The Art and Science of Traditional Medicine
Part 3: The Global Impact of Traditional Medicine
It is appropriate and timely that Chinese scientist Youyou Tu was awarded half of the 2015 Nobel Prize in Physiology or Medicine in recognition of her pioneering work on the antimalarial artemisinin, extracted from Artemisia annua, an ancient herbal remedy used to treat fever. This third issue in the Art and Science of Traditional Medicine series features another time-honored herb, ginseng. Also discussed are the systems and network pharmacology of TCM, pharmacognosy and regulation of traditional medicine in Europe, and how these best practices can be applied globally, but particularly in Africa. 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
Lieng 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

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.
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 it 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 province of Ontario and British Columbia and the American state of Wisconsin; and Panax notoginseng Burkf, found in southern China (1).

History and use

P. ginseng is likely to have originated in Manchuria (now in northeastern part of China) and in the ancient Three Kingdoms period 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. In 1711, the Royal Society published a letter from Father Jarrout, a Jesuit mission in China, containing a description of ginseng’s botany, habitat, and medicinal uses (3). P. quinquefolius was discovered by American settlers in the mid-1700s in New England. This plant had long been used by the Native Americans, who valued the root for its curative powers and life-enhancing capabilities. Ginseng has purported use for the treatment of cancer, diabetes, and cardiovascular dysfunctions, as well as for cognitive enhancement with an apparently low rate of adverse effects. In combination with other materia medica, P. ginseng and P. notoginseng have been used in complex Chinese formulations for treating anica pectoris (4, 5).

Processing, chemistry, and metabolism

Most ginseng is today cultivated 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 treatments (6). Ginseng can be a regulator of microRNAs (miRNAs) that modulate angiogenesis, apoptosis, cell proliferation, and differentiation. Processing methods for ginseng seeds and finished products is usually specified by the international standard ISO 17217-1:2014 specifications. 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. Distinctive 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

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, to modulate gene expression (11–14). We have previously reported that the dominance of Rg1 leads to angiogenesis, whereas Rb1 exerts an opposing effect (15) through activation of glucocorticoid (16) and estrogen (17) receptors. In addition to their classic genomic effects, ginsenosides can also function through transcription-independent, nongenomic activation of
Pharmacognosy in the United Kingdom: Past, present, and future

E
or centuries, pharmacognosy has been instrumental in developing both conventional and herbal medicines in Europe. Isolated phytochemicals from nature have been the source for new pharmacoeuticals and provided template chemical structures for drug discovery. In recent years, natural products 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 United Kingdom is popular, detailed knowledge of their pharmacological and clinical effects is often lacking, as are data on their pharmacokinetic and pharmacodynamic properties. While EU legislation now provides standards for the quality and safety of many herbal medicines, research to establish the ‘nature and quality’ of medicines is progressing 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 uses in the UK

Although herbal medicines and HMPs are the subject of regulatory control in the UK, herbal medicines are relatively popular (used by 35% of the population in the UK). There is a general lack of information about their safety. The information 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 the full potential of ginsenosides. For drug discovery, a high-throughput, multidisciplinary approach should be developed to bring new insights into the molecular actions of ginsenosides and how plant products interact with proteins. Finally, new robust clinical trials should be designed and implemented. Only good clinical outcomes can instill the confidence of the public with regard to products derived from this honor-treatment.

References
2. “A History of Ginseng,” in to products derived from this time-honored treatment. can instill faith in patients and the general public with regard to developing novel techniques for enriching bioactive materials that appear in this section were not reviewed or approved by the authors of this work.
40. K. J. Kim et al., DNA Int. 41, 247 (2004).

Acknowledgments
This work was supported by grants from the National Research Foundation of Korea to Y.S.K. (MCR2009-01346) and the Health and Medical Research Fund to A.S.T.W. (M111211911). 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.
relieve some conditions that do not normally require medical intervention, which include menopausal and cold symptoms (based on traditional use). In addition to traditional European medicines, including potentially toxic plants such as aconite, Digitalis, and belladonna, as well as other naturally derived remedies, such as purified ox bile and bileacids (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 herbal 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 species monographs are included, reflecting the incorporation of different practices into UK medicine, such as TCM (e.g., Salvia miltiorrhiza) and 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 the UK has enabled progress on 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 (HCPs) (8) as well as much variation between HCPs in the reporting of ADRs (9). The importance of this type of reporting is exemplified by St. John’s wort (Hypericum perforatum L.). In this case, ADR reporting through pharmacovigilance schemes led to the identification of several clinically important drug interactions and potential safety issues (10). To promote herbal medicines’ safety use, we recommend that HCPs improve their knowledge of such remedies and encourage them to report any ADRs and herb-drug interactions. Moreover, the preparation and supply of unlethed herbal medicines as permitted under the herbalist exemption should also be further scrutinized to improve the regulation of this practice and address potential quality and safety issues, while maintaining access to trained herbal medicine practitioners, which many patients value. Finally, the issue of efficacy needs to be addressed for more robustly for many herbal medicines. More research is needed to identify the active constituent(s) and their modes of action, and to determine their polyvalent nature, while understanding more about their pharmacokinetic and pharmacodynamic properties (similar to the process for conventional pharmaceuticals). It is essential to authenticate and standardize HMPs in order to define their safety, quality, and efficacy standards and to enable clinical trial data to be based on phytochemically characterized HMPs containing standardized levels of active constituents. Meanwhile, the fact that plants are incredible synthetic chemists and have already provided numerous lead chemical structures (e.g., paclitaxel and docetaxel) for 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


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 data, the results of a systematic literature research in the public domain, and market overviews provided by the member states. A draft monograph is published for a period of three years. The final monograph or a revision of both documents, which are published for comments together with a list of references. When a 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 monographs have been published online, and any interested party, applicant, or citizen can access the work of the HMPC (5).

Developing standards for herbal medicines

While herbal medicines are a unique and rich resource in the EU, all of the available data is scientifically evaluated to create a unified view of the safety and efficacy of herbal substances and their preparations. Monographs may include two varia-
tions: well-established use and/or traditional use. Well-established use is based on approval of a product for medicinal use in the EU market for at least 10 years. Efficacy must be proven by at least one published successful clinical trial or, if not possible, based on published data that meet the further requirements for efficacy and safety. For traditional herbal medicinal product registration, evidence for safety and efficacy is restricted to products that are administered orally, externally, or by inhalation and that treat minor complaints. Aliments that require a medical prescription, diagnosis, or supervision by a medical professional or are sold as products for which herbal medicines must comply with provisions for over-the-counter medicines.

The application of monograph standards

Within the last 10 years, the HMPC has released approxi-
mately 130 monographs (for examples, see Table 1). 12 list en-
tries, 13 public statements, and about 40 guidance documents (5). Only 25 monographs have been approved based on well-established information provided from the public data when a monograph could not be drafted for reasons such as
TABLE 1. Selected examples of Committee on Herbal Medicinal Products (HMPC) monographs for herbal substances. TU, traditional use; WEU, well-established use.

<table>
<thead>
<tr>
<th>Substance</th>
<th>TU/WEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harpagophyllum radix</td>
<td>Y</td>
</tr>
<tr>
<td>Hypericum herbacea</td>
<td>Y</td>
</tr>
<tr>
<td>Pelargonium graveolens</td>
<td>Y</td>
</tr>
<tr>
<td>Valeriana officinalis</td>
<td>Y</td>
</tr>
<tr>
<td>Passiflora incarnata</td>
<td>Y</td>
</tr>
<tr>
<td>Ginseng radix</td>
<td>Y</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Y</td>
</tr>
</tbody>
</table>

is an ongoing process. The legislation and practices over the last decade have demonstrated that it is possible to standardize and regulate evaluation of traditional medicines. By considering their individual characteristics and long-standing uses, traditional medicines have been made available to citizens in a more regulated environment. HMPC monographs and monographs related to herbal medicinal products in the EU serve as the basis of the regulatory 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, medical devices, and medicinal products (9). On the global front, there is a lack of any harmonized regulatory environment. HMPC monographs related to herbal medicinal products are essential for ensuring 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 with it a broad diversity of regulatory systems in different countries and regions. For example, there is a lack of internationally accepted definitions and standard requirements for quality, safety, and efficacy. Different concepts have been established to consider the characteristic properties of traditional medicines. Thus, companies face immense obstacles when trying to gain access to different markets for their herbal medicinal products. An international dialogue about scientific and regulatory issues is necessary to develop reasonable and adequate requirements. Such a conversation should also address topics such as translating indications into a cultural context or therapeutic environment (e.g., an additional diet or a parallel therapeutic environment) and providing reliable information to consumers and health care experts for the use of herbal medicinal 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 medicine (TCM) or Ayurvedic medicine (AM) in an European regulatory framework poses challenges. Discussions about the classification of traditional medicines and treatments relative to non-European traditional medicines (6) have resulted in the EU and traditional herbal Medicinal Product (TAM) committee in the European Union being tasked with assessing the risk profile of a given product and setting the manufacturing and quality assurance standards for such products. By considering their individual characteristics and long-standing uses, traditional medicines have been made available to citizens in a more regulated environment. HMPC monographs and monographs related to herbal medicinal products in the EU serve as the basis of the regulatory 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, medical devices, and medicinal products (9). On the global front, there is a lack of any harmonized regulatory environment. HMPC monographs related to herbal medicinal products are essential for ensuring reliable information to consumers and health care experts for the use of herbal medicinal 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 medicine (TCM) or Ayurvedic medicine (AM) in an European regulatory framework poses challenges. Discussions about the classification of traditional medicines and treatments relative to non-European traditional medicines (6) have resulted in the EU and traditional medicinal products committee in the European Union being tasked with assessing the risk profile of a given product and setting the manufacturing and quality assurance standards for such products. By considering their individual characteristics and long-standing uses, traditional medicines have been made available to citizens in a more regulated environment. HMPC monographs and monographs related to herbal medicinal products in the EU serve as the basis of the regulatory 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, medical devices, and medicinal products (9). On the global front, there is a lack of any harmonized regulatory environment. HMPC monographs related to herbal medicinal products are essential for ensuring reliable information to consumers and health care experts for the use of herbal medicinal products.

TABLE 1. Discoveries based on African medicinal plants.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Plant species</th>
<th>Constituents and therapeutic activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer</td>
<td>Catharanthus roseus (L.) G. Don (Apocynaceae)</td>
<td>Vincastrin, vinblastine, and others, to treat leukemias, Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Comfruit</td>
<td>Eclipta alba (Kunth) (Compositae)</td>
<td>Comfruitin, possible anti-angiogenic; induces apoptosis in proliferating tumor cells</td>
</tr>
<tr>
<td>Cholinesterase inhibitor</td>
<td>Physostigma venusalis Balf. (Fabaceae)</td>
<td>Physostigmine, derivatives, to treat myasthenia gravis (to neostigmine) and Alzheimer’s disease (rivastigmine)</td>
</tr>
<tr>
<td>Antihypertensive antipsychoptic</td>
<td>Rauvolfia vomitoria Abel (Apocynaceae)</td>
<td>Reserpine*, occasionally used clinically to treat hypertension and experimentally to deplete catecholamines</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>Sothelhornia fuliginea (F. R. Balf.) (Fabaceae)</td>
<td>Antiretroviral effects under investigation</td>
</tr>
<tr>
<td>Cardiotoxic</td>
<td>Strophantus gratus (Wall. &amp; Hogg) (Balf.)</td>
<td>Ouabain (formerly, used clinically to treat heart failure), experimentally to block Na+K+ATPase</td>
</tr>
<tr>
<td>Hallucinogenic</td>
<td>Tabanthera iboga (Apocynaceae)</td>
<td>Bogarone, possible treatment for narcotic addiction</td>
</tr>
</tbody>
</table>

*Reserpine had, however, been isolated 2 years earlier from Rauvolfia serpentina (L.) Benth. ex Kurz, found in India.
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, S. angolensis D.C. Stem bark (respiratory irritation), (3) Shell from Lualaba River (fruits (gonorrhea and hernia), theiformis) Aphloia (silk) (diuretic), (4) welding fontanel), (5) Pterocarpus Democratic Republic of the medicine stall in Lubumbashi, Democratic Republic of the Congo. Key: (1) Pterocarpus angolensis D.C. Stem (hemorrhoids, nappy/diaper rash), (2) Solanum insanum L. Fruits (gonorrhea and hernia), (3) Shell from Lualaba River (welding fontanel), (4) Tortoise shell (burns treatment), (5) Albizia adianthifolia stem bark (aphrodisiac and perianal swelling), (6) Diplorychnus condylocarpon (Nobil Ag.) Pichon stem (abdominal pain, wound healing), (7) Cassia sieberiana D.C. roots (hemorrhoids, skin irritation), (8) Mucuna poggiei Taub seeds (nappy/diaper rash; analgesic in pelvic pain).

The alarming incidence of bacterial multidrug resistance to antibiotics requires an urgent search for new antibacterials. The expression of virulence factors in many pathogens requires the full activation of quorum sensing (QS) processes: cell-to-cell bacterial communication mechanisms that detect critical cell numbers by producing and recognizing diffusible signal molecules termed “autoinducers.” The compounds coordinate the expression and regulation of virulence factors, biofilm formation, and motility. QS presents a promising series of targets to antagonize virulence in pathogens and/or disturb biofilm formation. For example, catechin and naringin inhibited the production of virulence factors in Pseudomonas aeruginosa PAO1; its constituent coumarin analogs interfere with the QS system’s expression of QS- (lasI and QS-regulatory (lasR) genes). Recently, the Malagasy species Dalbergia trichocarpa, traditionally used to treat diarrhoea and laryngitis, was shown to inhibit a wide variety of virulence factors in P. aeruginosa PAO1; its constituent coumarin esters interfere with the system's QS and las gene expression (16).

Access to care

General health system improvement

- Quality of herbal medicines
- Efficacy of traditional treatments
- Preserving the knowledge of traditional healers and the ecosystem

- Development of a decentralized health system adequate for nonurban populations
- Affordability of diagnostic, medical devices, and drugs

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 exploration, 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

**Authors:** Helen Sherston1, Brigitte Kopp1, Liselotte Krenn2, Brigitte Kopp2, Dean Sun3, Jan Dirk Sendker4*

**The 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 (formulae) 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).

**The 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 detoxification or alteration of their therapeutic efficacy. Paozhi encompasses techniques such as cutting, crushing, calcining, or frying with or without liquid adjuncts 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 formulæ. These two factors act on the chemical composition and biological activity of the resulting tang decoction that is finally consumed (3, 4).

**Chinese herbal decoctions**

TCM formulæ 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

*Corresponding author: paozhi.sendker@mtm.mw.tum.de

**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. According to TCM theory, paozhi processing yields decoction pieces with variable therapeutic properties. (3, 7).](image1)

**FIGURE 2. Selection of factors affecting the chemical composition of a tang decoction.**

![FIGURE 2. Selection of factors affecting the chemical composition of a tang decoction.](image2)

1 Trinity College Dublin, School of Pharmacy and Pharmaceutical Sciences, and Trinity International Development Initiative, Trinity Biomedical Sciences Institute, Dublin, Ireland
2 University of Vienna, Department of Pharmacology, Vienna, Austria
3 Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China
4 Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China

Traditionally, altered pharmacological properties can have a significant downstream effect on the efficacy and safety of the final product. A great example of this is the Chinese pharmacopeia which describes four different decoction pieces that may be derived from raw rhizomes of the plant Paeonia lactiflora (Paozhi). These pieces, from the same source, have different 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 formulæ 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 Fu Xi Xue Tang (FXT) (8). In addition, studies of the simple two-herb formula Danggui Buxue Tang (DBT), composed of Angelica membranaceus root and Angelica sinensis root, demonstrate how multiple parameters like decoction time, initial temperature, paozhi processing, or the ratio of the two herbal ingredients 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 co-decosystem. It was concluded that the observed synergism may result from physicochemical interactions between the chemical constituents of both herbal ingredients. Such interactions have been observed in several studies with other formulæ (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 hypericines 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 (8).

An exciting new finding is that traditional paozhi processing techniques may actually augment a decoction’s therapeutic efficacy based on physicochemical interactions. Preparing DBT with Angelica sinensis 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 concentration of the established 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 sinensis. 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 has an insignificant effect 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 above 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 production chain of CHMs can influence the composition and efficacy of tang decoctions through specific interactions between their constituents. The extent to which these effects are influenced by a single detail like the paozhi impact on one ingredient, thus invoking a butterfly effect. Unlike the proverbial butterfly, however, this is an example of modern scientific methodologies allowing the source of the disruption to be traced by correlating the chemical profile (metabolome) of the herbal preparation with its bioactivity. This approach can help in the identification and location of chemical features that directly influence an herbal medicine’s therapeutic efficacy by providing knowledge about the role of particular herbal ingredients or phytochemicals within a CHM is a prerequisite for the development of meaningful quality control measures, and thus a requirement for the international registration of TCM products. Without fully understanding the subtle contributing factors,
The human body functions as a dynamic ecosystem consisting of innumerable interacting systems, creating emerging properties and synergistic effects and extending beyond the physical barriers of the human organism, encompassing interactions with the environment. 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 treat are amenable to a system-oriented paradigm in which interventions include multitarget 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 human entails differentiation 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 multitarget approaches on regulatory pathways could provide new perspectives for system-level interventions (5).

Understanding system resilience to a multitude of environmental stressors is critical for personalized health and prevention options within a biopsychosocial context.

In medical plant research, isolates of single components are primarily used, which does not reveal the synergetic properties 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'-methoxyhydroemodine, isolated from the same plant (6). Reverse pharmacology, wherein a traditional preparation is taken as a starting point for studies held promise for studying the synergetic nature of herbal medicine (5), especially when combined with subtyping based on modern ‘omics technologies. Combining pheno- mechanical 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.

**DXXX 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 (DXXX), the first traditional Chinese herbal medical product registered in Europe and produced in China according to the European Traditional Herbal Medicinal Products legislation. DXXK is an extract of rhizomes from Dioscorea nipponica Mankino, a plant from the Diosco- reaceae (yam) family. Over 300 papers have been published on the extract’s pharmacology, safety, and mechanisms of action, 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 analyses. 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 pyrethroid (pyrethrin, which is also found in DXXK) acts as a vasodilator and modulates vascular smooth muscle function by regulating cell viability, migration, and cellular homeostasis (22–23). Recent studies have revealed that the significant anti-inflammatory effect may be attributed to its inhibitory effect on the NF-κB/COX-2 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, including myocardial dysfunction, atherosclerosis, hypertension, migraine, and muscular spasms. From a Western perspective, these disparate applications suggest that there may be...
Cardiovascular disease progression (afterimage and stress related)

Cardiovascular disease prevention using DXXK (afterimage and stress related)

FIGURE 2. Conceptual depiction of the preventive effect of Diao Xin Xue Kang Jiao Nang (DXXK) on the progression from a healthy to a diseased condition over time in the cardiovascular system. A state of resilience is maintained by preventing a homeostatic shift to a dysfunctional status (Leiner-Arjas et al., 2006). Over time, DXXK prevents the cardiac system from falling into a state of disease (Leiner-Arjas et al., 2006). The graph on the right highlights how interventions with DXXK can bring the system back to a healthy, resilient state, reducing the long-term influence of stressors.

condition over time. A stable angina. Eventually, the system may fall into a state in which it is unable to return to normal stasis conditions, even after direct stressors have been alleviated. That is, a person may develop unstable angina and even cardiac infarction (Figure 2, left). Clinical observations and phase 3 clinical study findings suggest that DXXK may prevent the system from progressing toward the state described (Figure 2, right) (32). The multitude of pharmacological effects related to the relaxation of vascular muscles observed with administration of DXXK can be explained by a putative systems-level organization change where an underlying dysfunctional regulatory process may be alleviated. If so, then DXXK may be achieving an improvement in the muscle function at a higher system level, resulting in reduction of vascular tension and, thereby, increases in the ability to produce active tissues. The effect of DXXK on muscles relates directly to DXXK’s systemic treatment pattern, namely muscle cramps in the neck, lower back, and legs as well as dysfunction of cardiac muscle. Moreover, this association is consistent with suggestions of integrating physiological and psychological deficits in both the diagnosis and intervention, a key perspective in psychoneuroendocrinology (35–37).

Future perspectives

Looking to the future, further studies are needed to obtain a more detailed accounting of system level actions, particularly with respect to the dynamics of higher organization systems and the development of an allostatic load into the theory that can cope with stressors within the boundaries of a healthy condition (31), resulting in a stable angina. Eventually, the system may fall into a state in which it is unable to return to normal stasis conditions, even after direct stressors have been alleviated. That is, a person may develop unstable angina and even cardiac infarction (Figure 2, left). Clinical observations and phase 3 clinical study findings suggest that DXXK may prevent the system from progressing toward the state described (Figure 2, right) (32). The multitude of pharmacological effects related to the relaxation of vascular muscles observed with administration of DXXK can be explained by a putative systems-level organization change where an underlying dysfunctional regulatory process may be alleviated. If so, then DXXK may be achieving an improvement in the muscle function at a higher system level, resulting in reduction of vascular tension and, thereby, increases in the ability to produce active tissues. The effect of DXXK on muscles relates directly to DXXK’s systemic treatment pattern, namely muscle cramps in the neck, lower back, and legs as well as dysfunction of cardiac muscle. Moreover, this association is consistent with suggestions of integrating physiological and psychological deficits in both the diagnosis and intervention, a key perspective in psychoneuroendocrinology (35–37).

Future perspectives

Looking to the future, further studies are needed to obtain a more detailed accounting of system level actions, particularly with respect to the dynamics of higher organization systems and the development of an allostatic load into the theory that can cope with stressors within the boundaries of a healthy condition (31), resulting in a stable angina. Eventually, the system may fall into a state in which it is unable to return to normal stasis conditions, even after direct stressors have been alleviated. That is, a person may develop unstable angina and even cardiac infarction (Figure 2, left). Clinical observations and phase 3 clinical study findings suggest that DXXK may prevent the system from progressing toward the state described (Figure 2, right) (32). The multitude of pharmacological effects related to the relaxation of vascular muscles observed with administration of DXXK can be explained by a putative systems-level organization change where an underlying dysfunctional regulatory process may be alleviated. If so, then DXXK may be achieving an improvement in the muscle function at a higher system level, resulting in reduction of vascular tension and, thereby, increases in the ability to produce active tissues. The effect of DXXK on muscles relates directly to DXXK’s systemic treatment pattern, namely muscle cramps in the neck, lower back, and legs as well as dysfunction of cardiac muscle. Moreover, this association is consistent with suggestions of integrating physiological and psychological deficits in both the diagnosis and intervention, a key perspective in psychoneuroendocrinology (35–37).
Interdisciplinary consultation and discussion among traditional and Western medical physicians, pharmacologists, and natural scientists. Development of a working hypothesis.

Test case: Finding herbs for PD

Comparing the efficacy of the crude herb, its active component of CC), both of which showed neuroprotective effects against oxidative stress-induced cytotoxicity (18). Subsequently, we extended our research to in vitro and in vivo models using different terminologies. There- side effects discovered during clinical screening processes can mimic 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).

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 3 represents a hypothesis-driven screening steps. After initial screening, transcriptomic, proteomic and metabolomic analysis can be performed to further substantiate mode-of-action hypotheses (14).
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 evolving as a systematic paradigm for drug discovery and development (2, 3). Network pharmacology adopts a network approach to represent and analyze the complex biological systems underlying diseases and drug actions. It thus aids in drug discovery, drug design, and drug development, sharing a holistic perspective that is characteristic of TCM (2–5). Today, the integration of TCM and network pharmacology (TCM-NP) provides an innovative research perspective for proponents of both reductionist and holistic medicine.

Treating a network as a therapeutic target

TCM-NP highlights a “network target, multicomponent therapeutics” approach (6). The core principle of a network target is to construct a biological network that can be used to decipher complex diseases. The network is then used as the therapeutic target, to which multicomponent remedies, such as herbal formulae, are applied (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 compound’s target profile by integrating chemical, pharmacological result by network propagation and integration, and bioinformatics are providing more actionable data and increasingly sophisticated analysis tools, thus accelerating the understanding of biological networks, a situation that will undoubtedly speed TCM-NP progress. For example, by exploiting the available data pool, a computational method, drugCIPHER, has been developed to predict an herbal compound’s target profile by integrating chemical, target, and network information from current FDA-approved drugs (7). A sibling method, CIPHER, also performed well in predicting disease genes (7). In recent years, the use of systems biology and bioinformatics technologies in TCM has been growing rapidly, as has the generation of TCM-NP data and our understanding of multilayered networks. Through this work, associations have been elucidated between herbs, compounds, molecules, microbes, phenotypes, and diseases for TCM syndromes, generating fresh insights into holistic traditional medicine.

Not only does network pharmacology reflect the holistic properties of herbal medicine, but the rich trove of data on the use of TCM as herbal combinations can assist in refining the model. Considering that we still have much to learn regarding biological systems and drug action/interactions, the field of network pharmacology can undoubtedly benefit by combining top-down strategies. Since certain herbal formulae have been shown to be clinically effective, the inclusion of this empirical knowledge of multicomponent therapeutics may permit exciting advancements in network pharmacology.

Application of TCM-NP in traditional medicine

TCM-NP promises to help elucidate the complex molecular mechanisms underlying the actions of traditional therapies as well as explore new indications for their use. Herbal formulae are traditionally used to treat so-called TCM syndromes (Zheng). Most medicinal herbs can be categorized as cold, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that Cold and Hot Syndrome molecular profiles, 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, warm, or hot, based on their composition and nature. One of the earliest TCM-NP studies showed that.

*Corresponding Author: shaoli@mail.tsinghua.edu.cn

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 Bioinformatic Chemistry, Tsinghua National Laboratory for Information Science and Technology/Department of Automation, Tsinghua University, Beijing, China.

Corresponding Author: shaoli@mail.tsinghua.edu.cn

FIGURE 1. An effect-switch model based on the network target can be used to understand the actions of herbal ingredients and how their activity can be modulated.

FIGURE 2. (A) Schematic of traditional Chinese medicine–network pharmacology (TCM-NP) methodology: (B) A representation of a Cold/Hot Syndrome molecular network (1,2); (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 1; S91, a gene encoding transcription factor PUL1; CDK18, cyclin-dependent kinase inhibitor 1B; CEBPB, cAMP-responsive element-binding protein, epsilon; RARB, retinoic acid receptor, beta; AQP9, aquaporin 9 (15).
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-assistant-counselor) theory of combining herbal formulas. A disease molecular network could accordingly be divided into Jun-Chen-Zuo-Shi subnetworks to aid in the determination of the optimal combination therapy (14). For instance, in a Realgar-Indigo natural formula, tetraenic acid is a Jun that can target the promyelocytic leukemia (PML) retinoic 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 that pure single-drug therapeutics 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 disease factors (disease or syndrome) afflicting the patient (3). In our studies, we analyzed the molecular networks of the Gegen-Qin-Lian-Tang (cold pattern) in rheumatoid arthritis patients. The results indicated that Nan Zhang is related to the Toll-like receptor signaling pathway, while Re Zhang impacts the calcium and peroxisome proliferator-activated receptor signaling pathways (4). Characteristic molecular signatures for each Zhang were also identified (5).

Based on the particular Zuo ingredients, we hypothesized that the active ingredient in red sage root, acts as a receptor oncoprotein in leukemia cells. Tanshinone, the active ingredient in red sage root, is now the widely used in TCM-based combinatory drug discovery. The recent development of ‘omics technologies and in silico methods for analyzing signaling pathways provide useful tools for understanding the pharmacology network of various fufang.

The application of ‘omics and in silico technologies

‘Omic technologies such as genomics, transcriptomics, proteomics, and metabonomics are high-throughput technologies used to analyze a variety of molecules simultaneously. These technologies have facilitated the study of the molecular pharmacology of fufang at multiple levels (6). 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

It is primarily an advantage of fufang is the ability to simultaneously target multiple points within the complex network of a disease. We established an evaluation approach to evaluate the merging of a 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 (AEs). MTE is the ability of the drug to target the affected disease network and recover 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 evaluation of ingredients considers three aspects: coverage of the fufang target network, the ability of the formula to represent the diversity of the HM’s gut bacterial metabolism, and the pharmacokinetics of herbal medicines (HMs) that integrates phytochemical and metabolite profiling.

FIGURE 1. A Poly-PK strategy. The pharmacokinetic (PK) study of multicomponent herbal medicines (HMs) that integrates phytochemical and metabolite profiling.

The polypharmacokinetics of herbal medicines

Authors: Wei Jia1,2,3*, Guang Xie1,2,3, Wuxing Sun1,2, Hui Li1,2, Shuangjin Li1,2, Jinfeng Fan1,2, Xiaoyuan Wang1,2

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 botanicals 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 products 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 HM PK. Phytochemical profiling and metabolite analysis can be 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, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients. The Poly-PK approach takes into account both the diversity of the HMs and, consequently, the treatment outcome for individual patients.
FIGURE 2. Poly-PK metabolomic profiles. The relationships among the three groups of metabolites associated with Pu-erh tea are visualized using correlation maps, as shown by red (positive) or blue (negative) lines.

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] endpoints) on HM ingredients. This unprecedented level of insight into the mechanisms of action for HMs.

Most HMs are administered orally and are therefore exposed to microorganisms in the gut. The symbiotic gut microbiota performs a wide variety of biochemical transformations in which phytochemical compounds are selectively metabolized into active or absorbable components by microbial enzymes. Thus, two sets of genomes—our genome and gut microbiome—coevolve and cooperate to absorb and metabolize the absorption, distribution, metabolism, and excretion of HM compounds, generating a patient-specific PK profile. Many HM ingredients that were believed to be nonabsorbable and nonactive, such as polysaccharides and lignans, may have significant activities in vivo after oral administration, highlighting the important role that the human gut microbiota plays in HM pharmacology (13-15). A Poly-PK strategy can characterize the development of a new HM by monitoring the endogenous and/or exogenous metabolites at different times, revealing the complex interactions between the multiple components in HM and in mammalian metabolic systems. The advent of the Poly-PK technology will greatly accelerate the holistic pharmacological evaluation of HM candidates and advance novel therapeutic developments. 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.

References
8. G. Xu et al., Proteome Res. 11, 3449 (2012).

The bioavailability barrier and personalized traditional Chinese medicine

The BBB 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) and polymorphisms of DMEs, ETs, and NRs can affect the pharmacokinetics of drugs, which ultimately influences the efficacy and/or toxicity of the respective herbal formulations (CHFs). This paper presents the reconstruction of a BBB-based network with new insights that help elucidate the therapeutic mechanism of CHFs.

Western medicine focuses on molecular-target based therapies; however, there are limitations in transforming genotype-based or disease-oriented medicine into personalized and network-based clinical therapy. 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. Determining how the components of CHFs will behave in the body is a pivotal aspect in determining treatment mechanisms of TCM. The BBB has a key function in controlling absorption, biotransformation, and clearance of drugs in vivo (3). Therefore, a BBB-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 BBB 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) and polymorphisms of DMEs, ETs, and NRs can affect the pharmacokinetics of drugs, which ultimately influences the efficacy and/or toxicity of the respective herbal formulations (CHFs). This paper presents the reconstruction of a BBB-based network with new insights that help elucidate the therapeutic mechanism of CHFs.
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) regulation 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 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) regulation 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.

Syndrome-based CHF

Personalized and harmonized CHF

Manipulated by BB-based network

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 modulator switches that facilitate the bioavailability of polyphenols (3).

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 glycyrrhizae, popularly used as a Sh ū herb in CHF, activates PXR (10).

In summary, the BB-based network manipulates disposition 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 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 modulator switches that facilitate the bioavailability of polyphenols (3).

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 glycyrrhizae, popularly used as a Sh ū herb in CHF, activates PXR (10).

In summary, the BB-based network manipulates disposition 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 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.

References
Transdermal treatment with Chinese herbal medicine: Theory and clinical applications

**Authors:** Qing Wu1, Ling Dong, Jiaping Liu*1, Dan Jiang*1

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 You Pian Wen (Wu Shi Ji, 1864). It was emphasized in this book that the principles of treatment for both external and internal application of CHM were the same (1). This statement was the forerunner of the theory of transdermal administration for CHM, and modern transdermal drug delivery systems (TDDS) use the same concepts, 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, historically, the most common way to apply transdermal herbal medicine is to use aromatic herbs that can act as natural solutions. The latest transdermal herbal preparations can be more effective, allowing more concentrated extracts of active herbal ingredients to be made, thus facilitating percutaneous absorption of the multiple components of the herbal formula. Inclusion of carrier compounds such as microemulsions (21), liposomes (22), and cyclodextrins (23) can improve the compatibility of complex components and polymer materials. The latest transdermal herbal preparations can be more easily prepared, undergoing improved quality control checks, and possess better stability than in the past (23). Moreover, pharmacological scientists are experimenting with the use of aromatic herbs that can act as natural transdermal vehicles for transdermal delivery (24), which will potentially broaden their clinical application in the future.

**Table 1. Diseases and the corresponding acupoints (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); JX (EX-N15); GH (BL43); Ahs</td>
</tr>
<tr>
<td>Respiratory infection in children</td>
<td>FS (BL13); DC (EX-BO1); GH (BL43)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>NG (PC6); XS (BL15)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>SQ (RN8); NG (PC6); YQ (XQ1)</td>
</tr>
<tr>
<td>Dysmenorrhea caused by endometriosis</td>
<td>ZJ (RN3); YQ (RN4); ZG (RN19)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>ZJ (RN3); YQ (RN4); 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>
</tbody>
</table>

**Simple obesity**

2W (RN12); YQ (BL24); Gh (RN6); TS (ST52); SD (ST28); GY (RN4) 6–18

*Chronic obstructive pulmonary disease (stable phase); DC, Ding Chuan; DH, Du Hai; DS, Da Zhi; PS, Pei Shi; Gu, Guo Huang; GS, Gui Shu; QY, Quan Yuan; GY, Guan Yuan Shu; JX, Jing Bai Lan; MM, Ming Men; NG, Ne Guan; PS, Pei Shi; QH, Qi He; SD, Shen Dou; SJX, Shen Ji Xun; SQ, Shen Qu; SS, Shen Shu; TS, Tie Shen; ZJ, Zong Ji; ZW, Zu San Li; ZH, Zheng Huan; AZ, An Gu Li; PW, Zhe Wang; JX, Ji Xun.*

**Doctors practicing TCM use their extensive knowledge and experience of syndrome differentiation in clinical practice to diagnose patients before choosing which acupoints to stimulate. How each acupoint relates to a disease is based on both TCM meridian theory and many hundreds of years of empirical knowledge. For example, a transdermal herbal patch could be applied on acupoint Shen Que (RN8) for treating diarrhea, menstrual pains, or indigestion; whereas a patch on acupoint Yong Quan (XKI) treats high blood pressure, neurasthenia, or acute cold. Some common diseases and their corresponding treatment acupoints are summarized in Table 1 (6–18). All have been carefully selected from published clinical research papers using controlled trials and at least 100 cases. Liu and colleagues systematically reviewed the use of an acupoint herbal patch for treating allergic rhinitis and chronic obstructive pulmonary disease (COPD) in the stable phase using a meta-analysis. They included 21 randomized controlled trials (RCTs) involving a total of 2,237 participants (allergic rhinitis) and 20 RCTs involving 2,438 participants (COPD). The authors concluded that an herbal patch alone, or in combination with Western medication (17, 29) could be effective for treating these diseases (19, 20).**

**Recent advances in transdermal herbal preparations**

Historically, the most common way to apply transdermal herbal preparations was using a black plaster. To prepare the plaster, herbs were fried in edible oil and red lead oxide (Pb) was added to the refined herb oil to form a sticky mass. In recent years, however, since the advent of medicinal polymers, use of a black plaster has gradually given way to adhesive plasters, gel plasters, or patches, which have the significant advantage of reducing skin irritation. The technologies for extraction have also improved, allowing more concentrated extracts of active herbal ingredients to be made, thus facilitating percutaneous absorption of the multiple components of the herbal formula. Inclusion of carrier compounds such as microemulsions (21), liposomes (22), and cyclodextrins (23) can improve the compatibility of complex components and polymer materials. The latest transdermal herbal preparations can be more easily prepared, undergoing improved quality control checks, and possess better stability than in the past (23). Moreover, pharmacological scientists are experimenting with the use of aromatic herbs that can act as natural transdermal vehicles for transdermal delivery (24), which will potentially broaden their clinical application in the future.
Acupuncture as a potential treatment for insomnia

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 needling on the Sishencong (EX-HN1) acupuncture point, 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 subjects with insomnia results from reducing sympatho-vagal 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 periaqueductal gray (VPAG), that modulates cardiovascular sympathetic excitatory bulbospinal neurons in the rostral ventrolateral medulla (RVM) has been suggested as a possible explanation for an acupuncture mechanism. Electrocupuncture stimulation at acupoints Neiguan (PC6), a commonly used acupuncture point for insomnia, and Jianzhai (PC5), activates ARC neurons in the ventral hypothalamus, 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 sympatheticexcitatory neurons in the RVM via endorphin, enkephalin, GABA, and serotonin (16). Since insomnias apparently show elevated GABAergic 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 adrenocorticotropic 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 effect 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).

Possible mechanisms of action

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


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).