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

Rudlei Wu, Associate Director, Asia
Custom Publishing
rwu@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 can be cited using the following format: [Author Name(s)], Science 350 (6259 Suppl), Sxx-Sxx (2015).
Ginseng: A panacea linking East Asia and North America?

According to ancient Chinese medical literature and Korean history, ginseng has been used since around 2000 BCE. It has been regarded as a very precious medicinal plant, on par with poppy, aloe, and garlic, the use of which goes back to the same period in other parts of the world. It is not surprising that the name Panax—meaning “all healing” in Greek—has been applied to this plant, because it has been used to treat various diseases from ancient times, and is also recognized, especially in Asian countries, as a health supplement that can increase energy and instill a sense of well-being. To date, fourteen species belonging to the Panax genus have been identified, and three species are widely circulated on the global market: Panax ginseng C.A. Meyer, cultivated mainly in Korea and northeastern China; Panax quinquefolius L. (American ginseng), grown mainly in the Canadian provinces of Ontario and British Columbia and the American state of Wisconsin; and Panax notoginseng Burkill, found in southern China (1).

History and use

P ginseng is likely to have originated in Manchuria (now the northeast part of China) and in the ancient Three Kingdoms of Korea (2). The first description of ginseng in the history of traditional Chinese medicine appeared in the pre-Han era (BCE 33–48), over 2,000 years ago (1). In 1713, the Royal Society published a letter from Father Jartoux, a Jesuit missionary in (BCE 33–48), over 2,000 years ago. In 1713, the Royal Society published a letter from Father Jartoux, a Jesuit missionary in.

Processing, chemistry, and metabolism

Most ginseng is today used as a health supplement, in the field for 4 to 6 years. Ginseng is classified into three types, depending on how it is processed after harvest: fresh ginseng (can be consumed in its fresh state), white ginseng (dried after peeling), and red ginseng, which requires special preparation (3). Ginsenosides are metabolized in the intestine after oral administration (8) into their metabolites, which may contribute the majority of bioactivities by regulating the transportation and metabolism of crucial substances in the human body. Metabolism mainly occurs in the gastrointestinal tract after oral administration (8), with sugar moieties being removed to generate the aglycones, 20(S)-protopanaxadiol (APPD), and 20(S)-protopanaxatriol (APPT), and the partially deglycosylated ginsenosides. Since most native ginsenosides are either poorly absorbed in the intestines or are quickly metabolized by deglycosylation, oxidation, and esterification in the intestine or the liver, they could be regarded as "prodrugs." Thus, understanding the pharmacokinetics and pharmacodynamics of native ginsenosides and their metabolites is critical for their clinical application.

Standardization

Currently, there are many ginseng products on the market and the quality control of these commodities is of paramount importance. Quality control of ginseng extracts and finished products is usually based on the determination of specific bioactive ginsenosides. Although the international standard ISO 17217-1:2014 specifies minimum requirements and test methods for ginseng seeds and seedlings (9), ginseng extract should also be standardized such that each batch contains an acceptable concentration range of active ingredients to guarantee quality and efficacy from product to product. Distinguishing between P ginseng and P. quinquefolius, which have similar chemical and physical properties but seemingly different pharmacological activities, is a challenge. Recently, all known ginsenosides were identified by metabolomics using high-performance chromatography/mass spectrometry analysis, and this large data set was statistically analyzed. In a targeted analysis, ginsenoside RF was confirmed as a chemical marker present in processed P ginseng, but not in processed P. quinquefolius (10).

Diverse pharmacological activities via multiple mechanisms

Given the structural similarity between ginsenosides and steroid hormones, we hypothesized that ginsenosides function as receptor agonists, partial agonists, or antagonists depending on the microenvironment. As shown in Figure 1, ginsenosides act by binding to steroid hormone receptors, such as androgen, estrogen, and glucocorticoid receptors (9), to modulate gene expression (11–14). The biological activities of these phytosteroids have been studied intensively with regard to their structure-activity relationships. Asian ginseng typically contains six types of ginsenosides: panaxadiols (Rb1, Rd, and Re) and panaxatriols (Rc, Rd, and Re) in contrast, American ginseng contains high levels of Rb1, Rd, and Re (6, 7).

Ginsenosides are extensively metabolized in the gastrointestinal tract after oral administration (8), with sugar moieties being removed to generate the aglycones, 20(S)-protopanaxadiol (APPD), and 20(S)-protopanaxatriol (APPT), and the partially deglycosylated ginsenosides. Since most native ginsenosides are either poorly absorbed in the intestines or are quickly metabolized by deglycosylation, oxidation, and esterification in the intestine or the liver, they could be regarded as "prodrugs." Thus, understanding the pharmacokinetics and pharmacodynamics of native ginsenosides and their metabolites is critical for their clinical application.

Materials that appear in this section were not reviewed or published a letter from Father Jartoux, a Jesuit missionary in.

FIGURE 2. Metabolism of ginseng. Ginsenosides can be converted into their metabolites that may contribute the majority of bioactivities by regulating the transportation and metabolism of crucial substances in the human body. Metabolism mainly occurs in the intestine and the liver by adenosine triphosphate (ATP)-binding cassette transporters (ABC transporters), cytochrome P450 enzymes (CYPs), and others.

Processing, chemistry, and metabolism

Most ginseng is today used as a health supplement, in the field for 4 to 6 years. Ginseng is classified into three types, depending on how it is processed after harvest: fresh ginseng (can be consumed in its fresh state), white ginseng (dried after peeling), and red ginseng, which requires special preparation (3). Ginsenosides are metabolized in the intestine after oral administration (8) into their metabolites, which may contribute the majority of bioactivities by regulating the transportation and metabolism of crucial substances in the human body. Metabolism mainly occurs in the gastrointestinal tract after oral administration (8), with sugar moieties being removed to generate the aglycones, 20(S)-protopanaxadiol (APPD), and 20(S)-protopanaxatriol (APPT), and the partially deglycosylated ginsenosides. Since most native ginsenosides are either poorly absorbed in the intestines or are quickly metabolized by deglycosylation, oxidation, and esterification in the intestine or the liver, they could be regarded as "prodrugs." Thus, understanding the pharmacokinetics and pharmacodynamics of native ginsenosides and their metabolites is critical for their clinical application.

Standardization

Currently, there are many ginseng products on the market and the quality control of these commodities is of paramount importance. Quality control of ginseng extracts and finished products is usually based on the determination of specific bioactive ginsenosides. Although the international standard ISO 17217-1:2014 specifi-
Pharmacognosy in the United Kingdom: Past, present, and future

For centuries, pharmacognosy has been instrumental in developing both conventional and herbal medicines in Europe. Isolated phytochemicals from natural sources have often been the basis for new pharmaceuticals and medical devices. Key challenges include appropriate uses and safety.

**Authors:** Melanie Jackson, R. Howes and Monique S.J. Simmonds

**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.**

allow HMP manufacturers time to comply with the directive’s requirement. The UK has yet to issue a list of herbal medicines that it requires to either have full marketing authorization or to be included in the herbal medicines registration (THR) scheme. The lack of UK HMPs that are intended for minor conditions and are suitable for self-diagnosis must meet the required standards for quality, safety and efficacy (e.g., Pharmacopoeia (EP) monographs and community herbal monographs that are evaluated by the Committee on Herbal Medicinal Products). THR HMPs are required to have been used medicinally for at least 30 years (prior to THR application), with at least 15 years of using the EU.

While these regulations have made advances in improving the safety and quality of registered HMPs, several issues still need to be addressed for the use of herbal medicines. Evidence for “traditional use” currently takes the place of hard scientific data from pharmacological tests and clinical trials. This highlights a major challenge for such medicines is quality control and standardization. In the European Union (EU), movements to harmonize the legislation surrounding traditional herbal medicines have aimed to improve their safety and quality. However, there are limitations and, in some respects, herbal medicines are still less well-regulated compared to conventional medicines. Although the use of herbal medicines in the UK is popular, detailed knowledge of their pharmacokinetic and pharmacodynamic properties is lacking, as are data on their pharmacological and anti-diabetic effects. While EU legislation now provides standards for the quality and safety of many herbal medicines, research to establish the evidence base and associated practices is proceeding at the same pace. Moreover, pharmacovigilance reporting practices could be improved to assist practitioners in gaining a better understanding of appropriate uses and safety.

**Herbal medicine use in the UK**

The use of herbal medicines in the UK is relatively popular (up to 35% of the population in the UK), there is a lack of uniformity of drug discovery is also an exciting prospect to obtain the full genome sequence of ginseng root as a precursor to manipulating the biosynthesis of specific ginsenosides and realizing their pharmacological potential. A high-throughput, multidisciplinary approach should be developed to bring new insights into the molecular actions of ginsenosides and how they interact with the first signaling networks that it impacts are interconnected. Finally, more robust clinical trials should be designed and implemented. Only good clinical outcomes can instill confidence in the general public with regard to products derived from this honor-won treated.

**References**

relate some conditions that do not normally require medical intervention, which include menopausal and cold symptoms (based on traditional use). In addition to traditional European herbal medicine, other preparations of herbal medicine from a variety of cultures are increasingly being used in the UK, including traditional Chinese medicine (TCM) and those from Ayurvedic, African, and South American traditions. Some of these are supplied under the herbalist exemption and not controlled by THR regulations.

In 1864, the first edition of the British Pharmacopoeia (BP) was introduced, containing the official monographs for medicines. This collection of standards comprised the required characteristics and tests for numerous herbal medicines, including potentially toxic plants such as aconite, Digitalis, and belladonna, as well as other naturally derived remedies, such as purified ox bile and leeches (6). Over the last 150 years, the development of conventional pharmaceutical drugs has increased considerably, while the use of herbal medicines in conventional “Western” medicine has declined. This trend is reflected in the current BP, with fewer monographs included than pharmaceutical drug monographs (7). However, with the introduction of THR and HMP quality standard requirements, the number of monographs for herbal medicines is now increasing once again in the BP and European Pharmacopoeia. Moreover, a higher number of Ayurvedic monographs are included, reflecting the incorporation of different practices into UK medicine, such as TCM (e.g., Salvia miltiorrhiza), and medicinal plants from Ayurvedic medicine (e.g., Withania somnifera (L. Dunal) root) (7).

Future directions

The introduction of the EU Directive (2004/24/EC) and THR scheme in 2004 have improved the safety and quality control issues of many HMPs; however, the impact of these regulations on safeguarding public health remains to be determined. To evaluate these issues, thorough monitoring of adverse responses to HMPs, either due to intrinsic (i.e., effects inherent in the plant itself) or extrinsic (i.e., effects resulting from quality control issues such as adulteration or substitution of the intended species) are essential. In general, there is an underreporting (via pharmacovigilance schemes) of adverse drug reactions (ADRs) by health care professionals. The large database of accumulated evidence collected over time has proven challenging because many products have a long history of different traditional uses in the different states. A new legislative approach was therefore developed in 2004 to harmonize the assessment of new and traditional herbal medicinal products (8). This new legislation worked to combine scientific evaluation and access to traditional herbal medicinal products (9).

Legal provisions for herbal medicines in the EU

The approval of medicinal products in the EU is linked to the assessment of quality, safety, and efficacy by a regulatory authority. Basic definitions for herbal substances, herbal preparations, herbal medicinal products, and traditional herbal medicinal products have been provided in Community Directive 2004/24/EC (10). The legislation also describes the different requirements for marketing authorization for new herbal medicinal products based on a full set of new efficacy and safety data; (2) marketing authorization for herbal medicinal products based on at least 15 years of such use in the EU. Additional safety data may be requested by a national regulatory authority when deemed necessary. This approach to approving traditional herbal medicines is only appropriate for products that are very safe. Therefore, this avenue is restricted to products that are very safe, whether a drug or herbal medicine. Five co-opts members represent special fields of expertise: pediatricians, general medicine, pharmacology, clinical pharmacist, and toxicologist. The core task of the HMPC is to standardize herbal medicinal products and traditional herbal medicine products in the EU by developing monographs and lists for herbal substances and their preparation. The establishment of monographs and other regulatory documents is a fully transparent process starting with a public “call for data.”

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.

Traditional herbal medicines in the European Union: Implementing standardization and regulation

A rapporteur is nominated by the HMPC and is responsible for the evaluation of information provided from the public. This data, the results of a systematic literature research in the public domain, and market overviews provided by the member states. A draft monograph is finally adopted by the HMPC, the entire set of documents, including an overview on the comments from the public consultation, is made available on the EMA’s website. Since 2013, the herbal medicine monographs have also been published, and any interested party, applicant, or citizen can access the work of the HMPC.

Developing standards for herbal medicines

With the introduction of THR and HMP standard requirements for the regulation of medicinal products in the EU market for at least 10 years, efficacy must be proven by at least one published successful clinical trial together with published data that meet the further requirements for efficacy and safety. For traditional herbal medicinal product registration, evidence for safety and efficacy are available in the long-standing use of a traditional medicinal product. The criteria for a product’s acceptance includes demonstrating its use in an herbal medicine for at least 30 years with at least 15 years of such use in the EU. Additional safety data may be requested by a national regulatory authority when deemed necessary. This approach to approving traditional herbal medicines is only appropriate for products that are very safe. Therefore, this avenue is restricted to products that are very safe, whether a drug or herbal medicine. Five co-opts members represent special fields of expertise: pediatricians, general medicine, pharmacology, clinical pharmacist, and toxicologist. The core task of the HMPC is to standardize herbal medicinal products and traditional herbal medicine products in the EU by developing monographs and lists for herbal substances and their preparation. The establishment of monographs and other regulatory documents is a fully transparent process starting with a public “call for data.”

Authors: Werner Knödlseder and Ioanna Chomos

Plant medicinal plants have been used in Europe since ancient times. The introduction of THR and HMP quality standard requirements has permitted under the herbalist exemption should also be prepared to control the development of conventional pharmaceutical drugs, which may not have been discovered via synthetic compound libraries, should not be ignored. Plants have an important role in the future of medicine and, whether they are used as herbal medicines or in drug discovery programs, it is essential that they are cultivated from sustainable sources and that their medicinal products are designed to meet the appropriate standards for quality and public health safety.

References

is an ongoing process. The legislation and practices over the last decade have demonstrated that it is possible to establish specific national and regulatory evaluation of traditional medi-
cines. By considering their individual characteristics and their meaningful uses, traditional medicines have been made available to citizens in a more regulated environment. HMPC mon-
ographs and monographs related to the pharmaceutical formas the basis of the regulation standards (8). Admittedly, there are still challenging issues in the EU surrounding specific topics such as assigning well-established uses and classifying certain products. The EU’s legislation is not specific regarding how to distinguish
between (herbal) medicinal products, food supplements, and medicinal products. On the global level, countries are currently discussing different legal frameworks and to develop harmonized 
solutions, which must take into account the different traditions for these monographs; the availability of marketed products with adequate quality, safety, and efficacy; and the means to provide reliable information to consumers and health care experts for the use of herbal medicinal products.

Globalization of traditional medicines

The ongoing globalization of traditional medicines has brought it a broad diversity of regulatory systems in differ-
ent countries and regions. For example, there is a lack of interna-
tionally accepted definitions and standard requirements for quality, safety, and efficacy. Different concepts have been established to consider the particular characteristics of tradi-
tional medicines. Thus, companies face immense obstacles when trying to gain access to different markets for their herbal medicines. An international dialogue about scientific and regu-
atory issues is necessary to develop reasonable and adequate solutions. Such a conversation should also address topics such as translating indications into the cultural context or therapeutic environment (e.g., an additional diet or a parallel physical treatment) or the material of a nonherbal origin, and classifying herbal products. 

The European legislation was primarily designed to deal with traditional herbal medicinal products with a well-known origin in Europe. However, the existence of therapeutic systems and products from traditional Chinese medicines (TCM) or Ayurvedic medicinal systems originating from non-European regions and issues related to non-European traditional medicines (6). A docu-
ment was released in the spring of 2014 that explained the European regulatory framework and the options and limitations for traditional products originating from non-European regions (7). In addition, the HMPC is working on creating monographs for the herbal substances used in Asian traditional medicines, such as TCM and Ayurvedic medicine.

Conclusions

Harnessing the process for evaluating and authorizing traditional herbal medicines in the 28 member states of the EU will continue to be a key challenge. However, the ongoing efforts to build a harmonized and robust regulatory framework will undoubtedly contribute to the development of safe and effective traditional medicine products.

Acknowledgments

The views expressed in this article are the views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or of any other national or international organization. The authors state no conflict of interest. The data and figures provided are based on data available in September 2014.

References

8. European Pharmacopoeia, 8th Ed. (European Directorate for the Quality of Medicines, Strasbourg, France).

Table 1

<table>
<thead>
<tr>
<th>Substance</th>
<th>TU</th>
<th>WEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harpagophytum radii</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypericum herb.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paeoniaceae</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Valerianaceae</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Passiflorae herb.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ginseng radix</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ginkgo folium</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 1. Selected examples of Committee on Herbal Medicinal Products (HMPC) monographs for herbal substances. TU, traditional use; WEU, well-established use.

Traditional African medicine: From ancestral knowledge to modern integrated future

TABLE 1. Discoveries based on African medicinal plants.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Plant species</th>
<th>Constituents and therapeutic</th>
<th>Anticancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Passiflorae herba</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Hypericum herb.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Valerianaceae</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Passiflorae herb.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Ginseng radix</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Ginkgo folium</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 1. Discoveries based on African medicinal plants.
African Cape flora (7) and African plants that contain effective antihyperglycemic agents (8). Parasitic infections are a major cause of death in Africa, and TAM herbs are widely used to treat them. However, unlike many diseases in developing countries, these diseases remain underresearched as they do not promise a good return on investment. Nevertheless, new lead antiprotozoal compounds have emerged from herbs used in TAM and are respected.

Conclusions

TAM currently supports the medical needs of millions of Africans. Based on experience gained from other traditional medicine systems, its modernization and integration with conventional medicine may offer a new and holistic view of health care, contributing to better universal health coverage in Africa, as advocated by the World Health Organization. This remains quite a challenge, as depicted in Figure 2, despite the rich source of new active compounds to be found in African flora. This flora is ripe for exploitation, as long as traditional medical uses and methods of administration are interpreted with caution, and the rights of local people and the environment are respected.

References

Traditional Chinese herbal medicine preparation: Invoking the butterfly effect

T he metaphor of the "butterfly effect"—in which the proverbial butterfly's flapping wings contribute to a tornado across the other side of the globe—is based in chaos theory and encapsulates the concept that a small change at one place in a complex system can have large effects elsewhere (1). Such an effect could be construed as contributing to the unique nature of Chinese herbal medicines (CHMs), whereby several specific variables that initially may have minor effects can have a significant downstream impact on the quality, potency, and therapeutic efficacy of the final product (2). Two of these factors are the pharmaceutical practices of paozhi processing of herbal drugs and the formation of hot-water decoctions from single or multiple herbal drugs (formulas) based on ancient tradition. These two factors act on the chemical composition and biological activity of the resulting tang decoction that is finally consumed (3, 4).

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.

T he art of paozhi

According to traditional Chinese medicine (TCM) theory, paozhi processing transforms raw herbal drugs into “decoction pieces,” thus instilling them with the desired properties for their medical application, including improved flavor and decreased toxicity or alteration of their therapeutic efficacy. Paozhi encompasses techniques such as cutting, crushing, calcining, or frying with or without liquid adjuvants such as vinegar or honey (3). A prominent example is the highly toxic crude root of Aconitum carmichaeli (Fuzi) which, after detoxification by paozhi processing, is incorporated into numerous TCM formulae used to treat joint pain and rheumatic disease (5, 6). Also, different kinds of decoction pieces can be derived from the same raw material by processing in different ways. For example, the Chinese pharmacopoeia describes four different decoction pieces that may be derived from raw rhizomes of the species Capsidi (7). These pieces, from the same source, have distinct activity and different sites of action within the human body (Figure 1). Despite its long tradition, it is only recently that the effects of paozhi have been systematically studied. The current understanding is that paozhi processing can alter the qualitative and quantitative chemical composition of herbal materials and can thus impact the final pharmacological or toxicological properties of the decoction pieces (3).

Chinese herbal decoctions

TCM formulae are typically composed of two or more processed herbal drugs that are jointly decocted. Traditional decoctions (tang) are prepared by repeated boiling of decoction pieces in water for 1 or more hours. The method may also require soaking in cold water before heating, or the introduction of single herbal components later in the process. The composition of the tang decoction can be changed by simple actions such as an initial soaking in cold water, which initiates innate enzymatic activity resulting in the alteration of chemical composition, as demonstrated by the formula of Fuzi Xiaxin Tang (FXT) (8). In addition, studies of the simple two-herb formula Danggui Buxue Tang (DBT), composed of Angelica membranaceous root and Angelica sinsenis root, demonstrate how multiple parameters like decoction time, initial temperature, paozhi processing, or the ratio of the two herbal ingredi- ents may impact the chemical composition and activity of the resulting tang decoction (Figure 2) (4, 9-11). In particular, in the examples of DBT and FXT, as well as other studies, the practice of joint decoction of herbal materials itself was found to affect the properties of the final product. With DBT, joint decoction showed a significantly improved cardioprotective effect on isolated rat hearts (12) and osteoblast differentiation (13) when compared to a mixture of individually prepared decoctions of Angelica and Astragalus roots. Significantly, the concentrations of some of DBT’s phytochemicals were found to be increased by 10% to 4,900% in the same studies due to coextraction. It was concluded that the observed synergy or interaction results from physicochemical interactions between the chemical constituents of both herbal ingredients. Such interactions have been observed in several studies with other formulae (see 8, 14-16).

Physicochemical interactions

Physicochemical interactions may affect the solubility of phytochemicals in simpler environments than a Chinese tang decoction. It has been observed that ubiquitous herbal constituents like sugars, amino acids, or small organic acids can function singly or in combination as natural deep eutectic solvents, which are able to dissolve phytochemicals and biological macromolecules up to 460,000-fold better than water (17). The solubility of phytochemicals in water itself can also be affected by the presence of other small organic molecules, as exemplified by hypericine from St. John’s wort, the solubility of which increases 120-fold in the presence of tannins (18). In contrast, a reduction in the solubility of different toxic alkaloids was observed in the presence of rhubarb root, a process believed to be linked to the formation of insoluble sediments (19). An exciting new finding is that traditional paozhi processing techniques may also augment a decoction’s therapeutic efficacy based on physicochemical interactions. Preparing DBT with Angelica sinsenis root that has been processed with rice wine according to the traditional protocol not only resulted in modified concentrations of Angelica phytochemicals, but also significantly increased the content of the observed Astragalus phytochemicals; the qualitative phytochemical changes were accompanied by an increase in estrogenic and osteo- genetic activity (19). Some of these physicochemical interactions have been recently modeled using ferulic acid, a constituent of Angelica sinsenis. The acid increased the concentrations of Astragalus phytochemicals and displayed a dose-dependent effect on the estrogenic and osteogenic activity of a decoction from Astragalus roots, but only when added before the decoc- tion process. Ferulic acid alone is completely inactive in these models (20). This example demonstrates that such complex physicochemical interactions may account for synergistic effects observed in TCM and thus contribute to other possible synergies that may occur due to pharmacokinetic or pharmacodynamic effects (14).

Conclusions

Modern scientific study of TCM is leading to an increased understanding of the complex interactions occurring between herbal components during the processing and extraction of these medicines. The examples given here indicate that the evolution of these ancient processes over millennia may actually have improved the therapeutic efficacy and safety of the resulting tang decoctions. The increased knowledge of these relationships provides support for the proper use of traditional procedures in the preparation of CHMs.

As discussed above, subtle changes in the complex produc- tion chain of CHMs can influence the composition and efficacy of tang decoctions through specific interactions between their constituents. The external environment can also be influenced by a single detail like the paozhi impact on one ingredient, thus invoking a butterfly effect.

Unlike the proverbial butterfly, however, the knowledge of modern scientific methodologies allows the source of the disruption to be traced by correlating the chemical profile (metabolome) of the herbal prepara- tion with its bioactivity. This approach can be regarded as a tool for the identification of chemical features that indi- rectly influence an herbal medicine’s therapeutic efficacy. Knowledge about the role of particular herbal ingredients or phytochemicals within a CHM is a prerequisite for the development of meaningful quality control assays, and thus a requirement for the international registration of TCM products. Without fully understanding the subtle contributing factors,

FIGURE 1. According to TCM theory, paozhi processing yields decoction pieces with variable therapeutic properties (3, 7).

FIGURE 2. Selection of factors affecting the chemical composition of a tang decoction. (Astragalus membranaceous, Angelica sinensis, and Fuzi were used in this example; FXT, Danggui Buxue Tang (DBT)). An exciting new finding is that traditional paozhi processing techniques may also augment a decoction’s therapeutic efficacy based on physicochemical interactions. Preparing DBT with Angelica sinsenis root that has been processed with rice wine according to the traditional protocol not only resulted in modified concentrations of Angelica phytochemicals, but also significantly increased the content of the observed Astragalus phytochemicals; the qualitative phytochemical changes were accompanied by an increase in estrogenic and osteogenic activity (19). Some of these physicochemical interactions have been recently modeled using ferulic acid, a constituent of Angelica sinsenis. The acid increased the concentrations of Astragalus phytochemicals and displayed a dose-dependent effect on the estrogenic and osteogenic activity of a decoction from Astragalus roots, but only when added before the decoction process. Ferulic acid alone is completely inactive in these models (20). This example demonstrates that such complex physicochemical interactions may account for synergistic effects observed in TCM and thus contribute to other possible synergies that may occur due to pharmacokinetic or pharmacodynamic effects (14).
modernization of TCM could negatively impact the unique properties and therapeutic activity of these medicines. Modern technologies and international collaborations will provide an excellent platform to fully explore and elucidate the complex interactions in herbal medicines in the future and thus aid the development of modernized CHMs that maintain the therapeu-

tic properties of their ancestors.

References
7. State Pharmacopeia Committee, Pharmacopia of the People’s Republic of China (China Medical Science and Technology Press, Beijing, 2010).

Bridging the seen and the unseen: A systems pharmacology view of herbal medicine

T he human body functions as a dynamic ecosystem consisting of innumerable interact-
ing systems, creating emerging properties and synergistic effects and extending beyond the physical barriers of the human organism, encomposing interactions with the environ-
ment. Understanding the human organism in its full complexity requires consideration of its different levels of organization (Figure 1, left) [1].

Medical questions regarding how a disease develops and how to prevent and intervene are amenable to a system-
oriented paradigm in which interventions include multtarget pharmacological strategies that can influence processes across systems (2, 3).

Although Western medicine has provided a very successful disease management system based on intervention at a single target, further improvements will rely heavily on new diagnostic tools to differentiate between disease subtypes and individual biological patterns.

Recognition of the uniqueness of each patient entails dif-
ferentiation at higher levels of organization, which requires a systems approach and expanded diagnostic insights (4). A better understanding of the biology and the influence of multi-
target approaches on regulatory pathways could provide new perspectives for system-level interventions (5). Understanding system resilience to a multitude of environmental stressors will shed light on personalized health and prevention options within a biosocialpsychosomatic context.

In medical plant research, isolates of single components are primarily used, which does not reveal the synergetic proper-
ties and full impact of the natural product. This was elegantly demonstrated in studies of Berberis fremontii (Fremont’s mahonia), which showed that the antimicrobial effects of the bioactive compound berberine were enhanced >100-fold when combined with an inactive component, 5'-methoxyhydroxy-carpin, isolated from the same plant (6). Reverse pharma-

cology, wherein a traditional preparation is taken as a starting point to identify its usefulness for studying the synergetic nature of herbal medicine (5), especially when combined with subtyping based on modern ‘omics technologies. Combining phenome-
onological-descriptions of a system from TCM with experimental data can provide a top-down guide that includes a wealth of information and may even facilitate novel insights.

DXXK as an example

An example of the application of a systems pharmacology perspective in multitarget pharmacology research can be illustrated by Diao Xin Xue Kang (DXXK), the first traditional Chinese herbal medical product registered in Europe and pro-
duced in China according to the European Traditional Herbal Medicinal Products legislation. DXXK is an extract of rhizomes from Dioscorea opposita Mankino, a plant from the Diosco-
reeae (yam) family. Over 300 papers have been published on the extract’s pharmacology, safety, and mechanisms of ac-

tion, and DXXK has been subjected to phase 1, 2, and 3 clinical trials with an estimated 16,000 patients enrolled (7). The main focus in these studies has been its use in the treatment of myocardial dysfunction, an indication included in the TCM description of the plant.

To obtain a systems view of the biochemical and functional effects of DXXK, pharmacological studies have examined various biochemical pathways, ranging from molecular to organ-level assessments. Analysis of DXXK’s phytopharmacological constituents revealed that its bioactivity could be attributed to a group of steroidal saponins, namely dioscin, diosgenin, prosapogenin A, and prosapogenin C (8–12). Saponins influence oxidative stress (12, 13), which is a major risk factor for vascular endothelial cell apoptosis, a process that is implicated strongly in the pathogenesis of cardiovascular disorders (14, 15). Steroidal saponins also exhibit vasodilator and protective effects on human vascular endothelial cells (16, 17). Clinical studies have shown that these saponins have protective effects against hyperlipidemia, including inhibition of platelet aggregation and reductions in cholesterol and triglyceride levels (18–20).

Studies at the cellular level have revealed that DXXK affects the renin-angiotensin-aldosterone system in a manner that is consistent with its antihypertensive properties (21). At the organ level, the phytoestrogen diosgenin, which is also found in DXXK, acts as a vasodilator and modulates vascular smooth muscle function by regulating cell viability, migration, and cal-
oblastic homeostasis (22–23). Recent studies have revealed that the significant anti-inflammatory effect may be attributed to its inhibitory effect on the NF-κB/COX2 pathway and relevant inflammatory mediators including prostaglandin 2, nitric oxide, tumor necrosis factor α, interleukin (IL) 1β and IL-6 (24).

In TCM, DXXK is used to treat a variety of conditions,

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.

FIGURE 1. An example of systems pharmacology in herbal medicine. Left, a systems view of human biology, with selected effects of Dioscorea opposita Mankino (DXXK). Right, the four traditional Chinese medicine (TCM) symptom clusters that are the main intervention targets for DXXK in China are illustrated for angina pectoris.
A dynamic systems view of the effects of DXXK on TCM. The TCM view of dynamics resonates with the classical philosopher Heraclitus. Major knowledge gaps remain in our understanding of how psychological and environmental factors influence health and in our discernment of higher system-level organization (40). A systems pharmacology approach that connects TCM symptom descriptions with biochemical pathway knowledge has the potential to bridge these gaps.

**References**

27. Y. H. Yuan, J. of Natural Products (India), 2, 123 (2009).
29. C. L. Xie et al., J. Ethnopharmacol. 139, 267 (2012).

**Acknowledgments**

The authors thank Charlotte Lokin for producing the artwork in Figure 1.

**Hypothesis-driven screening of Chinese herbs for compounds that promote neuroprotection**

P revention against the loss of neurons or the retardation of disease progression is the major challenge for the treatment of neurodegenerative disorders such as Alzheimer’s disease (AD) and Parkinson’s disease (PD). Currently established drug therapies treat mainly symptoms, leading to cognitive enhancement in AD or improved movement in PD. However, neuronal repair or prevention of further degeneration has not been convincingly demonstrated in humans (7). Common mechanisms of neuronal damage include, among others, oxidative stress, mitochondrial dysfunction, autophagy dysfunction, excitotoxicity, protein aggregation, and genetic defects (1-3). Practically all drugs for AD that are neuroprotective in both in vitro and in vivo preclinical models failed in large clinical trials. Due to this failure, the therapeutic potential of traditional Chinese medicine (TCM) has recently received increased attention. Multiple herbs have been tested in cell cultures or animal models. However, in a situation similar to that of synthetic drugs, the evidence of neuroprotective effects in clinical studies is still unsatisfactory, most likely due to the fact that the paradigm of treatment with a single chemical entity is not easily applicable to the complexity of TCM prescriptions (4).

**The screening modulation bottleneck**

In recent decades the search for novel plant-derived drugs has relied on hypothesis-free, high-throughput screening (HTS) using metabolomic, proteomic, and genomic methodologies (5). The professed goal has been to identify isolated single-target small molecular chemicals that are potent on compound libraries. However, even the largest plant compound libraries represent only a small fraction of the chemical space of neuroactive plants. Further, in vitro HTS hits often lack efficacy in vivo (7). One instructive example is Huperzine A, an alkaloid isolated from Huperzia serrata, which showed multiple beneficial effects in preclinical models, but failed in a phase 2 clinical study for AD (6). Research that primarily focuses on monocompounds isolated from plant extracts is limited: high pathophysiological effects will not be transferable from in vitro or animal models to clinical practice.

**Neuroprotection is a complex process involving multiple pathophysiological mechanisms; therefore it seems only rational to apply a multitargeted approach to a multifactorial treatment of AD.**

**Materials that appear in this section were not reviewed or assessed by Science/Editorial staff, but have been evaluated by an independent editorial team consisting of experts in traditional medicine research.**
Clinical trials

Evidence-based herbal medicine

Interdisciplinary consultation and discussion among traditional and Western medical physicians, pharmacologists, and natural scientists. Development of a working hypothesis.

Hypothesis-driven screening

The philosophy and practice of physiology and pathology vary significantly between TCM and Western medicine in that similar pathophysiological features are often described using different terminologies. Therefore, the application of traditional clinical knowledge to the Western system requires interdisciplinary and intercultural validation process to identify effective herbal candidates and develop the optimal experimental design.

Cell and animal models used to validate drug candidates from classical screening processes can mimic human pathophysiology to a limited extent. By contrast, the candidate herbs from a bedside-to-bench-to-bedside approach have already been tested successfully in humans. This latter, hypothesis-driven approach (as opposed to the hit-and-miss high-throughput approach) reduces the risk of running into cost-intensive dead ends due to inefficacy or unexpected side effects discovered during clinical trials. The process begins when candidate herbs are systematically reviewed in the scientific and medical literature for their in vitro, in vivo, and clinical actions, and discussed by an interdisciplinary panel of experts. A substan-tiated working hypothesis is then established by analyzing and integrating the traditional medicinal usage and current scientific data of individual herbs and their known bioactive compounds. Based on this knowledge, one can carefully select in vivo and in vitro models for the primary screening and efficacy assay steps. After initial screening, transcriptomic, proteomic and metabolomic analysis can be performed to further substantiate mode-of-action hypotheses (14).

Figure 1. WorkFlow of hypothesis-driven screening with examples from authors’ research. MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CC: Coptis chinensis. These hypothesis-based screenings should be followed by mechanistic studies to identify the mode of action of the drug as a prerequisite for the preparation of clinical trials. Figure 1 represents a hypothesis-driven screening process for the evidence-based validation of a TCM product. The aim is not to find just one single compound for a single pathway, but rather, to identify the combinations of herbs or substances, thus enabling the discovery of additive and synergistic effects, reflecting the current practice of TCM. Substantial optimization of this process is still required, but it provides a potentially valuable alternative to current, suboptimal classical screening methods.

Test case: Finding herbs for PD

Following careful consideration, the traditional formula Jia-Wei-Liu-Jun-Zi-Tang (Fu-Zhi-San and Ji-Xue-Tian) (13) for PD. Examples include modified (Huanglian-Jiedu-Tang usage and current scientific data of integrating the traditional medicinal components (15). Hypothesis-driven screening might at least in part be caused by transcriptional regulation of dopaminergic cells in the substantia nigra. Our data substantiate mode-of-action hypotheses (14). For PD is therefore essential and should result in valuable outcomes.

References

J. L. Cummings et al., Alzheimer Res. Ther. 6, 37 (2014).
M. S. Rafi et al., Neurology 76, 1389 (2011).
X. X. Song et al., Autophagy 10, 144 (2014).
J. H. Lu et al., Autophagy 8, 98 (2012).
D. Tang et al., Cell Biol. 190, 881 (2010).
F. Friedmann et al., J. Ethnopharmacol. 155, 607 (2014).

Acknowledgments

The authors would like to acknowledge Prof. Wolfgang Schwarz for the founding and establishment of a scientific Sino-German Network on TCM research. Thanks to Sarah Mirza for the illustration. This work was supported by the Hanse-Merkur Insurance Group and the Innovation Foundation Hamburg (Mr. & Mrs. Ko Chi-Ming Centre for Parkinson’s Disease Research Fund (For M. Li). Research Fund from the Hong Kong Government (For M. Li). Research Fund (HKBU 121009/14), the Innovation and Technology Fund (IT17072412), and the Health and Medical Research Council (10132091) from the Hong Kong Government (For M. Li).
Mapping ancient remedies: Applying a network approach to traditional Chinese medicine

Author: Shao Li*

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 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 (4–5). 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 (2, 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 one 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 (extensional) and time (temporal duration) (Figure 1A). In this way, multiple low-affinity actions can achieve a significant effect. By contrast, in the “off” scenario, the use of herbal ingredients that exert opposite or antagonistic actions on a target network (Figure 1B), or only weakly affect decreased 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 Lü-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 (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. Today, the integration of 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.

Application of TCM-NP in traditional medicine

TCM-NP promises to help elucidate the complex molecular mechanisms underlying the actions of traditional therapies and/or TCM syndromes, generating fresh insights into the field of network pharmacology. For example, a recent study demonstrated that the classic Lü-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 (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. Today, the integration of 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

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.

Ministry of Education Key Laboratory of Bioinformatics and Bioinformatics Division, School of Biomedical Sciences and Technology—Department of Automation, Tsinghua University, Beijing, China. Corresponding Author: shao@tsinghua.edu.cn

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; RAR, retinoic acid receptor, alpha; RB, retinoblastoma; MYC, v-myc avian myelocytomatosis viral oncogene homolog; CDK2, cyclin-dependent kinase 2; SNAP1, a gene encoding transcription factor PUL1; CDKN1B, cyclin-dependent kinase inhibitor 1B; CEBPB, cAMP-response element binding protein, epsilon; RARB, retinoic acid receptor, beta; AQP9, aquaporin 9 (15).
Drug discovery in traditional Chinese medicine: From herbal fufang to combinatory drugs

Authors: Bing H., Cheng L., Maolin W., Guang Z., Gao Ch., Xiao J., Xiang H., Zhihong B., Ge Z.

neuroendocrine-immune molecules, indicating a metabolism-immune imbalance. Meanwhile certain so-called cold herbs can target hub nodes in the Hot Syndrome molecular network, and vice versa, to restore the corresponding network balance (12) (Figure 2B). It was further found that active compounds in a cold herbal formula, Qing-Luo-Yin, could synergistically suppress the cytokine and vascular endothelial growth factor pathways in a hot network to treat disorders involving inflammation and angiogenesis (13).

Moreover, TCM-NP may provide a network-based interpretation for the Jun-Chen-Zuo-Shi (emperor-minister-associate-counselor) theory of combining herbal formulae. A disease molecular network could accordingly be divided into Jun-Chen-Zuo-Shi nodes and in the determination of the optimal combinatory therapy (14). For instance, in a Realgar-Indigo naturalis formula, tetrasaccharidetetraulose as a Jun can target the promyelocytic leukemia (PML) retinoid acid receptor alpha (RARα), a fusion protein involved in acute promyelocytic leukemia. This situation is mainly due to drug failure caused by lack of efficacy and/or safety. One important reason for this is the failure of single-drug therapeutics that are rarely able to fully address the complex nature of most human diseases (1). Producing combinatory drugs—combinations of multiple drugs against multiple disease targets—is an appropriate approach to address this issue (2).

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 primary (or syndrome) affecting the patient (3). In our studies, we analyzed the molecular networks of Han Zeng (cold pattern) and Ren Zeng (heat pattern) in hematologic malignancies. The patients indicated that Han Zeng is related to the Toll-like receptor signaling pathway, while Ren Zeng impacts the calcium and peroxisome proliferator-activated receptor signaling pathways (4). Characteristic molecular signatures for each Zeng were also identified (5).

Based on the particular Zeng combinatory drugs, the active ingredient in red sage root, acts as partially restoring those pathways that stop leukemia spreading. Indirubin and tanshinone work as "asistant" helping the primary Zeng and pathway (6).

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 primary (or syndrome) affecting the patient (3). In our studies, we analyzed the molecular networks of Han Zeng (cold pattern) and Ren Zeng (heat pattern) in hematologic malignancies. The patients indicated that Han Zeng is related to the Toll-like receptor signaling pathway, while Ren Zeng impacts the calcium and peroxisome proliferator-activated receptor signaling pathways (4). Characteristic molecular signatures for each Zeng were also identified (5).

Based on the particular Zeng combinatory drugs, the active ingredient in red sage root, acts as partially restoring those pathways that stop leukemia spreading. Indirubin and tanshinone work as "asistant" helping the primary Zeng and pathway (6).

Materials that appear in this section were not reviewed or assessed by Scientific Editorial staff, but have been evaluated by an international editorial team consisting of experts in traditional medicine research.

Acknowledgments

The authors thank the Taipeng Fan and his colleagues for their review of this work and their valuable comments and suggestions. This work is supported by the National Natural Science Foundation of China (8125025S and 91229201).

References

6. S. Li, B. Zhang, B. Zhang, BMC Syst. Biol. 5(Suppl. 1), S10 (2011).
14. S. Li et al., BMC Bioinformatics 15(Suppl. 11), S6 (2010).

FIGURE 1. Overview: From herbal fufang to combinatory drugs.

Evaluation & Optimization

Combimodal Drug

Molecular Network

Active Compounds

Jun

Chen

Zuo

Shi

The application of 'omics and in silico technologies

Recent advances in genomics, transcriptomics, proteomics, and metabolomics have enabled researchers to analyze a variety of molecules simultaneously. Several technologies have facilitated the study of the molecular pharmacology of fufang at multiple levels (8). However, the high cost of such studies has thus far limited the number of fufang studies using 'omics technologies. As a lower cost alternative, in silico methods using computational algorithms and cheminformatics can virtual screen large numbers of drug target interactions in order to construct pharmacology networks of fufang activity (9). In one example, the active compounds and mechanisms of actions of Gegen-Qin-Lian-Tang for the treatment of type 2 diabetes were determined by an in silico approach (10).

A network-based evaluation approach

In a primary advantage of fufang is the ability to simultaneously target multiple disease points within the complex network of a disease. We established an evaluation approach to evaluate the number of fufang and a human disease network to facilitate the translation of a fufang into a combinatory drug (Figure 1). This approach evaluated three effects of the drug: the major therapeutic effect (MTE), the associated therapeutic effect (ATE), and any ancillary effects (AE). MTE is the ability of the drug to target the affected disease network and cover normal function, similar to the role of Jun ingredients. ATE is the drug's ability to enhance the effects of the MTE and provide protection against negative side effects, as provided by Chen and Zuo. AEs refer to any additional assistive mechanisms, similar to the role of Shi ingredients.
The polypharmacokinetics of herbal medicines

Authors
Wei Jia1,2,3*, Tar-jeng Fan4, Xiaoning Wang5, Xiaoxing Xue6,7

The polypharmacokinetics (PK) of multicomponent herbal medicines (HMs) is a long-standing bottleneck for botanical drug and traditional medicine research. There are a number of reasons for this. One is the sheer number of plant-derived molecules that are typically present in HMs, which presents a substantial challenge to chemical and pharmacological evaluation. This is further complicated by the wide concentration range of the components. Another factor is the dynamic nature of chemical interactions between the plant-derived molecules and endogenous molecules. These interactions shape the PK of an HM and, consequently, the treatment outcome for individual patients. Monitoring the chemical components is made still more challenging by a lack of authenticated standards, by the complexity of both botanical and biological sample matrices, and by the need for cross-disciplinary expertise involving omics sciences, biochemistry, pharmacology, bioinformatics, and systems modeling. As a result, current research on the PK of HMs is still in its infancy. It is largely focused on in vivo characterization of one or two key HM components, the results of which may be difficult to link to the holistic treatment effects that result from drug-drug interactions (1).

A Poly-PK Approach

The traditional approach to understanding the pharmacology of a multicomponent agent is to study the effects of single active components on well-defined targets, such as specific enzymes or genes. However, it has proven impractical to integrate the results obtained using these reductive approaches to generate a systems understanding of concerted pharmacological interventions (2). The attempts to characterize the PK of poly-component herbal preparations have, however, demonstrated that the PK behavior of a given phytochemical is altered by coexisting constituents (3–5). The advent of comprehensive profiling technologies offers tremendous new opportunities for understanding multicomponent herbal medicines (HM). PK characteristics of tea polyphenols, for example, are coupled to multivariate statistical tools to generate multiparametric assessments. These allow us to create a concentration-time profile of a multicomponent HM, which we call a “Poly-PK,” as well as other health determinants associated with the intervention.

We recently proposed an integrated profiling approach. It uses tandem mass spectrometry (MS) to provide quantitative dynamic concentration profiles of bioavailable xenobiotic molecules that result from in vivo absorption, and hepatic and gut bacterial metabolism, of herbal agents (6, 7). This Poly-PK approach takes into account both the diversity of the HMs and the chemical composition and its complex effects on the metabolic pathways of the mammalian system. When HMs enter our body, there are significant PK profile changes over time, which fall into three categories as illustrated in Figure 1: (1) HM-derived compounds absorbed into the circulation, (2) new metabolites generated by the chemical transformation of HM compounds by hepatic enzymes and gut microbes, and (3) endogenous metabolites that are altered in response to the HM intervention. Certain essential PK variables, such as maximum plasma concentration (Cmax) and the time to reach Cmax (tmax), can be obtained directly from the measured concentration data, while parameters such as the area under the concentrati- on-time curve and the elimination half life (t1/2) can be generated using PK modeling software. Poly-PK in Action

We recently provided proof-of-concept for the above strategy (8). The study characterized the in vivo absorption and metabolism of two phytochemicals of Pu-erh, a fermented tea produced in Southwest China. Pu-erh, which contains a large array of polyphenolic constituents, has a range of pharmacological properties, including the ability to lower blood levels of total cholesterol, triglycerol and total cholesterol (9, 10). Urine samples were collected from volunteers at 0, 1, 3, 6, 12, and 24 hours after consumption of a two-week baseline phase, a two-week daily Pu-erh tea ingestion phase, and a two-week washout phase. The samples were provided with standard meals for six weeks.

We first isolated tea water extraction and urine samples collected at the different time points were analyzed using ultra-performance liquid chromatography-quadrupole time-of-flight (TOF) MS and gas chromatography-quadrupole time-of-flight MS. This analysis generated 1,075 detected features from Pu-erh tea and 6,028 from urine samples. Every metabolome database was subjected to uni- variate statistical analysis, yielding 2,652 variables that were significantly altered in the intervention (P < 0.05). Using multivariate similarity analyses to compare the altered variables to the Pu-erh tea metabolome or the predose urine metabolome, we identified 19 absorbed polyphenols, 26 metabolites of the absorbed polyphenols, and 118 endogenous metabolites altered due to tea intake. Subsequent analysis demonstrated, for the first time, a correlation among the dynamic concentration profiles of bioavailable tea components and the human metabolic response profile (Figure 2). This type of approach, in which scientists simultaneously monitor the PK behaviors of multiple phytochemicals in vivo, will lead to the direct elucidation of the pharmacological and molecular mechanisms underling HMs (8).

Perspectives

Over the past two decades HMs have been used increasingly as therapeutic interventions against a number of conditions (2, 11, 12). The pharmacology of HMs involves a “network” in which multiple components interact with multiple targets in vivo to exert a holistic treatment effect. The Poly-PK strategy described here uses an integrated phytochemical

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.
and metabolomic profiling strategy coupled with multivariate statistical analysis to simultaneously monitor multiple HM components for pharmacological evaluation. This approach reveals the interrelationships between xenobiotics and endobiotics as well as the metabolic impact using pharmacodynamic (PD) and pharmacokinetic (PK) strategy proposed here can simultaneously monitor the interrelationships between xenobiotics and endobiotics as well as the metabolic impact using pharmacodynamic (PD) and pharmacokinetic (PK) strategies. The Poly-PK technology will greatly accelerate the advent of the Poly-PK strategy can unravel the complex interactions between the multiple components in HMs and in mammalian metabolic systems. Furthermore, understanding the metabolic fate of a multicomponent drug is also a critical step toward developing the next generation of combinatorial chemical drugs, which will maximize the synergistic effects of certain drug components and help to prevent their undesirable metabolic side effects.

The advent of the Poly-PK technology will greatly accelerate the development and generation of patient-specific PK profiles, in which PK components by microbial enzymes. Thus, two sets of transformations in which phytochemical compounds are exposed to microorganisms in the gut. The symbiotic relationship between the human gut microbiota and HMs is also a critical step toward developing the next generation of combinatorial chemical drugs, which will maximize the synergistic effects of certain drug components and help to prevent their undesirable metabolic side effects. This metabotype affects our individual metabolism of, acquired from food consumption and/or drug treatments. As a metabotype, that is characterized by endogenous metabolites and a panel of exogenous metabolites as a metabotype, that is characterized by endogenous metabolites and a panel of exogenous metabolites.

The bioavailability barrier and personalized traditional Chinese medicine

The bioavailability barrier (BB) determines the concentration of drug being taken up by the human body, controlled by efflux transporters (ETs) and drug-metabolizing enzymes (DMEs), which are primarily regulated by nuclear receptors (NRs). Hence, polymorphisms of DMEs, ETs, and NRs can affect the pharmacokinetics of drugs, which ultimately influences the efficacy and/or toxicity of xenobiotic herbal formulas (CHFs). This paper presents the reconstruction of a BB-based network with new insights that help elucidate the therapeutic mechanisms of CHFs.

Western medicine focuses on molecular target-based therapy; however, there are limitations in transforming genotype-based or disease-oriented medicine into personalized and network-based clinical therapy (1). In contrast to Western medicine, CHFs achieve their effect through personalized modulation of a patient’s health status. However, CHFs have not been widely accepted because their treatment mechanism has not yet been well defined (2). Determining how the components of CHFs will behave in the body is a pivotal aspect in determining treatment mechanisms of TCMS. The BB has a key function in controlling absorption, biotransformation, and clearance of drugs in vivo (3). Therefore, a BB-based approach together with biological, biochemical, ‘omics, and computational technologies is a powerful driver for establishing today’s personalized TCM model.

The composition and characteristics of the BB network

The BBB can be defined as a physiological defense network, because it plays a central role in preventing xenobiotic interference in the human body (3). The network is composed mainly of ETs and DMEs that are distributed in the liver and intestine, responsible for drug distribution and elimination (Figure 1A). ETs and DMEs are regulated by nuclear receptors (NRs) that respond to pharmacological evaluation of endogenous ligands (4). DMEs include cytochrome P450 and conjugating enzymes such as uridine 5'-diphospho-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs). ETs refer to the transmembrane adenosine triphosphate (ATP)-binding cassette transporters.

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
8. G. Xu et al., J. Proteome Res. 11, 3449 (2012).
doxorubicin exhibits individual differences that maximize associated with reduced responses to the antiplatelet clopidogrel example, genetic variants of CYP2C19 and CYP2D6 are associated with the pattern or pathway coupling in the BB network. For 3 enzymes.

transporters; DMEs, drug-metabolizing UGTs, UDP-glucuronosyltransferases; MRP2, multidrug resistance protein 2; UGT, UDP-glucuronosyltransferases; SULTs, sulfotransferases; Ets, efflux transporters; DMEs, drug-metabolizing enzymes.

effect of the BB network during the bioavailability barrier (BB) network in the bloodstream. Multiple ETs and DMEs couple to create a complex network regulating disposition of drugs, particularly natural polyphenols abundant in CHFs (3).

Drug bioavailability depends not only on the activity of DMEs, but is also influenced by ETs (3). Therefore, variations in levels and activity of DMEs and ETs can markedly influence the pattern or pathway coupling in the BB network. For example, genetic variants of CYP2C17 and CYP2D6 are associated with reduced responses to the antiplatelet clopidogrel and the antiepstein tamoxifen, respectively. The antibacterial doxorubicin exhibits individual differences that maximize therapeutic efficacy and minimize side effects on the basis of genetic variants of the regulatory pregane X NR receptor (PXR), ETs (ABCB1, ABCD2, ABCCS, ABCB5, and RLIP76), and DMEs (CYP1A2, CYP3A4) (5). Therefore, the BB network is a critical determinant for implementing personalized medicine.

The BB network and harmonizing CHF efficacy and toxicity A personalized treatment paradigm is central to the holistic and integrated approach of TCM. CHFs provide a valuable way to study the underlying multitarget mechanisms of personalized TCM treatments. In TCM, the most important principle of formulating CHFs is the Jun-Chen-Zuo-Shi (emperor-minister-assistant-courier) principle, which holds that each herb has its own diverse function (6). The biological functions of a CHF are harmonized by BB filtration in the body to achieve ideal therapeutic efficacy with minimal toxicity (Figure 1B).

BB filtration can optimize absorption and biotransformation of active and toxic components in CHFs to create a “reharmonized” formulation. The BB mainly exhibits this harmonization effect by bidirectionally driving the bioavailability of active and/or toxic components. Specifically, the bioavailability of active components in CHFs can be enhanced by inhibiting the functions of DMEs and/or ETs in the BB, with consequent improvement in positive pharmacological effects. In contrast, the BB prevents the overabsorption of toxic compounds in CHF (Figure 1B). For example, Scutellaria baicalensis contains abundant amounts of diverse polyphenols that possess anticancer and antiaging effects (3). MRP2/BCRP and UGTs/SULTs block the bioavailability of polyphenols, resulting in a reduction in pharmacological effects (7). However, ETs can act as molecular switches that facilitate the bioavailability of polyphenols (8). Another example is Radix aconiti, an herb considered to be clinically unsafe. Toxic aconitum alkaloids like aconitine have low bioavailability because of the resistance produced by the BB that limits their toxicity (8). In particular, CYP3A4, coupled with P-gp, BCRP, and MRP2 in the BB, blocks the entry of specific toxins into the blood (9). Thus, the rational use of such toxic herbs could be controlled by limiting the final dosage to a relatively safe level, not beyond the “resistance” capacity of the BB network. Notably, NRs could interact with the active/toxic components to alter the functions of DMEs and ETs, and consequently affect BB filtration. For example, Radix glycyrrhiza, popularly used as a Sh herb in CHF, activates PXR (10).

In summary, the BB-based network manipulates disposition of the active/toxic components in CHF via dual-directional regulation to achieve the maximal efficacy and minimal side effects of CHF. As such, the BB-based network is able to act as an intelligent, adaptive system for self-defense, while genomic variations of ETs and DMEs result in an individualized BB, which ultimately personalizes TCM treatment by controlling the transport behaviors of CHF (Figure 2).

Perspectives

The BB network is a complex system, largely because of the interplay of its key elements of DMEs, ETs, and NRs. It differs markedly among different individuals due to their unique polymorphisms and genotypes (11). The BB can be treated as a personalized system that induces the same drug to produce a variety of actions and toxicities in different individuals. In the future, characterization of personalized BB-based networks will bring a new era in both TCM and conventional medicine.

The essence of TCM is an individualized therapeutic system using CHF (12), which is consistent with the principles of personalized BBS. By taking into account BB filtering, CHF can be optimized to produce harmonized, multicomponent, multitarget formulation to achieve optimal effectiveness and low toxicity. We therefore recommend that future CHF research should be implemented together with evidence-based, personalized, and advanced BB research methodologies. The precise molecular mechanisms underlying each personalized BB need to be elucidated. Applying omics-related technologies such as metabolomics, proteomics, genomics, and computational predictions to profile individual BB network differences caused by polymorphisms or BB interaction factors could help to assess the unique effects of CHFs in different individuals (Figure 2). In conclusion, the BB network works not only as an indispensable tool for clarifying the mechanisms underlying CHF, but can also be used for characterizing and optimizing personalized TCM therapies.

Syndrome-based CHF

Personalized and harmonized CHF

Manipulated by BB-based network

FIGURE 1. Composition of the BB network and its functions. (A) The molecular composition of the bioavailability barrier (BB) network in the liver and intestine. (B) The bidirectional activity of the BB network during harmonization, indicated by positive (left) and negative (right) symbols. (A) Liver to active (yellow circle) and toxic (red triangle) components of Chinese herbal formulas (CHFs); (P): p-glycoprotein; BCRP, breast cancer resistance protein; MRP2, multidrug resistance protein 2; UGTs, UDP-glucuronosyltransferases; SULTs, sulfotransferases; Ets, efflux transporters; DMEs, drug-metabolizing enzymes.

FIGURE 2. Personalized CHF therapy manipulated by the BB network.
Transdermal treatment with Chinese herbal medicine: Theory and clinical applications

Authors: Qing Wu1*, Dan Jiang2*

Transdermal treatment with Chinese herbal medicine (CHM) has a long history of clinical application and theory in China. The earliest record of its use can be found in the ancient classic, Huang Di Nei Jing (227 BCE). The practice of transdermal treatment continued to evolve, reaching its highest popularity during the Qing dynasty, as elaborated in the book Li Yue Pian Wen (Wu Shi-Ji, 1864). It was emphasized in this book that the principles of transdermal treatment for both external and internal application of CHM were the same (1). This statement was the forerunner of the theory of transdermal treatment for CHM, and modern transdermal drug delivery systems (TDDS) use the same concept, although the precise delivery method is different.

The process of applying transdermal herbal medicine is not as simple as putting it directly on the skin. It should be applied specifically at the relevant acupuncture points (acupoints). According to Wu Shi-Ji, “If a disease is due to an external factor, you should apply herbs to release it on location; however, when the disease has spread into the body, you should apply herbs to the relevant acupuncture points to treat it.” Thus, transdermal treatments exert their therapeutic actions not only by absorption of active ingredients from herbs, but also the stimulation of acupoints. This concept is one of the distinctive differences between Chinese transdermal herbal treatments and modern TDDS (Figure 1).

Acupoints for treatment

The theory of acupoints and meridians is an important part of traditional Chinese medicine (TCM). The meridian system (or channel network) is believed in TCM theory to be the path along which the qi and life energy flows. According to this theory, qi and blood fill the meridian system, the channels, and are transported throughout the body via these meridians, feeding the organs. Modern biologists have discovered that there are convergent points of the organs’ qi and blood along meridians (2). Placing an herbal patch directly on the acupuncture point therefore helps to maximize its therapeutic effects, with the aggregate effect being a combination of herbal action plus the acupoint response acting synergistically. The curative effect of an herbal patch placed on an acupoint is commonly regarded as superior to that of a patch placed on a non-acupoint (3). Reports on comparing responses of acupoints with non-acupoints indicate noticeable differences (4, 5).

As the use of transdermal medicine is being more widely accepted, there has been a growing interest in the research and development of transdermal herbal patches. There are many factors that can influence the effectiveness of transdermal herbal treatment. These include the nature of the herbal ingredients, the method of preparation and application of the patch, and the site of application. The use of transdermal herbal patches can be effective for treating various diseases, including chronic conditions such as diabetes, high blood pressure, and osteoarthritis. It is important to note that while transdermal herbal patches can be beneficial, they should not be used as a substitute for medical treatment and should be used under the guidance of a healthcare professional.

Transdermal CHM plaster on the acupoints of meridians

**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.**

FIGURE 1. A variety of systemic diseases can be treated by application of transdermal Chinese herbal medicine (CHM) patches on meridian acupoints. A combination of acupuncture stimulation and the active ingredient in the CHM elicits a healing response.

**TABLE 1. Diseases and the corresponding acupoints for treatment (6–18)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acupoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma in children</td>
<td>FS (BL13); XS (BL15); GS (BL17)</td>
</tr>
<tr>
<td>COPD (SP)</td>
<td>FS (BL13); XS (BL15); GS (BL17)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>DZ (DU14); FS (BL13); PS (BL20); SS (BL23)</td>
</tr>
<tr>
<td>Pneumonia in children</td>
<td>FS (BL13); GS (BL15); JL (EX-HN15); GH (BL43); ASh</td>
</tr>
<tr>
<td>Respiratory infection in children</td>
<td>FS (BL13); DC (EX-B01); GH (BL43)</td>
</tr>
<tr>
<td>Brady arrhythmia</td>
<td>NG (PC6); XS (BL15)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>SQ (RN18); NG (PC6); YQ (YQ11)</td>
</tr>
<tr>
<td>Dysmenorrhea caused by endometriosis</td>
<td>ZJ (RN2); YQ (RN4); ZG (RN19)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>ZJ (RN2); YQ (RN4); GH (BL24)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>SJX (ST37), TS (ST52), ZSL (ST36), MM (DU4); YQ (RN4)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>SQ (RN8)</td>
</tr>
<tr>
<td>Simple obesity</td>
<td>ZW (RN12); YQ (BL24); GH (RN6); TS (ST52); SD (ST28); DH (SP19)</td>
</tr>
</tbody>
</table>

*Corresponding Author: qwu@vip.sina.com

23. K. Xiong et al., Chinese Journal of Experimental Traditional Medical Formulae 17, 23 (2011).

Acknowledgments

Thanks to Dr. Yi Lan, Bochen Zhao, and Wenzong Wang for their contributions to this article.
Acupuncture as a potential treatment for insomnia

In insomnia—difficulty falling and staying asleep—is a frequent complaint, with about one-third of the general population worldwide presenting with symptoms (1). Although the neural mechanisms underlying chronic insomnia are poorly understood, substantial evidence has shown that it is a disorder of physiological hyperarousal involving both the central nervous system (CNS) and autonomic nervous system (ANS) (2, 3).

Acupuncture has been widely used for the treatment of insomnia in Asia. According to the theory of traditional Chinese medicine (TCM), the mind (or shen) is situated in the heart region; insomnia is considered to be a disorder of the heart, so acupuncture points on the heart and pericardium are often used in treatment (4). Recently, several systematic reviews have hinted that acupuncture may be an effective treatment for insomnia. However, deficits in study design and quality have meant that definitive conclusions could not be drawn (5).

Other studies have shown that acupuncture may be able to increase β-endorphin production and μ-receptor activity (6), both of which are associated with enhanced non-rapid eye movement (NREM) sleep. Acupuncture also appears to regulate various neurotransmitters and hormones involved in sleep regulation, including β-endorphin, serotonin, acetylcholine, nitric oxide, melatonin, dopamine, gamma-aminobutyric acid (GABA), and neuropeptide Y (NPY) (7-9). Further reports have suggested that acupuncture may be related to a significant increase in secretion of melatonin, a hormone involved in regulation of day-night cycles, in insomnia patients (10). In both animal and human clinical studies, evidence indicates that acupuncture inhibits sympathetic nervous system activity and regulates the hypothalamic-pituitary-adrenal (HPA) axis (11), which may contribute to its mechanism of counteracting insomnia. This review summarizes the evidence of the possible mechanisms through which acupuncture may modulate insomnia by acting on hyperarousal of the ANS and regulation of HPA activation.

Possible mechanism of action

Inhibition of sympathetic activity

Acupuncture is believed to modulate sympathetic and parasympathetic activity, as evidenced by its effects on the regulation of cardiovascular function, including lowering blood pressure in patients with hypertension (12) and decreasing the heart rate as well as skin blood flow in healthy subjects (13). An experimental study in healthy subjects found that needleling on the Sishencong (EX-HN1) acupuncture, commonly used in the treatment of insomnia, decreases the low-frequency component of the heart rate variability spectrum, which is an indicator of the balance between sympathetic and parasympathetic activities, suggesting that acupuncture enhances cardiac vagal tone and suppresses sympathetic activity (14). Acupuncture may alleviate insomnia by significantly decreasing heart rate variability in poststroke patients (15), suggesting that improvement in subjective symptoms results from reducing sympathetic nervous system activity.

The pathophysiological pathway by which acupuncture may facilitate the sleep–wake transition through inhibition of sympathetic activity is not fully understood. Nevertheless, the effects of acupuncture on the excitatory cardiovascular reflexes may provide some hints. A long-loop pathway involving the arcuate nucleus (ARC) and ventrolateral parietal gray (vPAG), that modulates cardiovascular sympathetic excitatory bulbospinal neurons in the rostral ventrolateral medulla (RVLM) has been suggested as a possible explanation for an acupuncture mechanism. Electroacupuncture stimulation at acupoints Neiguan (PC6), a commonly used acupoint for insomnia, and Jianzhai (PC5), activates ARC neurons in the ventral hypothalamic RVLM, which, in turn, provides excitatory projections to the midbrain vPAG. Activation of neurons in the vPAG stimulates cells in the raphe nuclei, which inhibit the activity of cardiovascular premotor sympathetic excitatory neurons in the RVLM via endorphin, enkephalin, GABA, and serotonin (16). Since insomnia apparently shows elevated sympathetic activity associated with ANS hyperarousal, the effects of acupuncture on sleep may involve this long-loop pathway.

Regulation of HPA axis

Acupuncture may improve sleep by regulating the HPA axis. Studies have shown that acupuncture reduces adrenocorticotropin hormone (ACTH), also known as corticotropin, and corticosterone/cortisol levels in animal models of stress (17) and in human subjects (18). However, precisely where in the HPA pathway acupuncture exerts its effects is not clear. More recently, an experimental study found that electroacupuncture at Zusanli (ST36) prevents chronic stress-induced activation of the HPA axis, as well as elevated sympathetic nervous system-related adrenal NPY (19). The study found that corticotropin-releasing hormone (CRH) levels were significantly reduced in acupuncture-treated animals. Findings suggest that acupuncture inhibits the HPA axis activity at or above the level of paraventricular nucleus (PVN) CRH, thereby preventing stress-induced elevations in circulating ACTH and corticosterone levels. Another study demonstrated that electroacupuncture at Zusanli (ST36) prevents an increase in stress-induced adrenal NPY messenger RNA (mRNA) expression (20). The increased adrenal NPY expression may result from central signals from either CRH or NPY, which are elevated in the PVN of stressed rats (Figure 1), suggesting that electroacupuncture inhibits the sympathetic NPY pathway by activating in the PVN.

Conclusions

Emerging evidence suggests that acupuncture treatment counters insomnia by reducing hyperarousal of ANS and through regulation of HPA activation. However, the mechanisms underlying acupuncture’s actions in insomnia are still far from clear. Further research measuring anatomical location and physiological function are warranted to better understand the mechanisms of acupuncture in the management of insomnia.

References


---

1School of Chinese Medicine, the University of Hong Kong, Hong Kong, China
2Department of Psychiatry, the University of Hong Kong, Hong Kong, China
3Susan Samueli Center for Integrative Medicine, School of Medicine, University of California, Irvine, CA, USA
4Department of Psychiatry, the University of Hong Kong, Hong Kong, China
5Corresponding Author: lxlao1@hku.hk

---

FIGURE 1. The possible pathway describing the effect of acupuncture on hypothalamic-pituitary-adrenal (HPA) activation. The stimulation of Zusanli (ST36) inhibits the HPA axis at or above the level of the paraventricular nucleus (PVN) through corticotropin-releasing hormone (CRH), thereby preventing the stress-induced elevations in circulating adrenocorticotropin hormone (ACTH) and corticosterone/cortisol levels. It may also prevent increases in stress-induced adrenal neuropeptide Y (NPY) messenger RNA (mRNA) expression.

---

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.
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 can be cited using the following format: [Author Name(s)], Science 350 (6259 Suppl), Sxx-Sxx (2015).