target proteins and mechanisms of action were found to be impacted at the molecular, cellular, tissue, and whole animal levels, supporting the contention that TCMs work on multiple targets through multiple pathways. In the case of S. miltiorrhiza, salvianolic acid B was determined to modulate several molecular targets, including matrix metalloproteinase 9, epidermal growth factor receptor, and integrin (18), and the major tanshinone derivatives were found to be cardioprotective and antioxidant agents (19).

Elaboration of an overall quality standard
A new quality control model that combines analytical fingerprinting to monitor batch-to-batch consistency, and a multi-component assay to assure authenticity and quality, has been developed and effectively applied to several Chinese herbal materials and their preparations (Figure 2). Based on the salviacins and the tanshinones, an overall quality standard for S. miltiorrhiza was established using the single standard to determine multicomponents (SSDDM) method, which uses a single reference standard to quantify the content of many related compounds in a mixture, and has been adopted by both the Chinese and United States pharmacopoeias. It is recommended that only pharmaceutical quality material be used in clinical evaluations in order to ensure product consistency and safety.

Conclusions
A multitude of intrinsic and extrinsic factors affect the quality, consistency, and stability of medicinal plants and their metabolites (12, 13). The regulated application of Good Agricultural and Collection Practices, Good Laboratory Practices, Good Manufacturing Practices, and Good Clinical Practices are necessary to assure high quality, safe, effective, and consistent TCM products for practitioners and patients (5). In order for TCM products to be accepted into a global, evidence-based health care system, it is imperative for robust international standards and procedures to be developed that govern their growth, collection, processing, and administration. Furthermore, the extreme complexity of TCMs necessitates the integration of new technologies and strategies for proper analysis of bioactive constituents, allowing the targets and pathways impacted to be fully understood (20).

References
Evolution of traditional medicines to botanical drugs

B otanicals constitute an important source for new drugs (1, 2). To facilitate botanical drug development, the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) established the Botanical Review Team in 2003 and published its first Guidance for Industry: Botanical Drug Products in 2004 (3). This guidance represents FDA’s thinking and provides recommendations on quality, nontoxic, clinical, and other unique aspects associated with botanical new drug development through the investigational new drug (IND) and new drug application (NDA) review process. CDER reviewed over 400 botanical IND applications and pre-IND meetings requests (Table 1). Most of INDs were allowed to enter phase 2 clini- cal trials for evaluation of preliminary safety and efficacy of the investigational botanical products in patients. FDA approved the first botanical NDA in 2007 for Veregen (Camellia sinensis) in 2008 (4, 5) and the second botanical NDA for Fulyzaq (crofelemer) in 2012 (6, 7). These two NDA approvals show that new therapies derived from natural complex mixtures can be developed to meet modern FDA standards of quality, safety, and efficacy. A small number of INDs are currently in phase 3 clinical trials, which may lead to more NDAs in the future.

“Totality-of-evidence” approach

For new botanical products intended to be marketed as drugs in the United States, applicants need to provide evi- dence of safety, efficacy, and any other relevant characteristics. Served as is expected for small-molecule products. Botanical products also need to meet standards for product quality, so the marketed product- batch characteristics will be consistent with that observed for product batches tested in the clinical studies (i.e., therapeutic consistency). However, quality control of botanical materials and end products is challenging because these products contain complex mixtures in which the active components may not form a homogenous, chemically comparable batch to batch variations (i.e., in chemical composition). The conven- tional chemical, manufacturing, and controls (CMC) data (primarily from chemical testing) used to ensure the quality of small-molecule products may be insufficient for botanical products. To address this challenge, FDA has developed a “totality-of-evidence” approach to demonstrate that knowledge and experience acquired from the review of botanical IND and NDA submissions. In addition to conventional CMC data, this approach also includes knowledge drawing on the experience including raw material control, clinically relevant bioassay(s), and other non-CMC data (including clinical data on the dose-response

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Developing influenza treatments using traditional Chinese medicine

H umans have been faced the threat of epidemics such as influenza throughout their existence. Traditional Chinese medicine (TCM) approaches could be applied in the following ways. First, the traditional Chinese medicine (TCM) components begin documenting their diagnostic and treatment principles related to epidemic diseases in the classic Chinese medical book, “Emperor Internal Medical Classic.” The unique treatments and herbal formulas used to combat influenza may serve as a source of inspiration and information for the development of new drugs.

Chinese herbal medicines and influenza

A major difference between Western and Chinese influenza treatments is the mode and targets of their actions. The first antiviral chemical drugs appeared in the West in the mid-1960s. Since then, many single-target therapeutics have been designed, but drug resistance is common. To circumvent this, Western medicine has incorporated multiple molecular targets into a single treatment using combination therapies, a practice now well accepted in the West. Chinese herbal formulas (CHFs), on the other hand, often act via multiple modes that target not only the virus, but also various components of the host’s immune response (Table 1), creating a synergetic effect. For example, jinchai capsules blunt viral replication by blocking adsorption of virions and preventing virus hyperalgesia-induced membrane fusion (3), while eudamiones block viral action by interfering with the AMPK/TSC2/mTOR signaling pathway, which is associated with virus-induced autophagy (4). Figure 1 summarizes the point of actions of CHFs when treating influenza.

Isatis indigotica roots and influenza

Isatis indigotica roots (IIR) (Banlangen) have long been used to treat seasonal influenza in China. Currently, more than 100 chemical constituents of IIR have been identified. Among them, the compounds of epigallocatechin-3-(S)-gallate (EGCG) and epicatechin (EC), which are the major components of IIR, have been demonstrated to kill or significantly inhibit the influenza virus. Studies from our laboratory have shown that polysaccharides from IIR could inhibit influenza virus from attaching to host cell surfaces through a process involving hemagglutinins (5). Moreover, an indole alkaloid has been found to play a major role in preventing viral infection of host cells (6), while compounds derived from IIR can block translocation of the nucleocapsid protein at the early stage of replication, primarily through modulation of NF-κB signaling (7), thus inhibiting viral replication (8). In addition, IIR has been shown to exert immune modulatory effects in vitro and in vivo. In lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages, the methanolic extracts of IIR inhibited degra- dation of iNOS and production of nitric oxide, prostaglandin E2 and interleukin (IL)-1β (9). The polysaccharides from IIR could promote proliferation of lymphocytes and macrophages, as well as production of IL-2 and interferon (IFN) in mouse models (10). Indulin B and its derivatives can suppress a number of pro-inflammatory cytokines/chemokines in infected human bronchial epithelial cells, human peripheral blood-derived macrophages, and alveolar epithelial cells (Table 1) (10, 11). Taken together, these data imply that IIRs play a variety of roles protecting against viral infection by targeting both the virus and the host—a markedly different effect than that of marketed chemically synthesized drugs.

Drug development strategies using TCM

High-quality and efficacious, safety assurance, and patient affordability are the key factors for drug development. TCM can inform research into these areas in the following ways.

Firstly, the strategies and principles underpinning the translational research used in TCM-based influenza treat- ments could be applied more broadly. Two possible ap- proaches can be taken: the standard, bottom up bench- to-bedside strategy, or a more innovative approach that transitions empirical medical knowledge from TCM into an evidence-based research strategy. We proffer that the latter better reflects the real-world interaction between basic sci- ence and the TCM clinical experience.

Secondly, basic research and clinical studies on CHFs could be conducted in parallel. For example, the effects of extracts and/or combinations of the active compounds from commonly prescribed CHFs could be investigated concur- rently with standardized clinical trials based on documented clinical experience.

Thirdly, well-defined methodologies for standardized as- sessment of the quality, efficacy, and safety of CHFs are still lacking. It is important to standardize the composition and the level of active CHF components in herbs before including them in a basic research project or clinical trial so as to maintain the data integrity.

Finally, TCM research is complex. It therefore behooves all researchers to develop interdisciplinary, innovative, and collaborative research projects, through which the scientific foundation of TCM can be elucidated and a new framework that incorporates modern medical science can be built.

We have been pioneers in an attempt to implement the above-mentioned strategies using IIR, launching the first randomized control trial in China in 2010. Various ‘omics
data can overcome the limited ability to characterize the entire botanical mixture or its active components, based on the analytical technology available. The approval of these two botanical NDAs demonstrates the success of an integrated approach and provides the industry with a practical framework for developing botanicals (including traditional medicines) to new drugs that are held to the same FDA standards as small-molecule drugs.

References


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technologies have been concurrently used to search for bioactive compounds, and we expect that additional active constituents with unique pharmaceutical activities will be found in the future. We have also combined the application of modern technologies with TCM clinical experience. For example, practitioners have noted that IIR appears to display beneficial clinical effects if administered during early onset of the disease (9). These studies suggest that further investigation of the mechanisms of IIR action is warranted. Importantly, using treatments with multiple sites of action may prevent or delay the generation of resistant viral strains.

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TABLE 1. Examples of TCM and Western anti-influenza drugs.

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<th>Antivirals</th>
<th>Target</th>
<th>Target subject</th>
<th>Mechanism of action or therapeutic effect</th>
<th>Year Documented</th>
<th>Reference</th>
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<tr>
<td>Cyanovirin-N</td>
<td>Surface glycoproteins of enveloped viruses</td>
<td>Virus</td>
<td>Inhibits entry of virus</td>
<td>1997</td>
<td>12</td>
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<tr>
<td>M2e</td>
<td>Influenza hemagglutinin</td>
<td>Virus</td>
<td>Impairs hemagglutinin intracellular trafficking</td>
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<td>13</td>
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<td>DAS181</td>
<td>Influenza viral receptor</td>
<td>Host</td>
<td>Removes viral receptor</td>
<td>2006</td>
<td>14</td>
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<tr>
<td>Oseltamivir/Rimantadine</td>
<td>Influenza M2 protein</td>
<td>Virus</td>
<td>Inhibits protein conduction of M2</td>
<td>1965</td>
<td>15, 16</td>
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<td>Favipiravir</td>
<td>Influenza RNA polymerase</td>
<td>Virus</td>
<td>Blocks viral RNA polymerase activity</td>
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<th>Chinese antiviral herbal formulas, and constituents</th>
<th>Single herb</th>
<th>Formula</th>
<th>Herbs</th>
<th>Constituents with unique pharmaceutical activities</th>
<th>Bioactive compounds</th>
<th>Additional active constituents</th>
<th>Expected outcomes</th>
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<tr>
<td>Ban Lan Gen (bats indigestive root)</td>
<td>Methanol extract</td>
<td>NF-κB signaling</td>
<td>Host</td>
<td>Inhibits nitric oxide and prostaglandin E2 production, and NF-κB signaling in macrophages</td>
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<tr>
<td>Ban Lan Gen (bats indigestive root)</td>
<td>Polysaccharides</td>
<td>–</td>
<td>Host</td>
<td>Promotes transformation of lymphocytes and production of IL-2 and IFN-γ</td>
<td>9</td>
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<tr>
<td>Jin Yin Hua (Lonicerajaponica)</td>
<td>Ethanol extracts</td>
<td>Antigen-Immune-modulatory, and anti-influenza protein in mouse serum</td>
<td>Host</td>
<td>Reduces lung index and advances lung lesions in influenza A97 (2013) virus-infected mice</td>
<td>1400s</td>
<td>25</td>
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<td>LianQiao (Forsythia suspensa)</td>
<td>Ethanol and water extracts</td>
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<td>Host</td>
<td>Regulates CCL5 and NF-κB signaling in human bronchial epithelial cells</td>
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<td>Mu Kong Shi Gan Tang</td>
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<td>Reduces time to fever resolution in patients with H1N1 influenza virus infection</td>
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<td>27</td>
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<td>LianHua Qing Wen capsule</td>
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<td>Reduces time to fever resolution in patients with H1N1 influenza virus infection</td>
<td>2004</td>
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</table>

FIGURE 1. Holistic intervention to treat influenza.

![Image of a diagram showing different treatment methods]
A novel drug discovery strategy inspired by traditional medicine philosophies

Authors: Xinfeng Zhao†, Tai-Ping Fan‡, Zijian Li‡, Jianjun Shi‡, Jun-Shi Zuo†, Yingjie Carl Hehme*, Zijian Li‡, Yaoyu Zhang‡, Jianjun Zeng‡

For thousands of years, traditional medicines in China (traditional Chinese medicine, TCM), Japan (Kampo medicine), Korea (traditional Korean medicine), Indonesia (Jamu) and India (Ayurvedic medicine), North America (phyotherapy), and Europe (herbalism) have been the primary means for maintaining health as well as preventing and treating human diseases (1). Over time, experiential knowledge derived from the medical application of natural products led to their incorporation into complex medicinal knowledge—materia medica—characterized by the understanding of nature unique to each culture. For almost 200 years, the traditional use of natural products has also represented a source of effective drugs (2-5). This strategy represents a successful approach to novel drug identification and development through isolation and purification of active ingredients from crude drug extracts, coupled with high-throughput and high-content screening, and subsequent analysis and testing according to the guidelines of the U.S. Food and Drug Administration and other regulatory agencies (6,7). However, the pharmacologically active ingredients of a polyphenome are not always the original natural molecules, but may be their host-specific metabolites or molecular complexes formed following co-administration with other herbs. This complexity has generated significant scientific challenges in the study of natural products (9,10). The multicomponent nature of traditional medicines leading to multiple potential molecular interactions, multiple targets, and numerous metabolic byproducts, suggests that a conventional reductionist approach will have limitations in identifying active ingredients, making a more network-oriented, holistic approach preferable (12).

The Jun-Shi medicinal compatibility model

To address the challenge innate in the complex composition of natural products, inspiration was taken from the theoretical principles underlying TCM (11). This includes meticulous documentation of clinical observations, which can inform the practice of traditional healing and help to develop guidelines and principles. The principles of these practices will be validated when successfully applied to practice clinical problems (12). We applied this approach to analyzing the Jun-Chen-Zuo-Shi principle of combining different materia medica in a specific manner when creating TCM compound formulations (Fufang). Additionally, as a strategy for drug discovery, we propose a simplified Jun-Shi model to identify the ingredients from TCM formulations that reach the bloodstream and the pharmacological effects they may have in the body.

Jun-Chen-Zuo-Shi and Qiqing (seven ways of pairing compatible herbs) are the basic theories behind the formulation of TCM treatment (13). This strategy guides the combination of different herbal medicines in Fufang, based on the healing/pharmacological properties and constituents of each herb. The Jun (primary) component is the principal phytocomplex targeting the major symptom of the disease. There are only a few varieties of Jun medicines that are administered as a single formula, usually in large doses. The Chen (minister) herbs synergize with Jun to strengthen its therapeutic effects, and may also treat secondary symptoms. The Zuo (assistant) medicine reduces or eliminates possible adverse or toxic effects of the Jun and/or Chen components, while also enhancing their effects and sometimes treating secondary symptoms. Finally, the Shi (courage) herbs facilitate delivery of the principal components to the lesion sites, or facilitate the overall action of the other components (14-15). The principles of Qiqing describe how herbs can be used independently, to reinforce (when both herbs have similar properties or enhance) or antagonize certain unwanted, negative side-effects. In practice, Qiqing helps to determine the optimal pairing and proportions of two medicinal herbs in a formulation.

We propose combining the principles of Jun-Chen-Zuo-Shi and Qiqing to create the notion of a Jun-Shi medicinal pair in order to pursue better therapeutic efficacy when compared with a single medicinal (16). A Jun-Shi medicinal pair also has the synergistic characteristics of a Fufang, targeting the active phytocomplexes to their designated sites of action. At the same time, the simpler composition of the Jun-Shi medicinal pair provides a less complex formulation for scientific analysis, which should reduce the complexity and difficulty when seeking new drugs from TCM-related sources. Based on these principles, we propose an innovative strategy for new drug discovery through the screening of in vivo effector compounds from Jun-Shi medicinal pairs. The Jun herb performs the primary action while the Shi herb potentiates this activity either by modifying the physicochemical properties of the Jun herb or facilitating its interaction with the pharmacological target. The identification of pharmacologically meaningful differences could therefore be made by comparing action and efficacy of the Jun herb with or without the Shi herb.

Testing the Jun-Shi model

The Fufang Danshen Diantong pill (Danshen) has successfully completed phase 2 clinical trials in the United States and is currently undergoing phase 3 trials (17), which made this a perfect candidate on which to test our strategy of drug discovery. We choose to focus on the Danshen (Radix Salviae miltiorrhiza) plus Bingpian (Borneol) pair of medicinals present in this pill to investigate our Jun-Shi compatibility model. The process is described in Figure 1. The levels of Danshen-derived phenolic acids such as 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoic acid (Danshensu) were found to be increased in rabbit heart by co-administration of Bingpian. Additionally, isopyrrol 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate (IDHP), a novel metabolite, was identified in Fufang Danshen and Bingpian, with an idiosyncrasy of Danshensu (18). Pharmacokinetic studies showed that this new compound was preferentially found in heart and brain tissues, in agreement with the lesion sites expected to be targeted by this drug. IDHP is consistent with the principles of TCM. Finally, the in vitro study of the IDHP suggested that IDHP is the effector compound with a therapeutic effect against myocardial and cerebral ischemia (19,20), strongly suggesting that IDHP is the target of thesynergistic activity in the traditional Chinese medicinal formulation in Fufang Danshen Diwan.

Materials that appear in this section were not reviewed or assessed by Science Editorial staff, but have been evaluated by an international editorial team consisting of experts in traditional medicine research.
Deciphering ancient combinational formulas: The Shexiang Baoxin pill

Authors

Liu R., Scott R., Wang Y., Oliver S., Fan W., Zhang W.

Abstract

A historical combinational formula, Shexiang Baoxin pill, comprising aspirin, simvastatin, ramipril, hydrochlorothiazide—used to treat hypertension and prevent heart attack and stroke (1). In traditional Chinese medicine (TCM), a polypill is a single medicine that contains multiple pharmaceuticals, and may even reduce ischemic myocardial infarction (MI) and may even reduce ischemic myocardial infarction (MI) and may even reduce ischemic myocardial infarction (MI). The small molecule cinnamaldehyde, abundant in Cortex cinnamomi (7), has been shown to be a strong vasodilator (17) and activates transient receptor potential channels (TRPV1 and TRPA1) involved in nociception (18, 19). Advanced separation and analysis techniques such as gas and liquid chromatography, coupled with mass spectrometry, have made it possible to fingerprint the exact chemical species that comprise Fugang-based therapies. To date, over 70 non-volatile and over 40 volatile chemical species have been identified in SBP (7, 8). Following oral administration of SBP in rats, as many as 22 of these pure compounds and eight metabolites could be observed in blood plasma (9, 10). These analytical techniques help to establish a “chemical fingerprint” for SBP, which allows for batch-to-batch comparison of individual lots at the medicinal and resultant drug, an important step towards quality control in manufacturing (11, 12), and reproducible safety and efficacy.

Such a chemical fingerprint is also vital for identifying active ingredients. For instance, several of the major classes of compounds that have been identified in SBP include bufadienolides, ginsenosides, and bile acids (Figure 2). Two bile acids identified, ursodeoxycholic acid and chenodeoxycholic acid, have been approved by the U.S. Food and Drug Administration (FDA) and marketed as chenodeoxycholic acid and ursodeoxycholic acid, respectively. Prescribed for the prevention and management of gallstones, these bile acids decrease the production of cholesterol and reduce hypertriglyceridemia, a strong risk factor for CHD (13). The bufadienolides that are abundant in V. biflorus SBP (17) are cardiac glycosides, can be metabolized into SBP, a plant-derived cardiac glycoside, FDA-approved class V anti-arrhythmic, and positive inotropic agent (14). The main bufadienolide in V. biflorus, bufalin, is also a Na+ ATPase inhibitor that increases cardiac contractility (15) and may perceptively downregulate the renin-angiotensin system during heart failure (16). The small molecule cinnamaldehyde, abundant in Cortex cinnamomi (7), has been shown to be a strong vasodilator (17) and activates transient receptor potential channels (TRPV1 and TRPA1) involved in nociception (18, 19). Advanced separation and analysis techniques such as gas and liquid chromatography, coupled with mass spectrometry, have made it possible to fingerprint the exact chemical species that comprise Fugang-based therapies. To date, over 70 non-volatile and over 40 volatile chemical species have been identified in SBP (7, 8). Following oral administration of SBP in rats, as many as 22 of these pure compounds and eight metabolites could be observed in blood plasma (9, 10). These analytical techniques help to establish a “chemical fingerprint” for SBP, which allows for batch-to-batch comparison of individual lots at the medicinal and resultant drug, an important step towards quality control in manufacturing (11, 12), and reproducible safety and efficacy.

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Recently, we initiated a more comprehensive study of the in vivo mechanisms of Fufang using a chemogenomic approach (Figure 2). For example, using drug-induced haploinsufficiency screening in Saccharomyces cerevisiae (22), functional information can be obtained from loss-of-function assays to systematically investigate the cellular response to either individual bioactive entities or combined subsets of SBP. Haploinsufficient strains that show hypersensitivity to SBP can reveal pathways and targets that respond to the drug, thereby providing clues about its mode of action in a cellular context. A previous compendium of cellular responses to small molecules allows mechanisms of novel compounds to be inferred on the basis of profile similarity to established drugs (23).

Metabolomic methods have already proven useful in characterizing SBP (in a rat model of acute myocardial infarction (MI)), numerous plasma and urinary biomarkers involved in oxidative injury, dysfunction of energy and amino acid metabolism, and inflammation have been identified using partial least squares discriminant analysis plots (24, 25). SBP given orally before MI can significantly reverse the in vivo mechanisms of SBP. Heterozygous strains that show hypersensitivity to SBP—nearly returning their levels to normal (26). SBP given orally before MI can significantly reverse the in vivo mechanisms of SBP.

Proper ratio of the “imperial” herb (the main ingredient), the “sensitive” herb (reduces side effects of the main herb), and the “servant” herb (aids in harmonizing the other herbs) to achieve the best therapeutic effect (5). By comparing formulations in which one herb has been removed, as well as single-herb preparations, a formulation for PHY906 was found that achieved the optimal therapeutic effect in combination with irinotecan (6). Different herbs appear to play different roles in the enhancement of antitumor activity and in protection against weight loss and mortality (6). These findings support the theory that the “polyherb” TCM formulation has a synergistic effect in vivo that is greater than the sum of the effects of its individual components and that its action cannot be accurately predicted by simply comparing the in vitro activities of the active compounds (27, 28). Fufang, a mixture of several TCM formulas composed of common herbs for the treatment of the abovementioned symptoms. Considering their long history of usage, these formulas should be relatively safe. Simple formulas consisting of a limited number of herbs were used to facilitate quality control and simplify analysis of the mechanisms of action. Among these formulas, we found that Huang-Qin Tang could enhance the therapeutic index of irinotecan, a chemotherapeutic agent for the treatment of metastatic colon and rectal cancer. This four-herb formula (Gynoryzha uralensis Fisch, Paenonia lactiflora Pall, Scutellaria baicalensis Georgi, and Ziziphus jujube Mill) has been used to treat gastrointestinal disorders for approximately 1,800 years. The formula named PHY906, was manufactured using standard operation procedures and following current good manufacturing practice standards.

Lessons from the development of the traditional Chinese medicine formula PHY906

**Authors:** Wang Lam, Shao-Hui Wu, Zaoli Jiang, Yang-Chi Cheng

**T**raditional Chinese medicine (TCM) has been practiced for thousands of years. While the historical usage of TCM is well documented, it is not broadly accepted by mainstream physicians who question the quality and consistency of TCM products, the scientific basis for usage, and the lack of evi-
dence-based clinical studies. Nonetheless, TCM formulas are currently being used to relieve the side effects of nonphar-macological toxicities caused by chemotherapy, including diarrhea, nausea, vomiting, and fatigue. We decided to further explore the mechanisms of action of TCM in chemotherapy, laying a groundwork for its potential use as an adjuvant treatment. We selected several TCM formulas composed of common herbs for the treatment of the abovementioned symptoms. Considering their long history of usage, these formulas should be relatively safe. Simple formulas consisting of a limited number of herbs were used to facilitate quality control and simplify analysis of the mechanisms of action. Among these formulas, we found that Huang-Qin Tang could enhance the therapeutic index of irinotecan, a chemotherapeutic agent for the treatment of metastatic colon and rectal cancer. This four-herb formula (Gynoryzha uralensis Fisch, Paenonia lactiflora Pall, Scutellaria baicalensis Georgi, and Ziziphus jujube Mill) has been used to treat gastrointestinal disorders for approximately 1,800 years. The formula named PHY906, was manufactured using standard operation procedures and following current good manufacturing practice standards.

**Quality control for TCM**

Since the sites of action and bioactive compounds found in TCMs are not always known, it is not sufficient to rely on either chemical (1) or biological analysis (2) alone for quality control (QC) purposes. We therefore developed Phytomics QC, an analysis system that integrates both chemical and biological data (3, 4) and shows promise in vivo (5). Analysis of the chemogenomic and metabolomic response signatures of SBP and other Fufang can clarify their impact on broader cellular processes and identify potential targets. From complexity to simplicity—A new development strategy for Fufang

As not all components in Fufang are active, a combination of its active components may provide a simplified Fufang that facilitates easier identification of therapeutic targets and mechanisms of action. Early attempts to develop a simplified formulation of Fufang (7, molecules in bold) have shown promising results in rat models of MI (26), illustrating the potential of integrating reductionist and systems biology approaches in the development of Fufang. Ultimately, by conducting rigorous quality control and purification, and removing extraneous compounds, such an approach would be equally applicable to create a new generation of polyproline for other diseases.

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**Materials that appear in this section were not reviewed or assessed by Science Editorial staff, but have been evaluated by an international editorial team consisting of experts in traditional medicine research.**
formulations could support the TCM theory that there may be a preferential response in certain organs to certain herbs. This work could lead to new applications for TCM.

**Challenges of TCM clinical trials**

Traditionally, TCM is prescribed as a decoction based on the diagnosis of a practitioner and the individual patient’s needs. It is therefore challenging to design randomized, placebo-controlled, dose-escalation studies. Herbal formulas have been administered in capsule form for many years, so placebo-controlled, dose-escalation studies. Herbal formulas required that the active ingredient from the herbal mixture be illustrated herbal mixtures. However, they advise that multiple diarrhoea in HIV patients, in 2012 (see page S32). FDA does not approve only two highly purified HMPL-004 (NCT01805791). Thus far, the U.S. Food and Drug Administration (FDA) has approved only two highly purified Fuzheng Huayu (NCT00854087), and Croton lechleri, warts, in 2006, and Fulyzaq (crofelemer), purified oligomeric development stages, including Dantonic (T89) (2009). The U.S. National Foundation for Cancer Research. We thank Sharon Lin and Peikwen Cheng for their critical reading of this manuscript. This work was supported by the National Cancer Institute (P01CA154295-01A1), the National Center for Complementary and Alternative Medicine (NC- CAM), and the Office of Dietary Supplements at the U.S. National Institutes of Health. Yun-Chi Cheng is a fellow of medicine research.

**The potential role of Chinese herbal medicines in cancer management**

The management of cancer involves multiple disciplines, including surgery, chemotherapy, radiotherapy, targeted therapy, biological therapy, and systemic therapy. In spite of scientific advances and the evidence-based practice of these treatments, limitations in their benefits still exist, resulting in the increasing use of complementary and alternative medicine (CAM) by cancer patients and survivors (1). Numerous preclinical and clinical studies of CAM have been documented over the past decade (1, 2). Recent surveys revealed that the overall prevalence of CAM use among cancer patients in Germany and the United States have shown that CAM usage was reported in 52–54% of cancer patients (5, 6). One of the modalities commonly used in Chinese cancer patients is Chinese herbal medicines (CHMs). A similar proportion (53%) of cancer patients in southwestern China using CHMs was reported (7). In addition to the clinical benefits of CHMs as a cancer therapy, some have been studied. This article aims to illustrate the potential role of CHMs in cancer management and their adjuvant value in conventional cancer therapy.

Possible CHM targets in cancer management

Although various active antitumor compounds have been isolated from CHMs (8), the therapeutic rationale for the treatment of cancer using CHMs is not limited to cytotoxicity. Other therapeutic principles include boosting the natural host immune response, improving quality of life, and preventing relapse after surgery (8–10).

In summary, although TCM formulas often vary, it is possible to make consistent preparations, as exemplified by PHY906. TCMs often have multiple sites of action and the active compounds acting at each site may be different. Systems biology and modern bioinformatics technologies are needed to fully explore the value of TCM for future medical applications.

**Acknowledgments**

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Active compounds isolated from herbs can also be developed as anticancer drugs, often aimed at specific targets (8). Certain extracts from single herbs, containing a complex array of constituent molecules, have been shown to exhibit direct or indirect antitumor activity (30–31). In this case, the extract could be considered to be a multitarget combination therapy. CHMs are generally administered as combinations of multiple herbs, emphasizing one of the CAM principles of delayed or cumulative toxicity that may occur as a result of interactions between CHM and chemotherapeutics can provide more information on the safety and/or potential benefit of adjuvant therapies. In this way, the full holistic benefits of Chinese herbal medicines for cancer management can be realized.

References
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TABLE 1. Possible targets of Chinese herbal medicines (CHMs) in experimental systems and their implications.

<table>
<thead>
<tr>
<th>Possible targets</th>
<th>Examples of CHM or isolated compounds</th>
<th>Experimental systems</th>
<th>Principal parameters measured</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotoxicity</strong></td>
<td>Androgapholide from Andrographis paniculata (17)</td>
<td>Cancer cell lines</td>
<td>inhibition of proliferation</td>
<td>Inhibit tumor growth at primary site</td>
</tr>
<tr>
<td></td>
<td>Curcumin from Curcuma longa (12)</td>
<td></td>
<td>induction of apoptosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ericalexin B from Isodon eciracly (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multidrug resistance hepatoma cells</strong></td>
<td>Reversal of P-glycoprotein-mediated multidrug resistance</td>
<td></td>
<td>inhibition of apoptosis</td>
<td>Improve chemotherapy efficacy</td>
</tr>
<tr>
<td><strong>Immunomodulation</strong></td>
<td>Astragalus species (16)</td>
<td>Immune cells (e.g., lymphocytes, dendritic cells)</td>
<td>production of cytokines and/or chemokines</td>
<td>Improve immune response strength attack system of immune cells against cancer cells</td>
</tr>
<tr>
<td></td>
<td>Consilus versicolor (17)</td>
<td></td>
<td>changes of certain immune cell types</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganoderma sinense (18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiangiogenesis</strong></td>
<td>Bigelovin from Inula heanthus-aquatica (19)</td>
<td>Endothelial cells</td>
<td>inhibition of tube formation</td>
<td>Inhibit new blood vessels formation towards and inside the tumor</td>
</tr>
<tr>
<td></td>
<td>n-Butilenephalide from Angelica sinensis</td>
<td></td>
<td>migration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclopentide RA V from Rubia yunnanensis</td>
<td>Zebrafish embryos</td>
<td>inhibition of blood vessels growth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor-bearing cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimetastasis</strong></td>
<td>Andrographis paniculata (22)</td>
<td>Invasive cancer cell lines</td>
<td>inhibition of migration</td>
<td>Prevent migration of tumor cells from primary organ to other organs</td>
</tr>
<tr>
<td></td>
<td>Camellia sinensis (23)</td>
<td></td>
<td>invasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganoderma lucidum (24)</td>
<td>Tumor-bearing cells</td>
<td>inhibition of metastasis</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1. Possible targets of Chinese herbal medicines (CHMs) in experimental systems and their implications.

**The School of Pharmacy, University of Reading, UK**
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**Department of Pharmacognosy, Université de Lubumbashi, D.R. Congo**

M. any complex herbal mixtures are already commonly used worldwide, either for primary health care or as complementary or alternative medicines (1). Ancient traditional remedies— notably traditional Chinese medicine (TCM) and Ayurveda—have been passed down and refined over their long history of clinical use. Often perceived as innocuous, some herbs exhibit delayed or cumulative toxicity that may not be obviously attributed to CHM, but instead identified by serendipity or unfortunate clinical findings. Given the large number of herbal products on the market and the relatively low budgets available for research to date, safety assessment in accordance with modern guidelines has been carried out on relatively few herbs (2). Despite these concerns, a recent survey of practitioners in Europe and China, although limited in scope, provides some reassurance that the vast majority of herbs in regular use are known to be relatively safe (3). Reports of serious adverse events regarding TCM mainly concern those that are used very rarely in Europe and extremely carefully in China (4). It is also important to differentiate between intrinsic herbal toxicity and malpractice: A recent Hong Kong study found that, of 52
clinical case reports of aconite poisoning, the majority were actually related to poor-quality herbs, poor prescribing practices, or dispensing errors (5). In Europe, adverse events have mainly resulted from contaminated products and a practitioner’s incompetence, rather than herbal medicines being inherently risky. The reasons why the safety of herbal products for clinical use may be compromised are summarized in Figure 1. Pharmacovigilance systems have only recently been established for herbal medicines, thus the true incidence of adverse events may be under-reported; nevertheless, the available data indicate that their overall safety is better than would be suggested by widely publicized incidents of administering adulterated products and herbs already known to be toxic.

Practical guidelines for evaluating the toxicity of herbal products are needed. Clinical and toxicological research on herbal medicines is in most cases inadequate for evaluating complex mixtures of incompletely characterized herbs, poor prescribing practices, and contaminants (mycotoxins and heavy metals, among others), mastery of sometimes complex processing methods, detection of new structural alerts, and avoidance of known toxicophore-bearing species. These measures are, however, inadequate for evaluating complex mixtures of incompletely known composition and where adverse events may take months or even years to be handled. However, they are indispensable for pathways, which focus on nonspecific phenomena at the cellular level and neglect pharmacokinetic and pharmacodynamic aspects relevant to clinical conditions that affect the nature and concentration of active moieties. Therefore, the recently developed in vitro and in vivo tissue and organ-on-a-chip models—which simulate the in vivo cell microenvironment—should also be considered for toxicological and pharmaceutical herbal assessment. Herbal matrix effects must also be considered in the experimental design of toxicity screens. In vitro and in silico models should therefore be used only for comparison of toxicity profiles or deciphering toxic activities at the molecular level rather than for direct estimation of toxicological risks. In silico methods linking components with potential targets can provide an indication of adverse effects that may result from having multiple constituents and signal the need for a closer investigation of relevant toxicological and pharmaceutical issues. Measuring the kinetic characteristics of metabolism, transport, disposition of active components, and matrix effects should provide the necessary information to ensure that in vivo studies effectively integrate these critical parameters, and offer the ability to consider the realistic exposure levels in various organs and the biological activities at concentrations relevant to human consumption (9, 10). In vivo models such as zebrafish, Drosophila, and Caenorhabditis elegans offer convenient methods for high throughput toxicity assessment and inform further toxicological considerations, but must be cautiously interpreted due to biological differences from human physiology.

Practical pharmacological and toxicological assessment of herbal medicines therefore needs to combine ’omics, bioinformatics, and network-centred systems biology with in vivo and in silico assays, targeting studies on biomarkers identified from animal experiments (11,12), as summarized in Table 1. At all stages, it is imperative to remember the multidimensional nature and variability of folk remedies, and that studies using wrongly identified or processed, contaminated, or adulterated preparations are not only useless but may also be toxicologically misleading (13).

Pharmacovigilance and the clinical assessment of herbal medicines

To compensate for the lack of safety evaluations of herbal drugs and their herbal formulae that need further toxicological investigation. Recent advances in ’omics and bioinformatics techniques have made it possible to investigate efficacy and toxicity at the organism level and in an individual manner. When further developed and validated, these methods should enhance the detection of insidious toxicities, provide the necessary background and information for effective pharmacovigilance, and aid mechanistic studies of specific herbal medicines. The complexity of herbal medicines is a major issue for safety assessments since the often large number of components have variable potencies and affinities for various targets. Toxicity testing with classical and traditional and used clinically. Special attention must be paid to insidious toxicities which are not easily detected by pharmacovigilance, including genotoxicity, carcinogenicity, and developmental toxicity.

and quantitative profiling data for the total extract, using appropriate analytical tools (7), in vitro and in silico models (2), and modern screening techniques (8). In vitro models using cell lines and organotypic cultures have allowed the identification of cellular systems form the basis of pharmacological and toxicological screenings and are generally low-cost, efficient, and easy to handle. However, they are indirect approaches, which focus on nonspecific phenomena at the cellular level and neglect pharmacokinetic and pharmacodynamic aspects relevant to clinical conditions that affect the nature and concentration of active moieties. Therefore, the recently developed in vitro and in vivo tissue and organ-on-a-chip models—which simulate the in vivo cell microenvironment—should also be considered for toxicological and pharmaceutical herbal assessment. Herbal matrix effects must also be considered in the experimental design of toxicity screens. In vitro and in silico models should therefore be used only for comparison of toxicity profiles or deciphering toxic activities at the molecular level rather than for direct estimation of toxicological risks. In silico methods linking components with potential targets can provide an indication of adverse effects that may result from having multiple constituents and signal the need for a closer investigation of relevant toxicological and pharmaceutical issues. Measuring the kinetic characteristics of metabolism, transport, disposition of active components, and matrix effects should provide

Table 1. Integrated strategies for the toxicological assessment of herbal drugs.

<table>
<thead>
<tr>
<th>Strategy Information yielded</th>
<th>Analytical chemistry</th>
<th>Information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro, in silico methods and nonmammalian animal models, or eventually combined with ’omics-based methods</td>
<td>Chemical profiles, identification of components of interest or concern</td>
<td>Identification of main pharmacological and toxicological issues</td>
</tr>
<tr>
<td>Mammanimal models, eventually combined with ’omics-based methods</td>
<td>Acute and repeated dose toxicities (animal models only)</td>
<td>Identification of toxic activity profiles</td>
</tr>
<tr>
<td>Pharmacokinetic data, metabolism</td>
<td>Identification of pharmacological and toxicological issues</td>
<td>Deciphering toxic activities at a molecular level</td>
</tr>
<tr>
<td>Clinical studies, eventually combined with ’omics-based, personalized methods</td>
<td>Identification of exposure or toxicity biomarkers</td>
<td>Genotoxicity, carcinogenicity, reproductive and developmental toxicity</td>
</tr>
<tr>
<td>Pharmacopoeniology and pharmacovigilance</td>
<td>Evaluation of safety in clinical use</td>
<td>Identification of clinically relevant adverse effects</td>
</tr>
</tbody>
</table>

Conclusion

Herbal safety is compromised when any element of the herbal medicine is contaminated and toxic. To meet the challenge, integrating emerging systems-based technologies with conventional means is essential. There remains a clear and urgent need for novel methods able to rapidly pinpoint indicators of major mid-term and long-term toxicities, to yield warning signals, and identify those herbal drugs and forms of plants that need further toxicological investigation. Recent advances in ’omics and bioinformatics techniques have made it possible to investigate efficacy and toxicity at the organism level and in an individual manner. When further developed and validated, these methods should enhance the detection of insidious toxicities, provide the necessary background and information for effective pharmacovigilance, and aid mechanistic studies of specific herbal medicines.

References


TABLE 1. Integrated strategies for the toxicological assessment of herbal drugs.
Combining ‘omics and comparative effectiveness research: Evidence-based clinical research decision-making for Chinese medicine

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ystematic reviews and meta-analyses of Chinese medicine trials have demonstrated issues with consistent quality, and an evidence gap between the practice of, and research on, traditional treatments. Clinical practice is built on knowledge, clinical experience, and patient preferences, all of which can be influenced by values and beliefs. Systems current in clinical medicine research, known as comparative effectiveness research, supports the development of evidence-based recommendations to enable informed decision-making in the clinic and more valid health policies that also meet the criteria for practicing “P4” medicine – predictive, preventive, personalized, and participatory. Creating a modern, strategic research framework for Chinese medicine that takes into account the stakeholders’ perspectives, follows a patient-centered approach, uses mixed methods research methodologies, and combines modern scientific techniques such as systems biology–based ‘omics technologies would be beneficial for bridging the gap between Chinese medicine theory and modern clinical research methodologies.

Background

Creating a modern evidence-based clinical research model compares “one disease, one treatment;” however, this strategy often does not have comparable clinical practices. Further, clinical trials based on the notion of study and control groups are usually designed in a standardized setting with a carefully selected patient group, and often produce results that are neither generalizable nor able to guide practice. Systematic reviews and meta-analyses summarizing such trials might even be misleading for various chronic diseases, but especially for complex conditions such as diabetes, cardiovascular disease, and pain, which often occur in patients with multiple comorbid diseases who are frequently taking medications. Decision-makers–clinicians, patients, and funders–require studies that are comparable with actual treatment options in real life settings. Comparative effectiveness research (CER) is intended to provide real-world evidence that helps clinicians and patients choose the options that best fit the individual’s needs and preferences of stakeholders ‘needs at all relevant steps and includes a number of different types of research designs, clinical trials being one of them. These so-called pragmatic trials are characterized by including more ‘real-life’ patients presenting in routine clinical care including

those that have comorbidities and use concomidation, providing more individualized treatments, using patient-relevant outcomes, and being performed in a setting that is ‘in line’ with the clinical care (1).

Chinese medicine has been historically based on a descriptive and phenomenological approach and has relied on complex mixtures of herbal medicines as well as nonpharmacological interventions such as acupuncture and lifestyle advice. Research on some of the individual treatment components of Chinese medicine (e.g., acupuncture) have already made relevant contributions to CER evidence (2) and provided guidance for the design of further acupuncture-based clinical trials. Practitioner-led Chinese medicine is a complex intervention that focuses on the whole system’s organization, and (prescribed) treatment and personal targets. Treatments are built on knowledge accumulated from ancient texts, experts, clinical experiences, and patient preferences, which are influenced by values and belief systems (3). Chinese medicine has a fundamental patient participation element, including general lifestyle aspects (e.g., diet and exercise) in the complex intervention strategies. Traditional Chinese diagnostics (or “syndrome differentiation”), a comprehensive analysis of clinical information from a Chinese medicine perspective, information derived from case taking, examining the patient’s pulse and tongue), is used to guide personalized treatment options (7). Each syndrome consists of symptoms that determine their own unique treatment protocol.

Integrating ‘omics technology with the biomedical techniques of modern clinical research would be helpful for determining personalized treatments (8). The beta version of the Personalized Healthcare Alliance, a separate and allows Chinese syndrome coding in addition to Western diagnoses (9). Currently, these Chinese syndromes are considered important tools for predicting disease (10, 11) and ongoing efforts are correlating them with measurable biomarkers. Recently, a systems biology-based approach has been utilized for Chinese medicine syndrome differentiation studies enabling the stratification of patient populations (8). This strategy may require long-term follow-up. Chinese medical trial design by having the ability to determine which patients are most appropriate for a specific intervention. One advantage of a systems biology-based approach is that the changes patients experience during routine clinical practice; the changes patients experience during routine clinical care, and have sample sizes that facilitate further subgroup analyses

1. Strategic clinical trial designs:

• Trials that include heterogeneous and ‘realistic’ patient samples, are performed in settings reflective of a patient’s routine care, and have sample sizes that facilitate further subgroup analyses
• Trial designs that balance multiple factors, including the type of study endpoints, the type of study outcomes, and study design, with both qualitative information (e.g., Chinese syndrome differentiation, patient preferences, and expectations) and quantitative information (e.g., systems biology–based ‘omics analysis)
• The development of guidance on the appropriate outcomes for future research
• Realistic treatment protocols that shift patient treatments toward a personalized care model that allows the use of complex interventions, including lifestyle factors, and reflects the changes patients experience during routine clinical practice; ‘omics-based analyses should be used to provide specific predictions followed by personalized treatments or, even better, preventive interventions. In the future, health care consumers will be increasingly equipped with their personal health information, including genome sequences, molecular profiles of diseased tissues, and biomarker panels (16). Participation from all major stakeholders will be needed to provide clinical and health policy guidance for this new medical era.

Moreover, one strategy CER could benefit from is incorporating at least genomics as part of a future research approach (17). Including ‘omics techniques into CER would be a new area for Chinese medicine–one yet to be incorporated into methodological CER guidance (18). It could directly bridge the gap between systems biology and traditional approaches of Chinese medicine theory and Western science. The trend toward P4 medicine in CER also creates an ideal setting to provide for informing patient populations. Further, the characteristics of P4 medicine dovetail with the foundations of Chinese medicine. Biological data can be used to generate recommendations that combine the underlying concepts of CER with systems biology–based ‘omics technologies in order to collect scientific evidence that can be used when the treatment of traditional medicine and optimize clinical decision-making.

Recommendations

When there is insufficient evidence for a treatment, a combination of both existing data from trials and systematic reviews of the literature should be used to inform future research and support evidence-based recommendations (16).

• Tools for systematic reviews and meta-analyses that provide comprehensive information about both the context of the studies and the extent to which the results are generalizable

• Secondary data-analyses of existing studies that utilize an evidence-based approach to identify possible associations between syndrome differentiation in Chinese medicine, other patient characteristics, and disease progression

Future clinical research on Chinese medicine would benefit from combining the evolving CER methodology, modern systems biology–‘omics approaches, and patients’ needs during routine care. In practice, this would require: Materials that appear in this section were not reviewed or assessed by Science Editorial staff, but have been evaluated by an international editorial team consisting of experts in traditional medicine research.

References


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