



Hormesis: mechanistic implications in herbal treatment in traditional Chinese medicine

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“Hormesis” is defined as any process in a cell or organism that exhibits a biphasic response to the exposure in increasing amounts of a substance or condition, wherein a low dose of the chemical agent or environmental factor, which is damaging at higher doses, induces an adaptive/beneficial effect on the cell or organism at lower doses (1,2). In the context of Pharmacology and Toxicology, hormesis is a dose-response phenomenon characterized by low-dose stimulation, and high-dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose-response relationship. Wang *et al.* (3) published a thought-provoking article which advocates the adoption of the term “hormesis” in the mechanistic approach to an understanding of the action(s) of herbal treatments in traditional Chinese medicine (TCM). The authors proposed that the stimulatory (at low doses) and inhibitory (at high doses) components of a hormetic dose-response action correspond to “regulating” and “curing” modes of action in TCM herbal treatments. While the “regulating” mode of action could in principle induce adaptive responses for the prevention of diseases, the “curing” mode of action would ameliorate (or possibly prevent) the clinical manifestations of the disease.

Medicinal herbs used in TCM can be broadly divided into two groups—namely, tonifying herbs and therapeutic herbs. Chinese tonifying herbs, which are commonly used for regulating body functions and thereby prevent diseases by restoring the Yin-Yang balance, are prescribed at relative low dosages for individuals with sub-healthy status (i.e., various patterns of “deficiency”). On the other

hand, therapeutic herbs, which are used for treating patients with a particular syndrome (i.e., “zheng”), are prescribed at higher dosages. As regards the dose-response relationship describing a given hormetic action, tonifying herbs, if administered at high dosages, may also produce a “curing” action, and therapeutic herbs at low dosages may be able to exert a “regulatory” action. More often than not, both tonifying and therapeutic herbs are used in multi-component herbal formulations in order to produce a holistic regulatory or therapeutic action, presumably by affecting multiple target organs in the body. In the practice of TCM, both tonifying and therapeutic approaches can be used during the course of disease treatment, wherein the cause(s) of the disease is inhibited (mostly by therapeutic herbs at high dosages), and be accompanied by a regulatory action produced by tonifying herbs at lower dosages in order to restore the Yin-Yang balance that has been disturbed by the pathogenic condition. This is the underlying guiding principle for formulating multi-component herbal preparations in TCM, of which various amounts of herbs are used under the framework of “Monarch, Minister, Assistant and Guide”, with “Monarch” and “Minister” herbs producing “curing” and “regulating” actions accordingly. Herbs serving the role of “Assistant” or “Guide” may reduce the toxic side effect(s) and/or increase the bioavailability of active herbal components to target organs.

The authors of the present commentary article reported published literature demonstrating the *in vitro* hormetic actions of herb-derived active components as well as herbal

formulations (3). In this connection, over the past two decades, our laboratory has been focusing on investigating the “regulatory” action of schisandrin B (Sch B, an active component isolated from *Schisandrae Chinensis Fructus*). We have demonstrated that Sch B at low concentrations/doses up-regulates the cellular glutathione antioxidant defense mechanism, thereby protecting various types of cultured cells (*in vitro*) and tissues (*in vivo*) against oxidant-induced damage (4). While high dosages of Sch B are required for ameliorating symptoms in chemically or immunologically-induced hepatitis in rodents (4), long-term, low dose Sch B treatment extends the average lifespan of mice, presumably by enhancing mitochondrial glutathione status in various organs (5). In addition, high doses of Sch B treatment were shown to suppress cancer growth and metastasis (6) as well as inflammation in experimental settings *in vitro* and *in vivo* (4). In a combination with *Panax Ginseng Radix* and *Ophiopogonis Japonicus Radix*, *Schisandrae Chinensis Fructus*, as a “Minster” component herb, constitutes Shengmai San (SMS), a formulation clinically prescribed for the treatment of coronary heart disease (7). Experimental and clinical studies have also shown that SMS pre-treatment or treatment protected against myocardial or cerebral ischemia/reperfusion injury and viral-induced myocarditis in rodents and patients (7,8). The pharmacological and therapeutic actions of *Schisandrae Chinensis Fructus* and Sch B as well as those of SMS have therefore suggested a hormetic mechanism underlying their beneficial effects in the prevention and/or treatment of diseases.

In addition to explaining the preventive and/or therapeutic effect of herbal formulations in TCM, a hormetic dose-dependent action could possibly serve as the rational basis for optimal dose determination of herbal preparations used for treatment in the practice of TCM. While the dosage for eliciting “regulating” actions can be determined by assessing the antioxidant and immunological responses (both being the main-stay of preventive health) in animal models, the dosage for producing “curing” actions must rely on documented clinical experience. Given that herbal treatments based on differential diagnoses in the framework of TCM are individualized with respect to particular signs and symptoms as well as biodata in a given patient, various dosages and/or different herbal formulations can be prescribed for individuals suffering from the same disease. Conversely, the same dosage and/or identical herbal formulation can be prescribed for patients with different types of diseases. With the recent advances

in systems biology that involves the application of platform technology such as genomics, proteomics, metabonomics, chemometrics and bioinformatics in TCM (9), the clinical efficacy of herbal formulations in patients can be rigorously assessed. Coupled with the differentiation of signs and symptoms using the four diagnostic methods in TCM, more information can be collected for the characterization of a given syndrome and thereby determine the optimal dosage regimen for the corresponding herbal treatment. This approach will hopefully allow the integration of TCM into modern medicine in the effective prevention and treatment of diseases.

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