

# Hormesis: a concept to understand the distinct indications of Chinese herbal medicine at different doses

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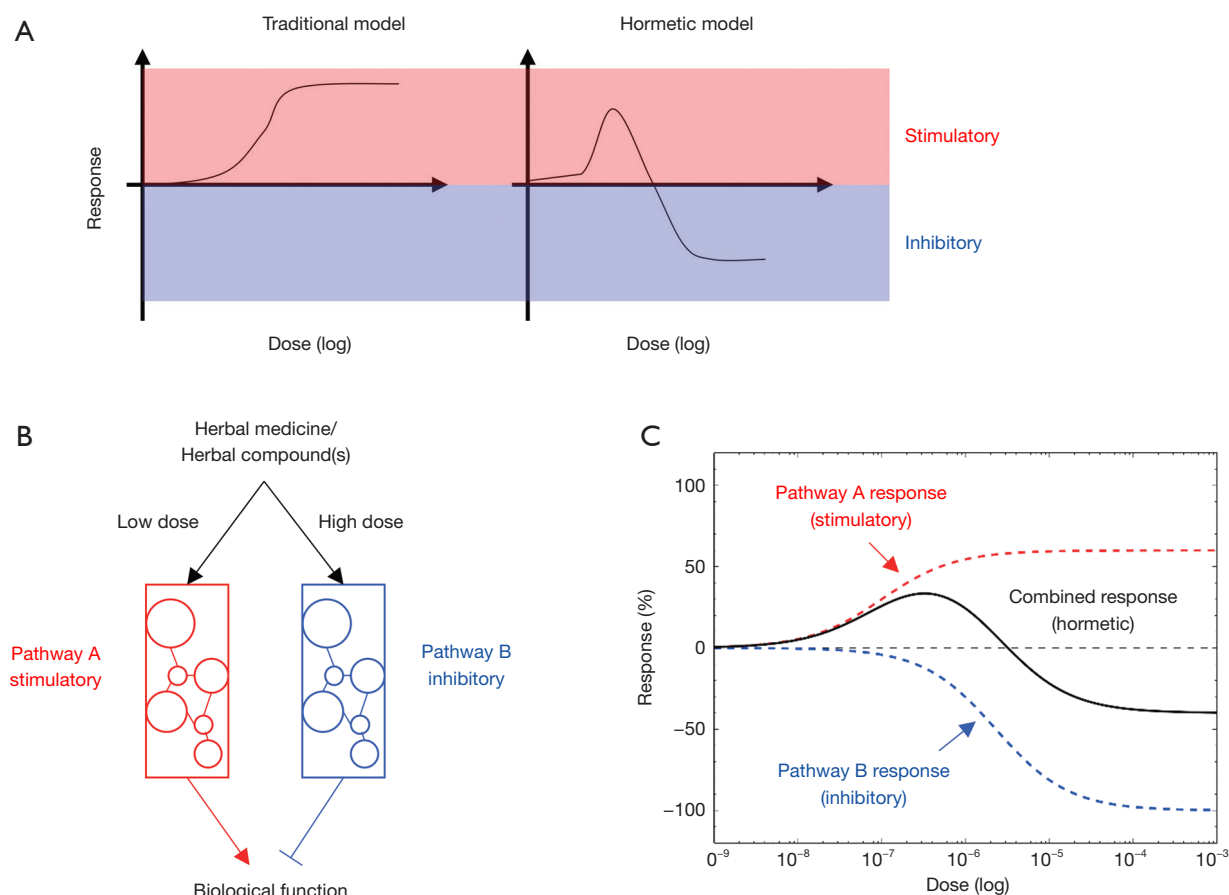
The term “hormesis” refers to a non-traditional dose-response model in the field of pharmacology and toxicology. In the traditional model, dose-response displays the “S-shape” curve, where the biological effect gradually increases by drug amount, and finally reaches the plateau (*Figure 1A*) (1). In contrast, the dose-response is biphasic in the hormetic model: stimulatory effect in the dose range, while inhibitory effect in the high-dose range (*Figure 1A*) (1). Furthermore, hormesis also refers to the low-dose beneficial effect and high-dose toxic effect. To be clearly, the stimulatory/inhibitory terms should be discussed in the context of therapeutic effect evaluation; while the beneficial/toxic terms should be used under the circumstance of safety study. To date, only a few studies utilized the hormetic model in the pharmacological study of Chinese herbal medicine/herbal compounds (2-6).

Recently, Wang *et al.* published a review entitled “Hormesis as a mechanistic approach to understanding herbal treatments in traditional Chinese medicine” on *Pharmacol Ther* (7). In this article, the authors proposed that: (I) hormetic dose-response mechanisms are valuable to understand the mechanism-of-actions of herbal medicines from Traditional Chinese Medicine (TCM); (II) the low-dose stimulatory effect and high-dose inhibitory effect in the hormetic model could respectively explain the “regulating” and “curing” aspects of TCM herbal treatments; (III) hormesis may stand as the Rosetta Stone to translate the ancient experiences of TCM into modern scientific

language. Obviously, the authors provided a new angle to the research community of Chinese Medicine. Importantly, the unique value of hormesis to TCM researchers should be more highlighted, because hormesis could explain the distinct indications of Chinese herbal medicine at different doses.

In the clinical practice, a number of Chinese herbal medicines do have dose-dependent, distinct therapeutic indications (*Table 1*). For example, *Radix notoginseng* can resolve blood stasis at low dose, and stop bleeding at high dose; while low-dose *Radix angelica sinensis* is used for insufficiency of blood, and the high-dose is for blood stasis (8). A more interesting case is about *Cortex magnolia officinalis*. Used in *Xiao Cheng Qi Tang* at low dose, the *Cortex magnolia officinalis* can treat constipation with slow bowel movement. In contrast, the dose of *Cortex magnolia officinalis* is much higher in the *Hou Po San Wu Tang*, which is used for treating constipation accompanied by abdominal pain (9). Since both *Xiao Cheng Qi Tang* and *Hou Po San Wu Tang* share the same herbs, such clinical experiences suggest that active ingredients in the *Cortex magnolia officinalis* may adopt the hormesis mechanisms: stimulating smooth muscle contractions at low dose range, while relieving convulsion at high-dose range (10).

In the preclinical studies, Chinese herbal medicines exhibit biphasic/hormetic effects both *in vitro* and *in vivo*. For example, berberine promoted cancer cell proliferation at low dose range (1.25–5  $\mu$ M), but inhibited cell



**Figure 1** The hermetic dose-response curve and a theoretical model to explain the hormetic response of herbal medicine or herbal compound(s). (A) In the traditional model, the dose-response is in “S-shape” curve, while in the hormetic model, the dose-response is in reverse “U-shape” curve: stimulatory at the low dose range and inhibitory at the high-dose range; (B) herbal medicine/herbal compounds may act through two distinct signaling pathways (pathway A at low dose and pathway B at high dose) to regulate the outcome of a single biological function; (C) the numeric simulation of combined response resulted from two independent sigmoid dose-response curves: the stimulatory response is in red, while the inhibitory response is in blue.

**Table 1** Chinese herbal medicine in treating distinct symptoms at different doses (8)

Herbal medicine	Low-dose indication	High-dose indication
<i>Radix notoginseng</i>	Blood stasis	Bleeding
<i>Radix angelica sinensis</i>	Insufficiency of blood	Blood stasis
<i>Cortex magnolia officinalis</i>	Constipation with slow colonic transit	Constipation with abdominal pain
<i>Radix ginseng</i>	Hypotension	Hypertension
<i>Radix astragali</i>	Hypotension	Hypertension

proliferation at high-dose range (10–80  $\mu$ M) (2). Another example is Z-ligustilide, an essential component from *Radix angelica sinensis* that has wide therapeutic applications for ischemic brain injury and cardio-vascular diseases. The low concentrations of Z-ligustilide protected PC 12 cells from oxygen glucose deprivation injury, and high concentrations of Z-ligustilide induced massive production of reactive oxygen species (ROS) (3). In our investigation into the biphasic effects of *Cortex magnolia officinalis* on bowel movement, we found that, honokiol increased rat colonic smooth muscle contractions at the low dose (1–30 nM), and

decreased the contractions at high dose (0.3–100  $\mu\text{M}$ ) in organ bath experiment (11). More interestingly, we found that 4-O-methylhonokiol, an active compound from *Cortex magnolia officinalis* and a structural derivative of honokiol, promoted the fecal pellet output at low dose range (0.01–1 mg/kg), but inhibited the defecation at high dose range (10–100 mg/kg) in mice (unpublished data). The hormetic effects of *Cortex magnolia officinalis* components observed in animal studies could perfectly explain the reason that it is used for constipation with slow bowel movement (stimulating smooth muscle contractions) at low dose, and for constipation with abdominal pain (inhibiting smooth muscle contractions) at high dose.

A simple theoretical model can explain the hormetic effects of Chinese herbal medicine or herbal compound(s). Firstly, Chinese herbal medicine/herbal compound(s) have polypharmacology properties. It may act on more than one signaling pathways to regulate the outcome of a single biological function. The simplest case is, it acts on two pathways: one has stimulatory effect on the biological function, while the other has inhibitory effect (Figure 1B). Secondly, the activation potency of herbal medicine/herbal compounds on the two pathways, are quite different. The stimulatory pathway could be activated by herbal medicine/herbal compound(s) at very low dose, and become saturated at the high dose. In contrast, the inhibitory pathway could only be activated at relatively high dose, and will be saturated at very high dose (Figure 1C). Thirdly, the combined effect could be simply the sum of output from stimulatory- and inhibitory pathway. Furthermore, the absolute amplitude of inhibitory effect should be greater than that of the stimulatory effect. Taken together, we can observe the hormetic response as drug dose increases: stimulatory effect at the low dose, and inhibitory effect at the high dose (Figure 1C). The numeric simulation results presented here suggest that the hormesis of Chinese herbal medicine/herbal compound(s) could be quantitatively studied.

For this simple model, a number of complex factors may complicate the study of hormetic effects of Chinese herbal medicine. For example, the variable content of herbal components (due to planting conditions, preparation processes, etc.) will affect the final amount of active compound(s) acting on the stimulatory- and inhibitory pathways. The interactions among compounds may also enhance or weaken the isolated actions of them on the pathways. The conditions of patient, whereas human or

animal, may alter the expression of molecular targets and/or connections within pathways, thus make the hormetic effects are hard to predict. The researchers must carefully control these factors during the investigation of hormesis of Chinese herbal medicine.

In conclusion, using Chinese herbal medicine at different doses to treat distinct diseases are common in TCM clinical practice, while the concept hormesis provides a useful framework to study the underlying mechanisms. Investigating hormesis of Chinese herbal medicine will not be just descriptive, but also quantitative, by utilizing proper theoretical models. In the future, outcome from these studies may help to form new rules for better application of Chinese herbal medicine in clinical practice. More importantly, it can help to develop new strategy for disease management and new drug discovery.

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