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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*).

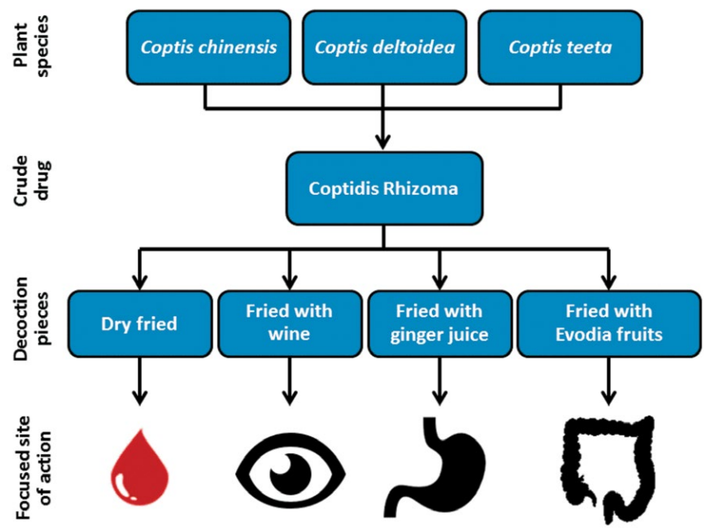

FIGURE 1. According to TCM theory, *paozhi* processing yields decoction pieces with variable therapeutic properties (*3, 7*).

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*).

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,

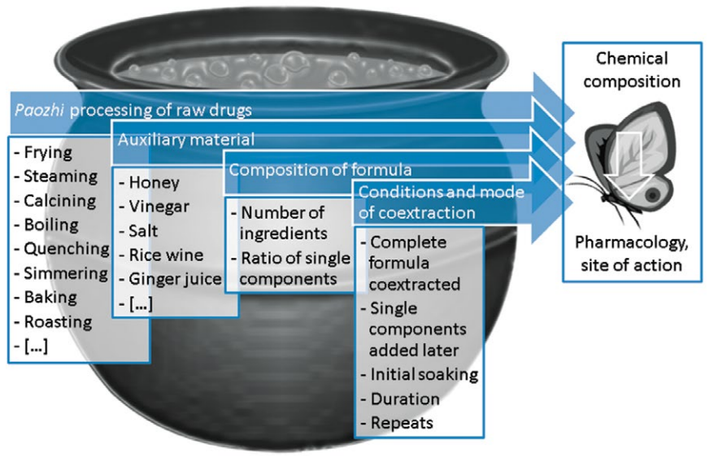

FIGURE 2. Selection of factors affecting the chemical composition of a *tang* decoction.

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