The Art and Science of Traditional Medicine

Part 1: TCM Today –
A Case for Integration
In this first installment of a three part series, “The Art and Science of Traditional Medicine,” we present a series of articles making a case for the integration of traditional Chinese medicine (TCM) into modern medical practice. From the new WHO Traditional Medicine Strategy to the application of systems biology in studying TCM, we aim to highlight the potential for creating an integrated, network-based health care system. The next two issues will cover herbal genomics and highlight the importance of quality control, standardization, regulation, and safety for traditional therapies. An overview of indigenous medicines in Europe, Africa, the Middle East, India, and the Americas will also be provided.

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This is the start of something big.
Traditional medicine (TM) holds great potential to improve people’s health and wellness. It is an important, yet often underestimated, part of health care. TM is found in almost every country in the world and the demand for its services is increasing every day. TM can contribute to addressing a number of global health challenges of the 21st Century, in particular in the area of chronic, noncommunicable diseases and population aging.

TM is often seen as more accessible, more affordable, and more acceptable to people and can therefore also represent a tool to help achieve universal health coverage. It is commonly used in large parts of Africa, Asia, and Latin America. For many millions of people, often living in rural areas within developing countries, herbal medicines, traditional treatments, and traditional practitioners are the main—and sometimes the only—source of health care. The affordability of most traditional medicines makes them all the more attractive at a time of soaring health care costs and widespread austerity.

In wealthy countries, TM meets an additional set of needs. People increasingly seek natural products and want to have more control over their health. They turn to TM to relieve common symptoms, improve their quality of life, and protect against illness and diseases in a holistic, nonspecialized way.

In an ideal world, TM would be an area of primary health care, but also for innovation and discovery. However, TM needs rigorous, scientific data to demonstrate its efficacy. It also needs evidence-based standards for quality and safety evaluation to support its appropriate regulation. I am happy to see included in this special feature of Science magazine, a series of perspectives on TM from a global team of experts, and would like to encourage more views to be shared and more robust research to be conducted in the area of TM in the future.

The general situation concerning the global use of TM was recently disseminated through the WHO Traditional Medicine Strategy 2014–2023. It makes clear that, to move into mainstream medicine on an equally trusted footing, TM needs a stronger evidence base. The need for stronger regulatory control covers not only the products, but also extends across the practice of TM in the future.

The rise of systems biology as a discipline, starting around five decades ago, has created a slow but unambiguous shift in the Western research paradigm. Reductionism, although still a respected philosophy, is no longer consistently the preeminent methodology of choice in biological research. Researchers around the world are coming around to the notion that, while we can learn much from understanding the finest details at a molecular level, particularly when it comes to treating disease, a deeper knowledge of the interactions between systems and networks is essential.

Conversely, taking a purely holistic approach can produce its own challenges. This is particularly true when quality control of medicinal products and reproducibility of results comes into question. No matter the weight of historical, anecdotal data, drug regulatory agencies such as the U.S. Food and Drug Administration (FDA) will not allow new therapeutics for human treatment without verifiable scientific evidence. Although there are many challenges inherent in meeting this requirement, traditional medicine researchers are applying modern ‘omics and the latest technologies in an attempt to standardize traditional treatments, especially through identification and isolation of bioactive compounds and careful analysis of their levels and activities in various herbal remedies.

In Buddhism, the Middle Way is described as the route to enlightenment—a path found by balancing opposing views, accepting neither extreme, but rather investigating both sides and finding a middle ground. Perhaps a Middle Way can be found for traditional medicine, one that takes the best of East and West and brings them together for the benefit of all.

Alan Leshner, Ph.D.
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Integrating traditional medicine into modern health care

Almost every culture has its distinct herbal traditions, each with its indigenous plants and unique practices. But one premise unites them all—herbs have remarkable properties that make them a source of potentially powerful medicines.

Thanks to early explorers like Marco Polo (1254-1324), materia medica has been travelling between East and West for centuries. It is now important for us to harness the traditional medicines from across the globe. In Britain, the rich history of traditional medicine use was given credence in the early 1500s by the Herbalists Charter of Henry the VIII (1491-1547). His contemporary in China, Li Shizhen (1518-1593) was a great naturalist who spearheaded a 40-year research project that led to the publication of Bencao Gang Mu, a pharmacopoeia and also a treatise on botany, zoology, mineralogy, and metallurgy.

To make the case that traditional medicine has valuable insights for modern society, an independent editorial team was gathered consisting of experts in a range of topics related to traditional medicine research. This team compiled a unique collection of state-of-the-art perspectives from global experts on traditional medicine research, the first installment of which is presented in this special feature. Further exciting articles will be published early in 2015.

We have chosen traditional Chinese medicine (TCM) to illustrate the art and science behind ancient healing, and how these practices of quality control, pharmacology and toxicology testing, carefully designed clinical studies, and proper regulation are applicable to all traditional medicines.

This first issue introduces the WHO Traditional Medicine Strategy (2014–2023), highlighting the global scientific challenges and showing how a systems biology approach can be applied to diagnosis, leading to integrated network-based medicine. Recent advances in mechanistic studies of acupunc
ture are also discussed. Some of the exciting areas in TCM research include the therapeutic potential of herbal remedies against influenza, cancer, diabetes, and cardiovascular diseases; the exploration of gut microbiota-targeted dietary interventions against chronic inflammation; and the study of the biological activities of complex polysaccharides present in medicinal plants. Chemogenomics and network pharmacology have been applied to predict molecular targets and decipher the mechanisms of action of pure compounds or phytoconstituents found in combinatorial herbal formulas. A better understanding of the philosophy of synergetic interactions of Jun, Chen, Zuo, and Shi classes of Chinese materia medica used in traditional formulations has led to a simplified Jun-Shi compatibility drug discovery strategy model.

Evaluating the safety of herbal medicines is critical to their wider acceptance as valid therapeutic agents. Integrated toxicological approaches have been successfully applied in this area, for instance to identify antifungal and probiotic substances in certain medicinal plants. As research into the broader application of traditional medicine continues, newer ‘omics technologies and poly-pharmacokinetics will also play an increasing role in bridging the gap between the personalized approach of Chinese medicine theory and modern clinical research methodology.

Acknowledgments

We are particularly grateful to Zhu Chen, vice-chairman of the Standing Committee of the National People’s Congress of the People’s Republic of China for inspiring us to undertake this project, to WHO Director-General Margaret Chan and her team, Commissioner Guojiong Wang of the State Administration of Traditional Chinese Medicine, and AAAS CEO Alan Leshner for their vision and support for this special feature. Thanks are also due to all authors, referees, advisors, and editors for focusing the journey ahead to translate ancient traditional medicines into the therapies of tomorrow.

The WHO Traditional Medicine Strategy 2014–2023: A perspective

here has been a continuing demand for, and popular use of, traditional and complementary medicine (T&CM) worldwide. In some developing countries, native healers remain the sole or main health providers for millions of people living in rural areas. For instance, the ratio of traditional health practitioners to citizens in Africa is 1:500, whereas the ratio of medical doctors to citizens is 1:140,000 (1). In the Lao People’s Democratic Republic, 80% of the population live in rural areas, with each village being served by one or two traditional health practitioners (2). Over 100 million Europeans are currently users of T&CM, with one-fifth being regular users; a similar proportion choose health care that includes T&CM. In South Korea (3), according to a national survey in China, practitioners of traditional Chinese medicine received 907 million visits from patients in 2009, which accounts for 18% of all medical visits to surveyed institutions. Further, the number of traditional Chinese medicine inpatients was 13.6 million, or 16% of the total in all hospitals surveyed (4).

In a few countries, certain types of traditional medicine (TM) have been completely integrated into the health care system, including China, the Democratic People’s Republic of Korea (North Korea), the Republic of Korea (South Korea), India, and Vietnam. In China, for instance, traditional Chinese medicine and conventional medicine are practiced alongside each other at every level of the health care service, and public and private insurance cover both forms of treatment (Box 1).

In many other countries, T&CM is partially integrated into the health care system, while in some countries there is no integration at all.

Recent changes, emerging challenges, and needs

Much has changed since the last World Health Organization (WHO) global strategy document was released in 2002. More and more countries are coming to accept the contribution that T&CM can make to the health and well-being of individuals and communities. In many countries, their health care systems. In the period 1999 to 2012, the number of members of WHO with national policies covering TM has increased significantly. This includes countries better regulating herbal medicines or creating national research institutes to study T&CM (5).

Governments and consumers are becoming more open to broaden TM’s scope and practice by considering them as an integrated part of health service delivery. In Africa, the number of national regulatory frameworks increased from one in 1999 (2002) to 28 in 2016 (6). Across the Atlantic, the Ministry of Health in Brazil has developed a national policy on integrative and complementary practices (7), while in the eastern Mediterranean region, five member states report having regulations specifically for T&CM practitioners (5). Member states in the southeast Asia region are now pursuing a harmonized approach to education, practice, research, documentation, and regulation of TM (5).

Despite significant advances, the regulation of T&CM products, practices, and practitioners is not occurring at an equal pace (6). Member states report that faster progress is being made in the regulation of herbal medicines, while that for T&CM practitioners and practitioners’ lagging. Of concern is that without regulation the safety, quality, and efficacy of T&CM cannot be assured if there is not appropriate regulation of practices and practitioners. This situation presents a unique challenge for many member states, where a lack of knowledge and experience exists regarding the formulation of national policy, leading to weak or not regulation and a lack of proper integration of T&CM services into the health service delivery system. It also reflects the need of all member states to push WHO to update its global strategy on TM.

The WHO Traditional Medicine Strategy 2014–2023

Responding to the needs and challenges identified by member states and building on the work done under the WHO Traditional Medicine Strategy 2002–2005 (10), the updated strategy for the period 2014-2023 devotes more attention than its predecessor to health services and systems, including T&CM products, practices, and practitioners. The two new objectives of the updated strategy are summarized below.

Objective 1: To build the knowledge base for active manage- ment of T&CM through appropriate classification of T&CM as a great diversity of products, practices, and practitioners in T&CM. The first strategic step towards achieving this objec- tive is to understand and recognize the role and potential of T&CM. The strategy recommends that member states acknowl- edge and appraise, in detail, which types of T&CM are used by their populations and devise their own country profile for T&CM practices. As the marketplace for T&CM becomes more global, harmonization and cooperation will become more important.

The second strategic step under this objective recommends that member states strengthen knowledge generation, col- laboration, and sustainable use of T&CM resources, including intellectual and natural resources.

Objective 2: To strengthen quality assurance, safety, proper use, and effectiveness of T&CM by regulating T&CM products, practices, and practitioners. The first strategic element under this objective is to recognize the role and

Authors

Zhang Qi and Edward Kelley

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importance of product regulation. The emphasis should be on the monitoring and implementation of established regulations of TM products. Since herbal medicines are now used internationally, products often used in parts of the world, the emphasis on that in which they were originally grown, developed, or manufactured can be addressed by benchmarking against appropriate reference standards. As more countries develop policies and regulatory frameworks, there is a need for them to evaluate their effectiveness and identify ways in which to improve and expand. TM practitioners and product regulation can be addressed by benchmarking against appropriate international standards.

Objective
To promote universal health coverage by integrating T&M services into health care service delivery and self-care health. One of the most significant questions raised about T&M in recent years has been how it might contribute to universal health coverage by improving service delivery in the health system, particularly primary health care. A first step is to capitalize on the potential of T&M to improve health services and health outcomes. Mindful of the traditions and customs of peoples of different cultures and countries, T&M practitioners should consider how T&M might support disease prevention or treatment as well as health maintenance and health promotion. This process should be aligned with safety, quality, and effectiveness standards and in line with patient choice and expectations. Based on each country's realities, it is recommended that governments integrating T&M into national health systems should be explored.

Next, it is important to ensure that consumers of T&M can make informed choices about self-care health. In many member states, self-selection of T&M products accounts for a large proportion of the market. Education of consumers, member states, together with ethical and legal considerations, should support and shape the key aspects of informed choice for T&M intervention.

The WHO resolution WHA67.18 urges member states to adapt, adopt, and implement the WHO Traditional Medicine Strategy. The strategy calls for the integration of T&M programs or work plans and to report to WHO on progress in implementing the strategy. The resolution also encourages WHO to support member states in the implementation of the strategy in the coming decade (11).

Conclusions
Around the world, T&M continues to grow in popularity. Progress in the regulatory gaining momentum, even as that of T&M practices and practitioners advances at a somewhat slower pace. Safety, quality, and effectiveness of T&M services is paramount, but cannot be ensured if appropriate practice of regulation and practitio-

BOX 1. Traditional medicine service integration in China.

In China, there are about 440,700 health care institutions providing TM services, with 520,600 beds, including all levels of TM hospitals and general hospitals, clinics, and health stations in urban and rural areas. About 90% of general hospitals include a TM department and provide TM services for all T&M medical institutions are governed by the same national legislation as conventional medical institutions. TM practitioners are allowed to practice in both public and private clinics and hospitals; and TM products can be prescribed, as well as T&M forms of health care services, or follow the advice of their doctors (12). An emphasis should be given to the significant potential of T&M to improve health services and health outcomes. Mindful of the traditions and customs of peoples of different cultures and countries, T&M practitioners should consider how T&M might support disease prevention or treatment as well as health maintenance and health promotion. This process should be aligned with safety, quality, and effectiveness standards and in line with patient choice and expectations. Based on each country's realities, it is recommended that governments integrating T&M into national health systems should be explored.

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The typical sham controls use the same ritual, the same practitioner reassurance, and the same counter-irritant effect of needles or pressure points as the comparison group (although the needles may be replaced with non-penetrating devices and the insertion points chosen do not lie on treatment meridians). Effectiveness trials typically compare a subject’s response to different treatments, which are randomly assigned and include either acupuncture or standard care.

A recent, systematic review of 29 trials, with approximately 18,000 study participants, resulted in some clear conclusions. The magnitude of acupuncture’s effect depends upon which group is used for a comparison (5). Specifically, when acupuncture was compared to no acupuncture (in effectiveness studies), the benefit appears to be quite sizable, approximately 50% reduction in pain severity. In contrast, when acupuncture is compared to a sham treatment (in efficacy studies), more modest effects are observed (Figure 2).

Although statistical significance is achieved, the reduction in pain severity is not as substantial, typically only 20%. Based on this analysis, it seems reasonable to conclude that needling itself may be contributing to acupuncture’s pain-reducing effects, and that the overall benefit is heavily dependent on context—on the reassurance and expectation produced by the acupuncture ritual.

Medium diagnoses may provide some clarity and community support. Nevertheless, although there is some evidence for efficacy of pharmaceutical treatments for some such conditions, often these disorders respond inconsistently or poorly to available treatments. There is also clinical concern that sometimes these diagnoses can contribute to an expectation of chronic functional impairment.

Traditional diagnoses often emphasize a temporary imbalance and promote an expectation that the subject will return to health. Although many patients with these conditions seek alternative remedies, most of the evidence of benefit is anecdotal. In resource-poor environments, people almost certainly suffer from the same set of symptoms, and anecdotally, at least, these complaints may sometimes be effectively addressed through the care of traditional healers. We are currently supporting a small number of trials that address whether the emotional and social support of interventions such as tai chi (7), yoga, or mindfulness-based meditation may capture some of the benefit of the healing traditions. Clearly, Western medicine does not have all the answers, and systems of care that allow thoughtful integration of healing traditions with modern medicine may offer help to troubled patients.

**References**

**FIGURE 1. Artemisinin.** (A) Artemisia annua, also known as sweet wormwood or qinghao. (B) The chemical structure of artesiminin.

**FIGURE 2. Acupuncture effects compared with controls.** The results of a meta-analysis of 29 high-quality randomized clinical trials of acupuncture are shown for three conditions. Differences in the average standardized mean (with 95% confidence intervals) for treatment relative to control is shown. When compared to no treatment, acupuncture produces striking improvement; however, when compared to sham treatments, the effect is more modest (5).
An international editorial team consisting of experts in traditional Editorial staff, but have been evaluated by Materials that appear in this section were not reviewed or

Bridging the gap

although there are many similarities between the Greek and Chimeric medicine, the medical systems that arose in the West and in the East are quite distinc- trably low, a highly reductionist, detailed view dominated, and in particular, systems biology, have been recognized as the scientific bridge between Western medicine and traditional medicine models, including traditional Chinese medicine (TCM) (2, 3).

Figure 1 illustrates how systems-based theories can bridge Eastern and Western models, as it connects ancient and modern ideas. The left forward image shows a dynamic correlation network of interactions between various genes, proteins, and metabolites. This nodal network reflects the particularized understanding of the complexity of biochemical pathways and the dynamic organization of the body that characterizes Western modern biology. The right forward imagery is a drawing of the Taoist Inner Landscape. In keep- ing with ancient Taoist tradition, the drawing provides a poetic description of the complex relationship among the various organ functions of the body. The background of the figure merges two very different, symbolic, mystical systems of thinking: the Vrtuman (Le proporzioni del corpo umano secondo Vitruvio) and the Taiji (often called the Yin-Yang symbol in the West) represents the Eastern, Taoist tradition of systems thinking. It depicts a dynamic relationship between the two components of a duality that encompasses the known universe. Interestingly, the Taiji, which symbolizes humanity as part of an eternal universe, has all the properties of a fractal.

Amalgamation in action

Figure 2 depicts an amalgamation of Western and Eastern medical system, realty, and factoring in what we call injury, dry mouth, and pain that is relieved by cold, while "cold" symptoms include clear urine, sharp pain, stiff joints, and pain that is relieved by warmth. This example demonstrates how TCM helps biomedical researchers to distinguish biological subtypes of RA in a manner that could lead to new treatments. It also promotes personalized lifestyle advice, and in the long term, through the application of modern biomedical technology in studies of RA, help to standardize the segregation of patients into TCM subtypes (13). The comprehensive symptom questionnaire used in the RA study was based on the TCM perspective of arthritis as a bi-syndrome. Following the questions and symptoms of RA are universally represented across peoples independent of culture, although variations in concepts and emphasis can be modelled for RA patients, and to engage the West and East. In both cases, these two patient groups display differences in the regulation of apoptosis, in CD4+ T cell gene expression lev- els, and in plasma and urine metabolite profiles. In another study that included all 20 metabolite variants associated with differences in muscle breakdown was used to distinguish between the "cold" and "hot" RA subtypes (5).

In similar recent work on pre-diabetes, Wei and colleagues (4) examined blood and urine samples from patients catego- rized by Chinese subtypes of pre-diabetes, namely, yin and yang deficiency with or without dampness, and qi and yang defici- ency with stagnation. The yin deficiency is associated with less food, sugar and amino acid level differences that may be indicative of the synchronization of physiological rhythms such as heart rate and breathing rhythms (3), and the study of meta- bolic processes that show oscillatory behavior (15). Another

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Yan Schroën1,3, Edward P. Wijn1,4, Thomas Haniemer1, Suowen Xu2, Jan van der Greef4,5

East is East and West is West, and never the twain shall meet?

Philosophers have pondered whether more than one set of theories from a variety of disciplines, developing an expanded system that would include both of science. A different approach to understanding reality and

The path ahead

We believe that Western diagnostics would benefit greatly from the integration of broader knowledge of relationships between symptoms, including chronic disease. TCM descriptions of syndromes. TCM descriptions offer potential directions for detailed, explanatory biomedical research, bringing us closer to TCM prescriptive models of health in which more and more relationships between diagnoses, pathology, and behavior are uncovered (12). Arguably, the dearth of understandings regarding the general effectiveness of TCM as a conventional clinical tool, in which the combination of broader knowledge of relationships between diagnoses, pathology, and behavior are uncovered (12) and the study of coherent oscillations as a hallmark of dysregulation of sequence network of interactions between various genes, proteins, and metabolites. This nodal network reflects the particularized understanding of the complexity of biochemical pathways and the dynamic organization of the body that characterizes Western modern biology. The right forward imagery is a drawing of the Taoist Inner Landscape. In keeping with ancient Taoist tradition, the drawing provides a poetic description of the complex relationship among the various organ functions of the body. The background of the figure merges two very different, symbolic, mystical systems of thinking: the Vrtuman (Le proporzioni del corpo umano secondo Vitruvio) and the Taiji (often called the Yin-Yang symbol in the West) represents the Eastern, Taoist tradition of systems thinking. It depicts a dynamic relationship between the two components of a duality that encompasses the known universe. Interestingly, the Taiji, which symbolizes humanity as part of an eternal universe, has all the properties of a fractal.

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intriguing area being examined is the coherent, spontaneous ultra-weak photon emission patterns of organisms (16, 17). Recent work suggests that photon distribution dynamics may provide insights into regulatory coherence at a high systems level (18, 19). Indeed, these coherent light functions may be directly involved in communication in addition to influencing biochemical networks (20, 21). It should also be clear that modern quantitative technologies developed in the West have a great deal to offer to Chinese diagnostics. Especially relevant are methodologies that provide information about the large-scale organization of systems as well as the dynamics of such organization (Figure 2). Integration of Western and Chinese medicine thinking has enormous potential for synthesizing modern technological systems as well as the dynamics of such organization (Figure 2). Although Chinese and Western medicine develop typically via a symptom relationship approach, while in Chinese medicine, these efforts have not achieved the desired results (22). Moreover, because of the highly interconnected nature of the human interactions that provide information about the large-scale organization of systems as well as the dynamics of such organization (Figure 2). Integration of Western and Chinese medicine thinking has enormous potential for synthesizing modern technological systems as well as the dynamics of such organization (Figure 2).  

**Zheng: A systems biology approach to diagnosis and treatments**

Traditional Chinese medicine (TCM) is an ancient medical practice system which emphasizes regulating the integrity of the human body and its relations with natural environments. As a key concept in TCM, Zheng (meaning syndrome or pattern) is the overall physiological and/or pathological pattern of the human body in response to a given internal and external condition, which usually is an abstraction of internal disharmony defined by a comprehensive analysis of the clinical symptoms and signs gathered by a practitioner using inspection, auscultation, olfaction, interrogation, and palpation of the pulses (1). Correctly identifying the Zheng is fundamental for the diagnosis and treatment of diseases. Moreover, Zheng has been historically applied as the key principle guiding the prescription of herbal formulas (Figure 1). A lack of research on Zheng has left us with little understanding of its underlying biology or the relationships between different Zhengs, diseases, and drugs. Moreover, there have been attempts to integrate Zheng differentiation with modern biomedical diagnostic methods, though these efforts have not achieved the desired results (2). Many well-known herbal recipes, such as Liu Wei Di Huang Wan and Jin Kui Shen Qi Wan, have long been used for the clinical treatment of Zheng disorders; however, Zheng-guided treatments are still scarce due to the lack of evidence-based interpretations of syndromes and treatment efficacies. Thus, investigating the biological basis of Zhengs from a molecular and a multiscale level, which makes them difficult to understand at a biological and mechanistic level. Thus, we propose that a comprehensive Zheng map be constructed that links together all the Zhengs on their molecular and cellular relationships. Further, we suggest creating the “Zhengome” as a new ‘omics field, in which a network is the basic research unit used to investigate the hierarchy present in the human body, from the molecular to the systems level. A comprehensive understanding of the Zhengome requires us to bring together multiple sources of evidence, from shared genes to protein-protein interactions, shared environmental factors, common treatments, and phenotypic and clinical manifestations, in order to capture the relationships between the different Zhengs. Zheng uses the Yin-Yang, exterior-interior, cold-heat, and deficiency-excess definitions to describe the Zhengs according to their molecular and cellular conditions, which are then managed by Zheng-specific recipes (Figure 1). Modern ‘omics techniques combined with bioinformatics and bionetwork models through a systems biology approach have

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been applied to investigate the differences between Zhengs and to identify novel biomarkers. For instance, rheumatoid arthritis (RA) patients differentiated on the basis of “hot” and “cold” Zhengs have been shown to be associated with different underlying genomic and metabolic profiles, with the RA hot group showing more apoptotic activity than the cold group (6). Additionally, Li et al. used a network-based computational model to understand Zheng in the context of the neuro-endocrine-immune network and found that cold and hot Zhengs were closely related to a metabolism-immune imbalance (5). Wang and colleagues investigated the urinary metabolome of patients with Pi-deficiency syndrome and its two subtypes of Yang Huang (active) and Yin Huang (chronic), and identified several biomarker metabolites (6). However, most of the current studies have relied on only one or two approaches for molecular profiling and have lacked an efficient method to integrate data obtained at different ‘omic’ levels. These studies also did not look at combining the analysis of molecular data with clinical variables, possibly missing an opportunity to generate more convincing conclusions. Considering the limitations of past studies, future efforts should integrate an analysis for all levels of ‘omics’ (e.g., genomics, transcriptomics, proteomics, and metabolomics) from a large number of patient samples for different Zhengs and include an investigation of the prognostic and therapeutic utilities of the data as well. Combining these molecular data with patients’ clinical information could provide evidence-based theoretical interpretations for Zhengs and enable an assessment of Zheng-based therapeutic approaches.

Zhengs may change dynamically during disease progression. Differentiating the specific Zheng involved in each stage of a disease could provide valuable guidance for prescribing a dynamic therapeutic recipe. Using dynamic network modeling, a disease process can be conceptualized as spatio-temporal changes in network structures. The changes associated with a Zheng under dynamic therapy can be used to identify the key factors in the dynamic biological networks. Appropriate network perturbation models and subsequent robustness and sensitivity analysis could help unveil potential disease-related genes or therapeutic targets involved in a disease’s progression or evolution (7). The relationships between the different aspects of a disease (e.g., main symptoms versus complications) in a specific Zheng as well as the psychological, social, and environmental factors should be taken into account during the modeling and simulation process in order to uncover the dynamic nature of complex diseases. Combining a Zhengome approach with dynamic modeling has the potential for establishing an accurate and quantitative Zheng research model, as well as for creating a new system for performing disease research.

Zheng-driven drug discovery

Despite considerable progress in genome, transcriptome, proteome, and metabolome-based high throughput screen methods, and in rational drug design, drug discovery often encounters considerable costly failures that challenge the feasibility of the future drug discovery system. Zheng-driven drug discovery has shown tremendous success for traditional drug discovery throughout Chinese medicine’s history. However, since this concept is completely new to Western medicine, it is no easy task to incorporate Zheng-driven drug discovery into modern drug discovery workflows.

Here, we propose the “Zheng to TCM” and “TCM to Zheng” strategies within the framework of systems pharmacology to investigate biological systems and develop new therapeutics (Figure 2). The first strategy, Zheng to TCM, proposes developing a pipeline from Zheng diagnosis to TCM drugs, including differentiating Zhengs, identifying Zheng-related diseases and the associated genes and proteins, reverse targeting of drug effects, constructing and analyzing network/systems, and finally identifying effective herbal medicines (8). In effect, this strategy can be considered a reverse targeting and screening approach that is designed to uncover drugs from natural products that can target multiple Zhengs or related diseases. The goal of this method is to help researchers identify the active components within medicinal plants and multi-ingredient synergistic herbal formulas or drug combinations (9). In fact, this novel strategy has already been successfully applied in a q-bio study, where we identified the active compounds in the qi-enriching and blood-toxifying herbs, their targets, and the corresponding pathways involved in the treatment of qi and blood deficiency syndromes (10).

The second strategy, TCM to Zheng, consists of a whole-system evaluation process starting with herbs or herbal formulas and culminating in identifying the Zhengs. This process includes the initial collection and classification of herbal medicines; screening the ingredients for absorption, distribution, metabolism, excretion, and toxicity (ADME/T); performing targeted drug screenings and tissue localization; constructing and analyzing networks; and finally identifying Zhengs/diseases (10). Using this strategy, it is possible to identify novel multitarget drugs in natural products (11). One particularly striking example is the systematic analysis of blood stasis and qi deficiency syndrome in coronary heart disease and the herbal drugs used to treat the syndromes. The results indicate that the herbs for eliminating blood stasis have pharmacological activity that acts to dilate blood vessel, improve the microcirculation, reduce blood viscosity, and regulate blood lipids, while qi-enriching herbs help in the potential for enhancing energy metabolism and anti-inflammatory activity (12). The TCM to Zheng strategy can also help to elucidate the pharmacological effectiveness of herbs and formulas.

In our ongoing work investigating Pi-deficiency syndrome (PDS) in the context of Zheng, we are analyzing patient samples using the sequencing alternative polyadenylation sites (SAPAS) method, RNA sequencing (13), lipid metabolomics, proteomics, and transcriptomics in order to decipher the pathogenesis and complex responses of the human body to PDS. From a drug development perspective, we plan to systematically investigate the Si Jun Zi decoction, a widely used herbal recipe for PDS, within the framework of the “TCM to Zheng” strategy, so as to understand why this recipe can regulate the immune response, stimulate blood circulation, and adjust gastrointestinal digestive functions. Despite the progress in Zheng-guided drug discovery, its future success requires the integration of multidisciplinary technologies, together with furious innovations in computational and systematic biology, to facilitate the understanding of multifactorial diseases and the development of new therapies.

References
## Integrated network-based medicine: The role of traditional Chinese medicine in developing a new generation of medicine

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According to the philosophy of traditional Chinese medicine (TCM), health is the state of harmony between individual internal physiological networks (IPNs) and external environmental networks (EENs). Aberrant interactions between and within these networks cause complex diseases. TCM is grounded in these holistic principles, integrating philosophies from art and science; it stresses the maintenance of balance, or homeostasis, between the systems of the body and nature.

We believe that this kind of network-based holistic approach to medicine offers a useful counterpoint to today's biological reductionism-based thinking. We champion integrated network-based medicine (INBM) which takes a systems approach to understanding the individual’s body as a whole, as opposed to relying on discrete components such as gene mutations, in order to explain illness (1). Built on the principles of IPNs and EENs, INBM offers a comprehensive medical system that integrates fundamental theories, diagnostic methods, and therapies based on a holistic and dynamic network-based approach.

### The INBM system

Reductionist approaches to medicine, such as phenotype-based and target-based biomedicine (TBBM), are limited by their failure to consider the interactive nature of the human body and its environment. TBBM often views a disease as a tissue/organ-based condition that presents a single target for treatment, such as the elimination of a pathogen or the suppression of a disease-associated molecular target. This narrow focus can miss a broader range of pathogens and their failure to consider the interactive nature of the human body and its environment. TBBM often views a disease as a tissue/organ-based condition that presents a single target for treatment, such as the elimination of a pathogen or the suppression of a disease-associated molecular target. This narrow focus can miss a broader range of pathogens and their overall impact on drug on the glucose metabolic network (3). This has raised the possibility that the drug will have new therapeutic uses (4). Efforts to focus on a single target can also have deleterious effects on the body's overall system. An example is indomethacin, a conventional Western-medicine drug. Indomethacin exerts an anti-inflammatory effect by inhibiting prostaglandin E2 (PGE2) synthesis (5), but this suppression of PGE2 also affects a receptor for mucus secretion, leading to gastric mucosa damage (6, 7). A holistic view of the body's network of connections will anticipate such positive and negative impacts of medical treatments.

### INBM requires rigorous conceptual design and practical implementation, and TCM has many principles and resources to help achieve this. These include "pattern differentiation in diagnosis and treatment of diseases," which can be regarded as a basic principle for individualized INBM (8). The "three m’s" of Chinese herbal medicine (CHM) provide another example: these are "multi-chemical components," "multi-pharmacological effects," and "multi-action targets and pathways." The complex herbal formulae of CHM are intended to holistically modulate a person's physiological/pathological networks and, in developing new drug combinations, the "three m’s" offer a useful optimization tool (9).

Figure 1 illustrates how the "three m's" approach to the positive and negative impacts of medical treatments.

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**Figure 1.** How integrated network-based medicine (INBM) works. TCM, traditional Chinese medicine.

**Figure 2.** The impact of Chinese herbal medicine (CHM) components on signal transduction pathways involved in immune activation. PMA, phorbol myristate acetate; MHC, major histocompatibility complex; TCR, T cell receptor; CRAC, calcium release-activated channel; Ca2+, calcium ions; B7, B cell activation antigen B7; CD28, Cluster of Differentiation 28; Src, proto-oncogene tyrosine-protein kinase Src; Syk, spleen tyrosine kinase; P38K, phospholipaseDinositol-4,5-bisphosphate 3-kinase; PLC-γ1, phospholipase C γ1; DAG, dimeric acidic glycoprotein (clusterin); IP3, inositol trisphosphate; PDK1, pyruvate dehydrogenase lipoamide kinase 1; PKCB, Protein kinase C B; JNK, Jun N-terminal kinase; Akt, serine/threonine-specific protein kinase, also known as protein kinase B; β-TrCP, β-transducin repeat-containing protein; IKKβ, IκB kinase β; IKKγ, IκB kinase γ; NFAT, nuclear factor of activated T cells; IκBα, IκB kinase α; NFκB, nuclear factor κB; AP-1, activator protein 1.

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An improved understanding of the molecular mechanisms that underlie the antifibrotic activities of herbs would be of great clinical relevance. Recent studies have demonstrated that many herbs, through various mechanisms, can inhibit the progression of fibrosis. For example, Panax ginseng and Rhizoma Coptidis have been shown to inhibit the growth of cancer cells, suggesting that they may have potential antifibrotic effects.

**Materials and Methods**

**Model**

- **Drug**: Identify drug candidates to be tested in in vivo studies.
- **Trial**: Establish and evaluate clinical trials. Lower risk/benefit ratio for drug discovery.

**Mechanism**

- Perform mechanistic studies for efficacious drugs.

**Results**

- **Botanicals**: A double-edged sword.
  - **Herbs**: Botanicals are an important source of antifibrotic activities. For example, halofuginone, a derivative of fibroblast growth factor (FGF), is known to induce fibrosis. However, for example, halofuginone-induced fibrosis can be reversed by activation of the AMPK (AMP-activated protein kinase) pathway.
  - **Herbs**: Many herbs have been shown to inhibit the progression of fibrosis. For example, Panax ginseng and Rhizoma Coptidis have been shown to inhibit the growth of cancer cells, suggesting that they may have potential antifibrotic effects.

**Discussion**

- **Conclusion**: The development of INBM will enhance our understanding of the molecular mechanisms that underlie the antifibrotic activities of herbs. This will be of great clinical relevance and could lead to the development of new therapies for fibrotic diseases.

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**References**

L. thionae, an herb commonly used in Australia to treat symptoms of menopause and rheumatic arthritis (28), and Leonurus japonicus Houtt, an herb commonly used in TCM for glycemic and obesogenic effects (15, 29). Additionally, we previously found that ethanolic extracts from unprocessed main roots of Aconitum carmichaeli Debe, have potent in vitro proinflammatory activities (30). Consequently, a comprehensive survey of Aconition species is known to cause acute renal failure and has been linked to end-stage renal disease (ESRD) in a case report by the U.K. Medicines and Healthcare Products Regulatory Agency (31).

The increasing and avoiding exposure to pro-fibrotic botanicals is profound. For instance, about one-third of the Taiwanese population consuming AA-containing herbs between 1997 and 2003 (32, and AAN previously accounted for up to 10% of all ESRD in Taiwan) (32). The banning of AA-containing herbs, together with other efforts such as public-awareness campaigns, education of patients, funding for research to chronic kidney disease, and provision of integrated care, has turned Taiwan into one of the few regions with recent decrease in incidence (23).

Moving forward

Due to the contradictory and complex roles botanicals play in fibrotic diseases, there is an urgent need for studies that investigate efficacy, safety, and good practices for botanical-based remedies. Since fibrotic diseases are multifactorial conditions and botanicals are typically heterogeneous, an efficacy-based strategy is particularly well-suited for studying antifibrotic botanicals (Figure 1).

• Such a strategy is highly dependent on disease modeling. It is worth emphasizing that innovation is needed to develop high-quality in silico, in vitro, and animal models that can facilitate the investigation of antifibrotics and direct profibrotic activities.

Because evidence-based medicine is a relatively new concept in many countries (34), many clinical reports on herbal treatment of fibrotic diseases are criticized for poor quality. Diseases for which the literature has been recently reviewed include liver fibrosis (35), pulmonary fibrosis (36), multiple sclerosis (36), and adhesive small bowel obstruction (37). An efficient and cost-effective strategy ultimately demands high-quality clinical trials to prove antifibrotic effects and invites interregional cooperation for the development of consensus on the most promising botanicals, which is challenging due to the inidious nature of fibrosis and the variability in the distribution channels and legal status of botanicals.

Finally, traditional use is only indication but certainly not a proof of either safety or efficacy (40). To harness and understand the potential medicinal properties of herbal therapies, and for the prevention of fibrotic diseases, future research and innovation must focus on efficacy and safety, and must be built on and controlled by political will, which we have rarely seen at length (47). Development and refinement of good practices, however, can only be achieved with sustainable funding.

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J-Needle: Detecting the biological mechanisms of acupuncture

Authors

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A long standing obstacle to the full integration and acceptance of acupuncture in conventional medicine lies in the difficulty of relating EMT (epithelial-mesenchymal transition) (32) to proof of either safety or efficacy (32). Development and refinement of good practices for acupuncture (32) include liver fibrosis (35). An intelligent needle (35) moves forward

Due to the contradictory and complex roles botanicals play in fibrotic diseases, there is an urgent need for studies that investigate efficacy, safety, and good practices for botanical-based remedies. Since fibrotic diseases are multifactorial conditions and botanicals are typically heterogeneous, an efficacy-based strategy is particularly well-suited for studying antifibrotic botanicals (Figure 1).

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Finally, traditional use is only indication but certainly not a proof of either safety or efficacy (40). To harness and understand the potential medicinal properties of herbal therapies, and for the prevention of fibrotic diseases, future research and innovation must focus on efficacy and safety, and must be built on and controlled by political will, which we have rarely seen at length (47). Development and refinement of good practices, however, can only be achieved with sustainable funding.
Progress has already been made, based on recent reports of ATP being released from keratinocytes (Figure 1). In 2009, Burnstock et al. suggested that ATP acted as a nonadenergic, noncholinergic neurotransmitter in the gut (1) and in 1972 he named the extracellular actions of ATP “purinergic signaling” (since ATP is a purine nucleotide), and formulated the purinergic signaling hypothesis (2).

In 2009, Burnstock proposed that purinergic signaling could be involved in the physiological mechanisms mediating acupuncture effects. This hypothesis suggested that mechanical deformation of skin by needles or application of heat or electrical current leads to the release of large amounts of ATP from keratinocytes, fibroblasts, and other cell types in skin (Figure 1). The released ATP then activates P2X3 ion channel receptors on sensory nerves within the skin and tongue that transmit messages via sensory ganglia and the spinal cord to the brain stem and hypothalamus. These brain regions contain motor neurons that control autonomic functions, including cardiovascular, gastrointestinal, respiratory, and urinary output—common targets of acupuncture treatments. These sensory neuron messages also modulate the pathways that lead to centers in the cortex responsible for conscious awareness of pain and other visceral sensations (3). A number of subsequent studies have been published that also implicate purinergic signaling in various aspects of acupuncture, detailed below.

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References
from keratinocytes (4–6) and possibly from Merkel cells, which contain high levels of ATP (7, 8). ATP has also been shown to be released from keratinocytes upon heating (9), (iii) immunohistochemical data demonstrating the presence of P2X3 receptors on sensory nerve fibers in the skin (10–12) and tongue (13); (iii) in vivo, stimulation of trigeminal nerve preparation, mechanical activation of the tongue with De Frey hairs was shown to result in a discharge in the lingual sensory nerve fibers that was mimicked by ATP activation and blocked by P2X3 receptor antagonists (14); and (iv) both presynaptic inhibition via adenosine A, and P2Y receptors, and enhancement via P2X and A2A receptors at synapses in the central nervous system have been reported (15).

Subsequent papers have built upon and extended evidence in support of purinergic signaling underlying acupuncture effects. Several studies have associated the skin cells affected by acupuncture techniques with purinergic signaling. For example, ATP has been shown to be released from human keratinocytes in response to mechanical stimulation by hypo-osmotic shock (16), as well as from keratinocytes in response to heat (17). Additionally, mast cells, which accumulate around the acupuncture needles, also release ATP in response to mechanical stimulation (18). Another skin cell type, human subcutaneous fibroblasts, can release ATP in response to bradynkinin and histamine (19, 20). Tsutsui et al. demonstrated that mechanical stimulation can evoke the propagation of calcium waves between human keratinocytes, induced by ATP and activation of P2Y receptors (21, 22), which is consistent with the earlier results from Koizumi et al. (5). Tuina (traditional therapeutic massage) and moxibustion (a traditional Chinese medicine therapy using a moxa, often made from dried mugwort, either used as a fluff or processed into a cigar-shaped stick) can be used indirectly, with acupuncture needles, or burned on to the patient’s skin) may also act via the purinergic signaling pathway (23). Papers describing the release of ATP from human epidermal keratinocytes via connexin hemichannels and vesicles involving vascular nucleotide transporter have recently been published (24–26). A 2010 study has claimed that adenosine, following breakdown of released ATP during acupuncture, can act as a prejunctional inhibitor of neurotransmission via A receptors, resulting in anti-nociceptive actions (27). Valuable reviews are available describing the neural pathways from different skin regions to structures in the brain stem and higher brain centers. These pathways are important because different acupuncture sites may activate different neural pathways impinging on specific nuclei in the brain stem that control autonomic functions potentially modulated by acupuncture (Figure 2) (28, 29).

Purinergic signaling and electroacupuncture
Electroacupuncture is a form of acupuncture where a small current is passed between pairs of acupuncture needles. This is thought to augment traditional acupuncture and is believed to be particularly helpful in treating pain. The supraspinal antinociceptive effect of electroacupuncture has been associated with P2X3 receptor activation in the midbrain periaqueductal gray region (30). Moreover, the analgesic effect of electroacupuncture on chronic neuropathic pain has been shown to be mediated by P2X3 receptors in rat dorsal root ganglion neurons (31). Following these studies, electroacupuncture was shown to result in a reduced expression of P2X3 and P2X2 receptors in the dorsal root ganglion of rats with chronic neuropathic pain (32) and visceral hypersensitivity (33). Electroacupuncture at Hi-6 Mu points can also reduce P2X4 receptor expression in colon and spinal cord in visceral hypersensitivity (34). Moreover, in a review by Lin et al., the neuroprotective effects of acupuncture were reported to act via increasing brain derived neurotrophic factor (BDNF) expression via stimulation of ATP (35).

Conclusions
Evidence in support of the hypothesis of purinergic signaling mediating the physiological mechanisms underlying acupuncture effects has been accumulating over recent years. To help further test this hypothesis, I propose that experienced acupuncturists focus on acupuncture sites that induce effects that can be quantified, such as an increase or decrease in heart rate or blood pressure, and identify specific neurons that are activated in the brain using noninvasive scanning techniques. If acupuncture-induced effects can be identified and quantified, researchers could then test whether ATP mimics the responses and if P2X3 receptor antagonists block the effects. Moreover, we suggest that researchers conduct experiments recording responses from sensory neurons in the skin and tongue in animal models and distinguish between low-threshold fibers involved in acupuncture and high-threshold fibers that mediate nociception, as well as recordings from the motor nerves in the brainstem responsible for autonomic functions.
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