

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 therapeutic properties of their ancestors.

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

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The human body functions as a dynamic ecosystem consisting of innumerable interacting systems, creating emerging properties and synergetic 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).

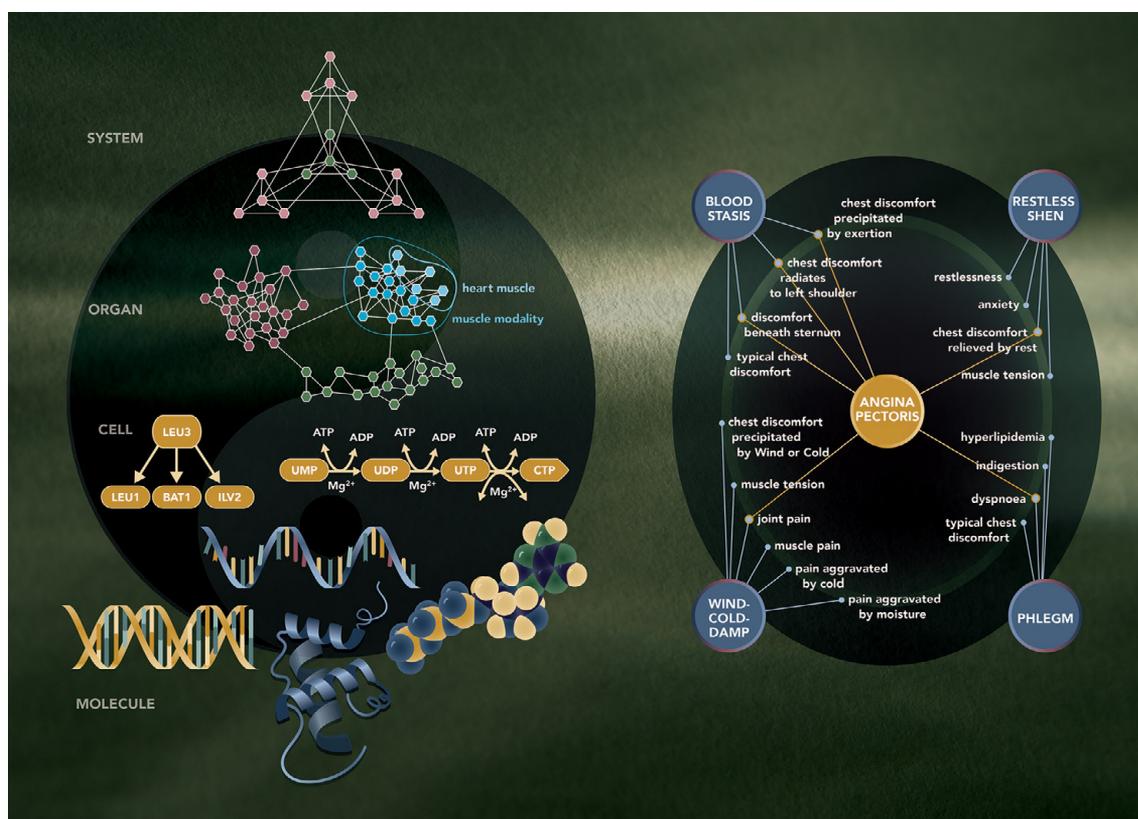
Medical questions regarding how a disease develops and how to prevent and intervene are amenable to a system-oriented paradigm in which interventions include multitarget pharmacological strategies that can influence processes across systems (2, 3).

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 will shed light on 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* (Frémont's mahonia), which showed that the antimicrobial effects of the bioactive compound berberine were enhanced >100-fold when combined with an inactive component, 5'-methoxyhyd-nocarpin, isolated from the same plant (6). Reverse pharmacology, wherein a traditional preparation is taken as a starting point, holds promise for studying the synergetic nature of herbal medicine (5), especially when combined with subtyping based on modern 'omics technologies. Combining phenomenological 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.

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**FIGURE 1.** An example of systems pharmacology in herbal medicine. Left, a systems view of human biology, with selected effects of *Diao Xin Xue Kang* (DXKK). Right, the four traditional Chinese medicine (TCM) symptom clusters that are the main intervention targets for DXKK in China are illustrated for angina pectoris.

### DXKK 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* (DXKK), the first traditional Chinese herbal medical product registered in Europe and produced in China according to the European Traditional Herbal Medicinal Products legislation. DXKK is an extract of rhizomes from *Dioscorea nipponica* Mankino, a plant from the Dioscoreaceae (yam) family. Over 300 papers have been published on the extract's pharmacology, safety, and mechanisms of action, and DXKK 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 DXKK, pharmacological studies have examined various biochemical pathways, ranging from molecular to organ-level assessments. Analysis of DXKK'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 DXKK affects the renin-angiotensin-aldosterone system in a manner that is consistent with its antihypertensive effects (21). At the organ level, the phytoestrogen diosgenin, which is also found in DXKK, acts as a vasodilator and modulates vascular smooth muscle function by regulating cell viability, migration, and calcium homeostasis (22, 23). Recent studies have revealed that the significant anti-inflammatory effect may be attributed to its inhibitory effect on the NF- $\kappa$ B/COX-2 pathway and relevant inflammatory mediators including prostaglandin 2, nitric oxide, tumor necrosis factor  $\alpha$ , interleukin (IL) 1 $\beta$  and IL-6 (24).

In TCM, DXKK is used to treat a variety of conditions, including myocardial dysfunction, atherosclerosis, hypertension, migraine, and muscle spasms. From a Western perspective, these disparate applications suggest that there may be

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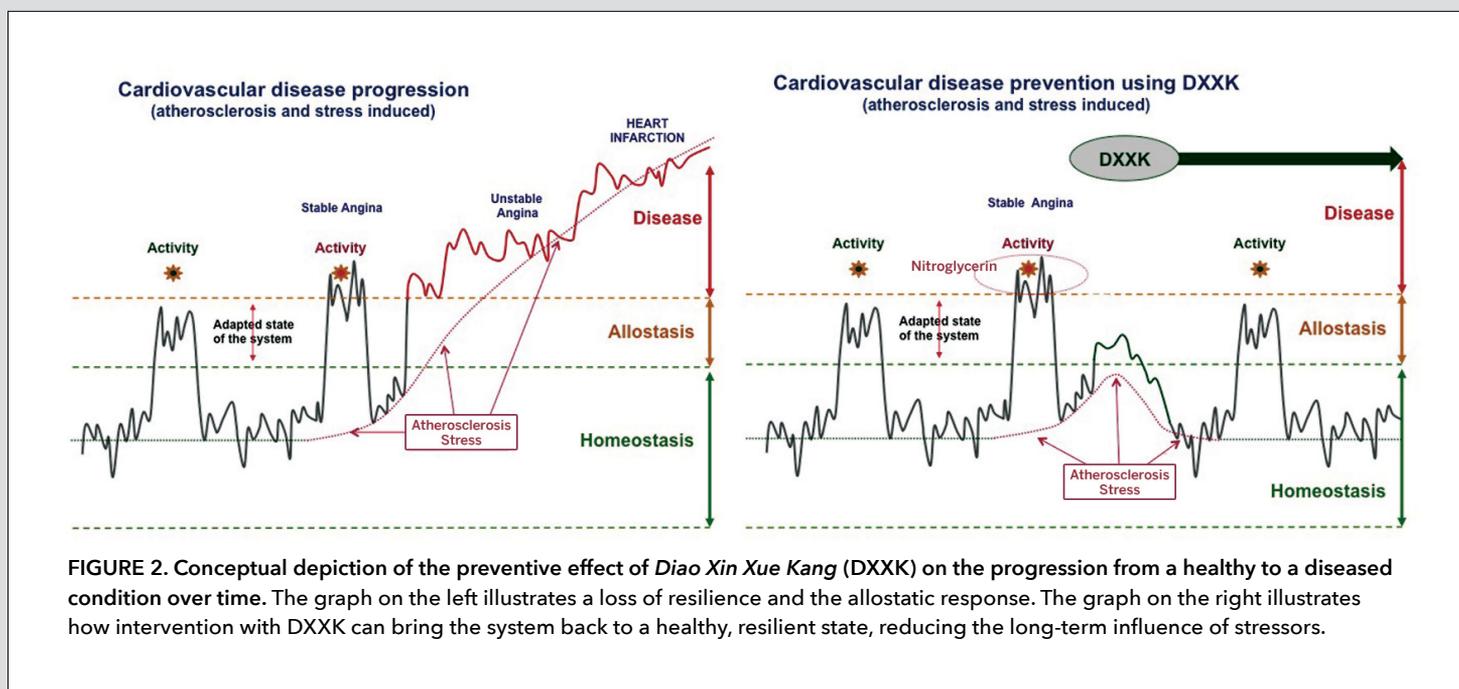
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shared regulatory pathways related to these conditions. In a more general sense, TCM offers attractive ways to generate a systems view on inter-disease relationships owing to its unique knowledge of symptom patterns, which can be translated into Western concepts.

However, some important and intrinsic characteristics underlying the complexity of the TCM concepts can be lost in translation. Elucidating this missing information can build a bridge between Western and Chinese medicine, providing insights into large-scale organization (Figure 1, left). In particular, symptom relationships can help to bridge Chinese and Western perspectives on disease states (Figure 1, right) and can point to associations among regulatory pathways, a likely level at which major synergistic effects can be uncovered.

### Where East meets West

Closer examination of points of interconnectedness between Chinese disease subtypes and Western pharmacology suggests that key elements in DXXK bioactivity involve the musculature. This is consistent with DXXK's ability to induce relaxation of vascular muscles (25–28) and reduce stress-related tension in intestinal, cardiac, and skeletal muscles (the latter involving the neck), as well as to reduce muscle spasms in the lower back and legs (29). Interestingly, Leino-Arjas et al. demonstrated a relationship between cardiovascular risk factors such as atherosclerosis and lower back pain (30).

A dynamic systems view of the effects of DXXK on cardiovascular disease progression is illustrated schematically in Figure 2. A healthy system can respond to and exchange information with its environment efficiently. Stressors can move a resilient system into a temporary state of allostasis. Systems should return to homeostasis when the offending stressors have been alleviated. The development of an allostatic load leads to the loss of ability to 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 diseased state (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 wherein an underlying dysfunctional regulatory process may be influenced. 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 oxygen flow to active tissues. The effect of DXXK on muscles relates directly to DXXK's TCM symptom 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 known manifestations of stress in the musculature, such as lower back pain (33) and heart attacks (34). The physical manifestations of chronic stress highlight an important aspect of integrating physiological and psychological determinants 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 elucidation of biochemical variations among different clinical subgroups. Furthermore, enhancing our knowledge of biological rhythmicity and dynamics will be important for attaining a fuller understanding of systems biology in medicine (38, 39). Indeed, the notion of dynamic system rhythms being reflected in the manifestation of symptoms over time is key in TCM. The TCM view of dynamics resonates with the classical

idea of *Panta rhei*, or “everything flows,” credited to the Greek 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.

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

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**P**rotection against the loss of neurons or the retardation of disease progression is the major challenge for the treatment of neurodegenerative disorders like Alzheimer's disease (AD) and

Parkinson's disease (PD). Current 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 (1). 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 were 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 neuroprotection 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 modality 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 based on compound libraries. However, even the largest plant compound libraries represent only a small fraction of possible chemical diversity of natural products (6). 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 (8). Research that primarily focuses on monocompounds isolated from plants carries a high risk that the observed effects will not be transferable from in vitro or animal models to clinical practice.

Neurodegeneration is a complex process involving multiple pathophysiological mechanisms; therefore it seems only rational to apply a multitargeted approach to a multifactorial

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