FROM THE AAAS OFFICE OF PUBLISHING AND MEMBER SERVICES

CUSTOM PUBLISHING OFFICE SPONSORED SUPPLEMENT

The Art and Science of Traditional Medicine Part 3: The Global Impact of Traditional Medicine

It is appropriate and timely that Chinese scientist Youyou Tu was awarded half of the 2015 Nobel Prize in Physiology or Medicine in recognition of her pioneering work on the antimalarial artemisinin, extracted from Artemisia annua, an ancient herbal remedy used to treat fever. This third issue in the Art and Science of Traditional Medicine series features another time-honored herb, ginseng. Also discussed are the systems and network pharmacology of TCM, pharmacognosy and regulation of traditional medicine in Europe, and how these best practices can be applied globally, but particularly in Africa. Attraction garnered by the Nobel award hopefully will generate interest in traditional medicines from other parts of the world, including the Middle East, the Indian sub-continent, and the Americas.

- Read the special supplement (PDF, 4MB)

This special supplement brought to you by the Science/AAAS Custom Publishing Office.
The Art and Science of Traditional Medicine
Part 3: The Global Impact of Traditional Medicine
Join AAAS. Get instant access to Science. Support all of the sciences.

When you subscribe to Science, you become part of the American Association for the Advancement of Science (AAAS), a nonprofit community of more than 120,000 members worldwide who believe in the power of science to make the world a better place. AAAS is hard at work promoting science in government, schools, and in the public commons around the globe.

AAAS’s award-winning journal Science offers the top peer-reviewed research across multiple disciplines. With your subscription, you’ll get:

- 51 weeks of home delivery of Science.
- Instant online retrieval of every Science article ever published, dating back to 1880
- Full access to the Science mobile site and apps
- Career advice, webinars, blogs and fascinating features exclusively for AAAS members
- Members-only newsletters, and much more

With increasing public skepticism about science—and public funding for research more uncertain than ever—our work has never been more important. Join hands with us today!

Visit promo.aaas.org/joinaaas. Together we can make a difference.

It is appropriate and timely that Chinese scientist Youyou Tu was awarded half of the 2015 Nobel Prize in Physiology or Medicine in recognition of her pioneering work on the antimalarial artemisinin, extracted from Artemisia annua, an ancient herbal remedy used to treat fever. This third issue in the Art and Science of Traditional Medicine series features another time-honored herb, ginseng. Also discussed are the systems and network pharmacology of TCM, pharmacognosy and regulation of traditional medicine in Europe, and how these best practices can be applied globally, but particularly in Africa. Attention garnered by the Nobel award hopefully will generate interest in traditional medicines from other parts of the world, including the Middle East, the Indian sub-continent, and the Americas.

Editorial Team
Tai-Ping Fan, Ph.D. (Guest project editor)
University of Cambridge, UK
Josephine Briggs, M.D.
National Center for Complementary & Alternative Medicine, NIH, USA
Liang Liu, M.D., Ph.D.
Macau University of Science & Technology, Macau SAR, China
Aiping Lu, M.D., Ph.D.
Hong Kong Baptist University, Hong Kong SAR, China
Jan van der Greef, Ph.D.
University of Leiden and TNO, The Netherlands
Anlong Xu, Ph.D.
Beijing University of Chinese Medicine, China

Editor: Sean Sanders, Ph.D.
Assistant Editor: Tianna Hicklin, Ph.D.
Proofreader/Copyeditor: Bob French
Designer: Amy Hardcastle

Bill Moran, Global Director
Custom Publishing
bmoran@aaas.org
+1-202-326-6438

Rudiei Wu, Associate Director, Asia
Custom Publishing
ru@aaas.org
+86-186-0082-9345

The content contained in this special, sponsored section was commissioned, edited, and published by the Science/AAAS Custom Publishing Office. It was not peer-reviewed or assessed by the Editorial staff of the journal Science; however, all manuscripts have been critically evaluated by an international editorial team consisting of experts in traditional medicine research selected by the project editor. The intent of this section is to provide a means for authors from institutions around the world to showcase their state-of-the-art traditional medicine research through review/perspective-type articles that highlight recent progress in this burgeoning area. The editorial team and authors take full responsibility for the accuracy of the scientific content and the facts stated.

Articles
S54 Ginseng: A panacea linking East Asia and North America?
S57 Pharmacognosy in the United Kingdom: Past, present, and future
S59 Traditional herbal medicines in the European Union: Implementing standardization and regulation
S61 Traditional African medicine: From ancestral knowledge to a modern integrated future
S64 Traditional Chinese herbal medicine preparation: Invoking the butterfly effect
S66 Bridging the seen and the unseen: A systems pharmacology view of herbal medicine
S69 Hypothesis-driven screening of Chinese herbs for compounds that promote neuroprotection
S72 Mapping ancient remedies: Applying a network approach to traditional Chinese medicine
S74 Drug discovery in traditional Chinese medicine: From herbal fufang to combinatory drugs
S76 The polypharmacokinetcs of herbal medicines
S79 The bioavailability barrier and personalized traditional Chinese medicine
S82 Transdermal treatment with Chinese herbal medicine: Theory and clinical applications
S84 Acupuncture as a potential treatment for insomnia

Contents
S53
S84
Mapping ancient remedies: Applying a network approach to traditional Chinese medicine

Over the thousands of years that traditional medicine has been practiced, a wealth of clinical experience and a large number of herbal formulae have been accumulated to support the practice of traditional Chinese medicine (TCM). It is challenging to assess TCM therapies that are mechanistically unclear, in particular because many ingredients in an herbal formula may exert their effects on the body through low affinity binding to multiple different targets. This is at odds with the current “one target, one drug” approach most often associated with Western therapies, which is committed to the pursuit of drugs that bind to a single target with high affinity and specificity. At the same time that the single target-based, high-throughput screening assays that are the hallmark of reductionist research are being questioned due to high failure rates (1), network pharmacology is evolving as a systematic paradigm for drug discovery and development (2, 3). Network pharmacology adopts a network approach to represent and analyze the complex biological systems underlying diseases and drug actions. It thus aids in drug discovery, drug design, and drug development, sharing a holistic perspective that is characteristic of TCM (2–5). Today, the integration of TCM and network pharmacology (TCM-NP) provides an innovative research perspective for proponents of both reductionist and holistic medicine.

Treating a network as a therapeutic target

TCM-NP highlights a “network target, multicomponent therapeutics” approach (6). The core principle of a network target is to construct a biological network that can be used to decipher complex diseases. The network is then used as the therapeutic target, to which multicomponent remedies, such as herbal formulae, are applied (5, 6). Here, a network-based model incorporating an “effect-on” and “effect-off” switch can be proposed as a means to understand how herbal medicine might work. For the model to be “on,” multiple ingredients (or a single ingredient as a special case) in an herb or herbal formula should induce additive or synergistic effects on a set of interacting targets within a given network, such that the final outcome reaches a threshold to produce a measurable pharmacological result by network propagation and integration in both space (spatial extension) and time (temporal duration) (Figure 1A). In this way, multiple low-affinity actions can achieve a significant effect. By contrast, in the “off” scenario, herbal ingredients that exert opposite or antagonistic actions on a target network (Figure 1B), or only weakly affect decentralized targets in a network (Figure 1C), may not produce effects that reach the measurable threshold. This model can help to explain why the actual efficacy of herbal ingredients can be greater than the sum of the effects of individual ingredients (7, 8). For example, a recent study demonstrated that the classic Liu-Wei-Di-Huang formula can exert diverse therapeutic actions on metabolic and immune disorders by regulating a set of networked targets through different groups of bioactive ingredients (9).

According to the proposed effect-switch model, an optimal combination of herbal ingredients from herbal formulae can be considered worth pursuing if it satisfies the criteria for a network-based effect switch: turning on desirable effects and turning off undesirable effects (including side effects and toxicity).

TCM-NP methodologies

Through the development of computational and experimental methods, TCM-NP aims to map both disease genes (including gene products) and herb targets in a network, and provide information on bioactive compounds, synergistic combinations, mechanisms of action, and modern indications for herbal formulae by measuring the network association (e.g., modularity, connectivity, feedback, and dynamics) between disease genes and herb targets (Figure 2A). Representing complex biological systems as networks provides a foundation for the exchange of scientific and clinical data between modern and traditional forms of medicine. Now, ‘omics technologies, knowledge databases, and bioinformatics are providing more actionable data and increasingly sophisticated analysis tools, thus accelerating the understanding of biological networks, a situation that will undoubtedly speed TCM-NP progress. For example, by exploiting the available data pool, a computational method, drugCIPHER, has been developed to predict an herbal compound’s target profile by integrating chemical, target, and network information from current FDA-approved drugs (10). A sibling method, CIPHER, also performed well in predicting disease genes (11). In recent years, the use of systems biology and bioinformatics technologies in TCM has been growing rapidly, as has the generation of TCM-NP data and our understanding of multilayer networks. Through this work, associations have been elucidated between herbs, compounds, molecules, microbes, phenotypes, and diseases and/or TCM syndromes, generating fresh insights into holistic traditional medicine.

Not only does network pharmacology reflect the holistic properties of herbal medicine, but the rich trove of data on the use of TCM as herbal combinations can assist in refining the network. Considering that we still have much to learn regarding biological systems and drug action/interactions, the field of network pharmacology can undoubtedly benefit by combining top-down and bottom-up strategies. Since certain herbal formulae have been shown to be clinically effective, the inclusion of this empirical knowledge...
FIGURE 1. An effect-switch model based on the network target can be used to understand the actions of herbal ingredients and how their activity can be modulated.

- Node: a biological entity (e.g., molecule, pathway, biological process)
- Edge: a physical or functional interaction

FIGURE 2. (A) Schematic of traditional Chinese medicine-network pharmacology (TCM-NP) methodology. (B) A representation of a Cold/Hot Syndrome molecular network (12). (C) Part of the Realgar-Indigo naturalis components targeted network. PML, promyelocytic leukemia; RARA, retinoic acid receptor, alpha; RB, retinoblastoma; MYC, v-my c avian myelocytomatosis viral oncogene homolog; CDK2, cyclin-dependent kinase 2; SP11, a gene encoding transcription factor PU.1; CDKN1B, cyclin-dependent kinase inhibitor 1B; CEBPB, cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein, beta; CEBPE, CCAAT/enhancer binding protein, epsilon; RARB, retinoic acid receptor, beta; AQP9, aquaporin 9 (15).

Application of TCM-NP in traditional medicine

TCM-NP promises to help elucidate the complex molecular mechanisms underlying the actions of traditional therapies as well as explore new indications for their use. Herbal formulae are traditionally used to treat so-called TCM syndromes (Zheng). Most medicinal herbs can be categorized as cold, cool, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndromes are closely associated with a number of networked...
Drug discovery in traditional Chinese medicine: From herbal fufang to combinatorial drugs

Authors:
Bing He†, Cheng Lu†, Maolin Wang, Guang Zheng, Gao Chen, Miao Jiang, Xiaojuan He, Zhaoxiang Bian, Ge Zhang*, Aiping Lu*

Today, drug discovery is a critical issue in the pharmaceutical industry. Although global spending on drug discovery and development has risen sharply in the last decade, the approval rate for new drugs is declining. This situation is mainly due to drug failure caused by lack of efficacy and/or safety. One important reason for this is that common single-drug therapeutics are rarely able to fully address the complex nature of most human diseases. Producing combinatory drugs—combinations of multiple drugs against multiple disease targets—is an appropriate approach to address this issue.

Traditional Chinese medicine (TCM), a medical system based on natural products, has been widely used in East Asia for thousands of years to provide treatments and cures for disease. The long history and extensive documentation of TCM clinical practices have accumulated a considerable number of fufang (herbal compound prescriptions) that exhibit in vivo efficacy and safety, and provide a unique resource for combinatory drug discovery.

TCM: Synergy of multiple ingredients

The documented history of TCM dates back more than four thousand years to the times of Shennong (Yan Emperor), while mature TCM theory was established during the Song dynasty (960–1279 CE). TCM theory is based on a holistic, interconnected view of the world. The patient is considered as a system in which the normal balance of Yin/Yang has been disrupted. The first step in the TCM diagnosis process is to determine the particular Zheng (pattern or syndrome) afflicting the patient. In our studies, we analyzed the molecular networks of Han Zheng (cold pattern) and Re Zheng (heat pattern) in rheumatoid arthritis patients. The results indicated that Han Zheng is related to the Toll-like receptor signaling pathway, while Re Zheng impacts the calcium and peroxisome proliferator-activated receptor signaling pathways. Characteristic molecular signatures for each Zheng were also identified.

Based on the particular Zheng and characteristics of the patient, a suitable fufang was chosen for treatment. Fufang were formulated based on the TCM principle of Jun-Chen-Zuo-Shi, with Jun (literally “emperor”) being the principal ingredient that targets the primary causes and symptoms of...