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Traditional Chinese herbal medicine preparation: Invoking the butterfly effect

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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*).

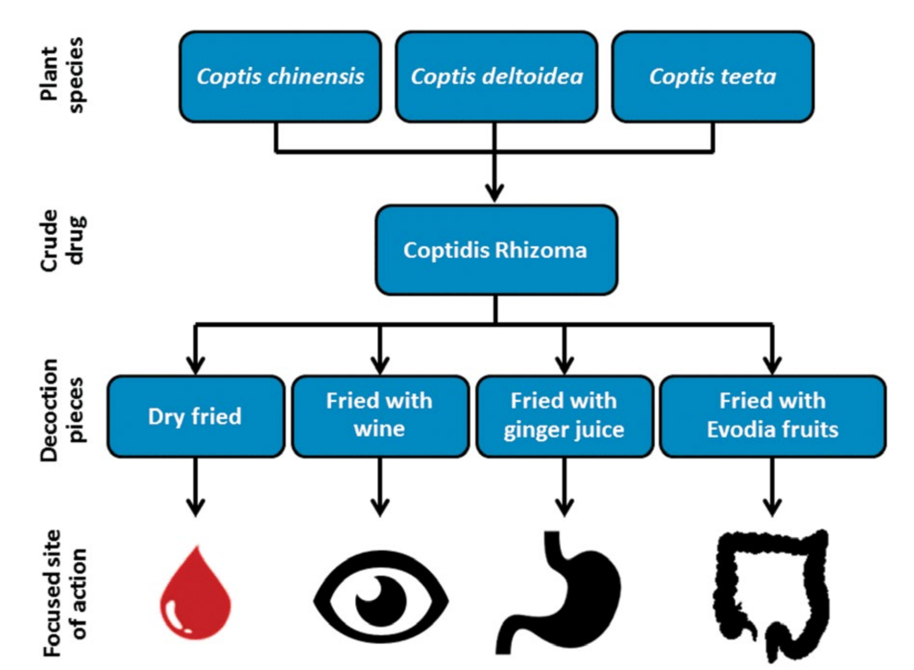

FIGURE 1. According to TCM theory, *paozhi* processing yields decoction pieces with variable therapeutic properties (*3, 7*).

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 adjuvants such as vinegar or honey (*3*). A prominent example is the highly toxic crude root of *Aconitum carmichaelii* (*Fuzi*) which, after detoxification by *paozhi* processing, is incorporated into numerous TCM formulae used to treat joint pain and rheumatic disease (*5, 6*). Also, different kinds of decoction pieces can be derived from the same raw material by processing in different ways. For example, the Chinese pharmacopeia describes four different decoction pieces that may be derived from raw rhizomes of the species *Coptis* (*7*). These pieces, from the same source, have distinct activity and different sites of action within the human body (Figure 1). Despite its long tradition, it is only recently that the effects of *paozhi* have been systematically studied. The current understanding is that *paozhi* processing can alter the qualitative and quantitative chemical composition of herbal materials and can thus impact the final pharmacological or toxicological properties of the decoction pieces (*3*).

Chinese herbal decoctions

TCM formulae are typically composed of two or more processed herbal drugs that are jointly decocted. Traditional decoctions (*tang*) are prepared by repeated boiling of decoction pieces in water for 1 or more hours. The method may also require soaking in cold water before heating, or the introduction of single herbal components later in the process. The composition of the *tang* decoction can be changed by simple actions such as an initial soaking in cold water, which initiates innate enzymatic activity resulting in the alteration of chemical composition, as demonstrated by the formula of *Fuzi Xiexin Tang* (FXT) (*8*). In addition, studies of the simple two-herb formula *Danggui Buxue Tang* (DBT), composed of *Astragalus 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 coextraction. It was concluded that the observed synergism results from physicochemical interactions between the chemical constituents of both herbal ingredients. Such interactions have been observed in several studies with other formulae (see *8, 14–16*).

Physicochemical interactions

Physicochemical interactions may affect the solubility of phytochemicals in simpler environments than a Chinese *tang* decoction. It has been observed that ubiquitous herbal constituents like sugars, amino acids, or small organic acids can function singly or in combination as natural deep eutectic solvents, which are able to dissolve phytochemicals and biological macromolecules up to 460,000-fold better than water (*17*). The solubility of phytochemicals in water itself can also be affected by the presence of other small organic molecules, as exemplified by hypericine from St. John's wort, the solubility of which increases 120-fold in the presence of tannins (*18*). In contrast, a reduction in the solubility of different toxic alkaloids was observed in the presence of rhubarb root, a process believed to be linked to the formation of insoluble sediments (*8*).

An exciting new finding is that traditional *paozhi* processing techniques may also augment a decoction's therapeutic efficacy based on physicochemical interactions. Preparing DBT with *Angelica 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 concentrations of the observed *Astragalus* phytochemicals; the qualitative phytochemical changes were accompanied by an increase in estrogenic and osteogenic activity (*19*). Some of these physicochemical interactions have been recently modeled using ferulic acid, a constituent of *Angelica 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 was completely inactive in these models (*20*). This example demonstrates that such complex physicochemical interactions may account for synergistic effects on the biological activity of CHMs and thus contribute to other possible synergisms that may occur due to pharmacokinetic or pharmacodynamic effects (*14*).

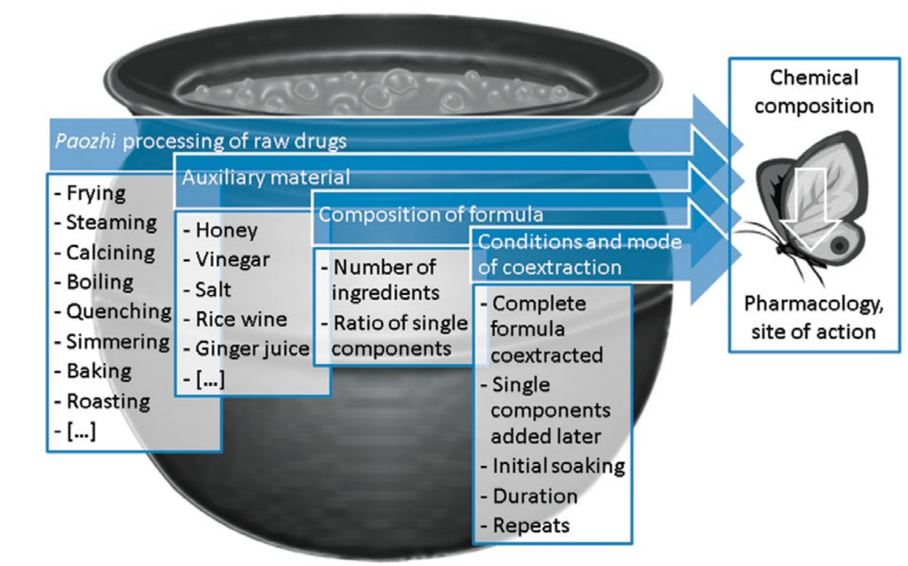

FIGURE 2. Selection of factors affecting the chemical composition of a *tang* decoction.

Conclusions

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

As discussed above, subtle changes in the complex production chain of CHMs can influence the composition and efficacy of *tang* decoctions through specific interactions between their constituents. The extent of such interactions may be influenced by a single detail like the *paozhi* impact on one ingredient, thus invoking a butterfly effect.

Unlike the proverbial butterfly, however, the application of modern scientific methodologies allows the source of the disruption to be traced by correlating the chemical profile (metabolome) of the herbal preparation with its bioactivity. This approach can also effectively aid the identification of chemical features that indirectly influence an herbal medicine's therapeutic efficacy (*21*). Knowledge about the role of particular herbal ingredients or phytochemicals within a CHM is a prerequisite for the development of meaningful quality control assays, and thus a requirement for the international registration of TCM products. Without fully understanding the subtle contributing factors,

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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′-methoxyhydnocarpin, 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.

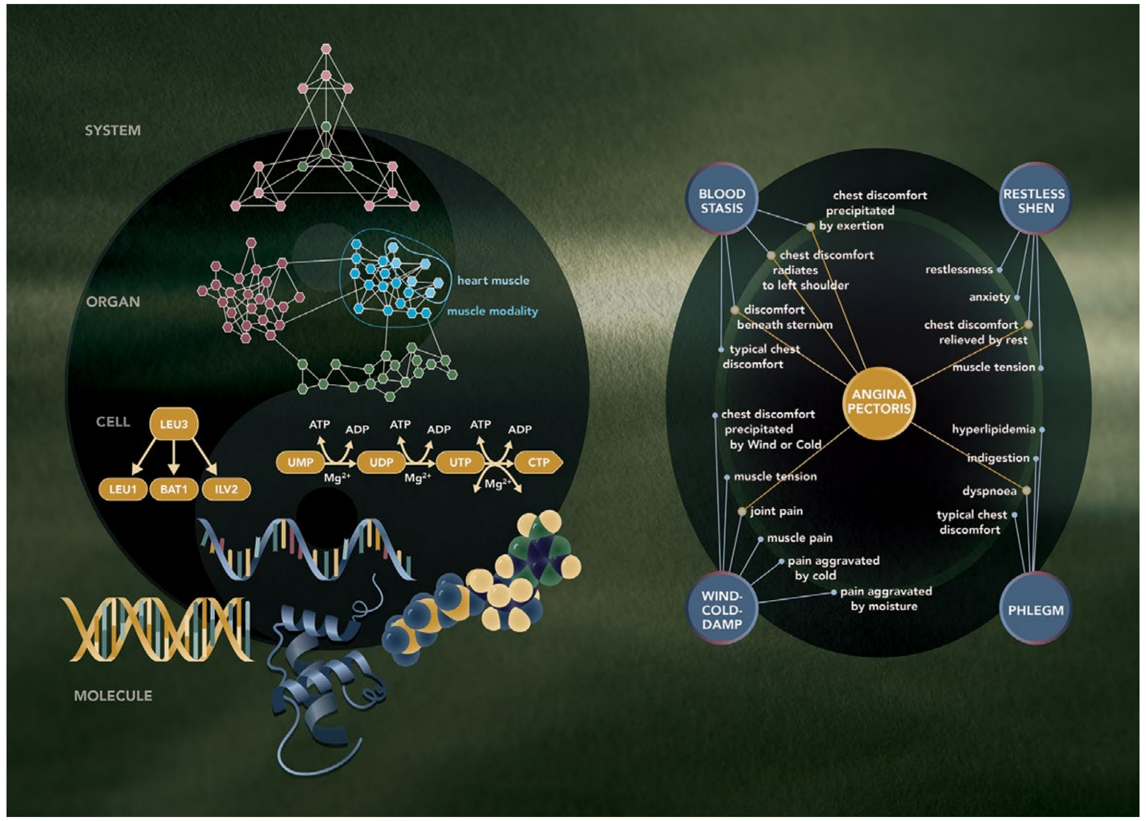

FIGURE 1. An example of systems pharmacology in herbal medicine. Left, a systems view of human biology, with selected effects of *Diao Xin Xue Kang* (DXXK). Right, the four traditional Chinese medicine (TCM) symptom clusters that are the main intervention targets for DXXK in China are illustrated for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

DXXK as an example

An example of the application of a systems pharmacology perspective in multitarget pharmacology research can be illustrated by *Diao Xin Xue Kang* (DXXK), the first traditional Chinese herbal medical product registered in Europe and 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 Dioscoreaceae (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 assessments. Analysis of DXXK's phytopharmacological constituents revealed that its bioactivity could be attributed to a group of steroidal saponins, namely dioscin, diosgenin, prosapogenin A, and prosapogenin C (*8*–*12*). Saponins influence oxidative stress (*12*, *13*), which is a major risk factor for vascular endothelial cell apoptosis, a process that is implicated strongly in the pathogenesis of cardiovascular disorders (*14*, *15*). Steroidal saponins also exhibit vasodilator and protective effects on human vascular endothelial cells (*16*, *17*). Clinical studies have shown that these saponins have protective effects against hyperlipidemia, including inhibition of platelet aggregation and reductions in cholesterol and triglyceride levels (*18*–*20*).

Studies at the cellular level have revealed that DXXK affects the renin-angiotensin-aldosterone system in a manner that is consistent with its antihypertensive effects (*21*). At the organ level, the phytoestrogen diosgenin, which is also found in DXXK, acts as a vasodilator and modulates vascular smooth muscle function by regulating cell viability, migration, and calcium 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 muscle spasms. From a Western perspective, these disparate applications suggest that there may be

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