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Hormesis as a mechanistic approach to understanding herbal treatments in traditional Chinese medicine

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ABSTRACT

Traditional Chinese medicine (TCM) has been long practiced and is becoming ever more widely recognized as providing curative and/or healing treatments for a number of diseases and physiological conditions. This paper posits that herbal medicines used in TCM treatments may act through hormetic dose-response mechanisms. It is proposed that the stimulatory (*i.e.*, low dose) and inhibitory (*i.e.*, high dose) components of the hormetic dose response correspond to respective "regulating" and "curing" aspects of TCM herbal treatments. Specifically, the "regulating" functions promote adaptive or preventive responses, while "curing" treatments alleviate the clinical symptoms. Patterns of hormetic responses are described, and the applicability of these processes to herbal medicines of TCM are explicated. It is noted that a research agenda aimed at elucidating these mechanisms and patterns would be expansive and complex. However, we argue its value, in that hormesis may afford something akin to a Rosetta Stone with which to interpret, translate, and explain TCM herbology in ways that are aligned with biomedical perspectives that could enable a more integrative approach to medicine.

1. Introduction

Traditional Chinese medicine (TCM) has been practiced for thousands of years and is widely recognized as providing curative and/or healing treatments for a number of diseases and physiological conditions (Chen, Lin, Chen, & Yao, 2013; Gao, Inagaki, Li, Kokudo, & Tang, 2013; He, Pan, Yao, & Zhang, 2016; Liu et al., 2014; Wu & Dong, 2015). During the long history of TCM, TCM practitioners emerged, such as Bian Que. (401–310 BCE) in the Warring States period, who was lauded as a "legendary doctor." Other practitioners were noted for their innovative and inventive practices. For example, Hua Tuo (140–208) during the Eastern Han Dynasty used an herbal concoction called máfèisàn to practice anesthesia, and Li Shizhen (1518–1593) during the Ming Dynasty was known for his highly influential book *Compendium of Materia Medica* (*Bencao Gangmu* in Chinese). Stemming from this history, in its present form, TCM continues to be used in the treatment of a variety of diseases. For example, artemisinin, extracted from the herb *Artemisia annua*, is employed against malaria (Hsu, 2006) and polysaccharide peptide isolated from *Coriolus versicolor* is used for cancer treatment in China (Chan & Yeung, 2006; Wong et al., 2005). Because of its historical and cultural role in China and its potential to enhance health and general well-being, TCM is widely accepted within contemporary China and is growing in international popularity (Li & Zhang, 2013; Zhang, Xie, Zhang, Kong, & Li, 2013). For instance, approximately 85% of clinical practitioners in Japan use Kampo, the Japanese term for TCM (Motoo, Seki, & Tsutani, 2011), and TCM is becoming more widely practiced in many Western countries, including the United States (Qi et al., 2013; Scheid, Tuffrey, Weijburg, Bovey, & Ward, 2015).

However, TCM treatment, especially the use of herbal medicines, is complicated and variable. In general, TCM often employs combined prescriptions of multiple herbs for disease treatment. The TCM book *Treatise on Cold Injury* (*Shanghan Lun*) compiled by Zhang Zhongjing (150–219 CE) recorded 112 herbal prescriptions that collectively contained 536 different types of herbs, nearly five on average (Wang et al., 2012). Each of these herbs would be expected to contain multiple active ingredients that were often unknown. Therefore, a prescription with multiple herbs may contain numerous unidentified agents. Moreover,

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the variation in the proportion of the herbs may alter the clinical effectiveness of treatment mixtures (Dong et al., 2006; Wang et al., 2012). This is seen in the use of *Coptis Rhizoma* (Tang et al., 2009) and *Euodiae Fructus* (Pan, Bligh, & Smith, 2014), which, because of their antibacterial and antiviral activities, are traditionally used in combination to treat gastric diseases. Different therapeutic ratios of the two herbs were recommended in various medical texts (Qian & Yang, 2014; Tan, Han, Guan, & Wang, 2006; Zhao et al., 2009), amongst which the ratio of 6:1 manifested the most effective curative response (Qian & Yang, 2014). In addition, the mutual dependence between various components can also affect the overall therapeutic outcomes of an herbal prescription. An example of this is seen in the combination of *Coptis Rhizoma* and *glycyrrhiza*, in which the berberine and glycyrrhizin in the two herbs can react in the decoction (*i.e.*, formation of the liquor resulting from concentrating a substance by heating or boiling, especially in a medicinal preparation from a plant root), forming insoluble products and resulting in a loss of therapeutic potential (Kamigauchi, Kawanishi, Sugiura, Ohishi, & Ishida, 2016; Noguchi, 1978).

As a result of such complexity and variability, the combination of different herbs (which is referred to as compatibility) in TCM treatment procedures remains based on an empirical set of principles that is referred as Monarch, Minister, Assistant, and Guide (see Table 1 for definitions) (Chen, Pei, & Lu, 2013; Shaw, Lin, & Tsai, 2012). Doses of herbal medicines are prescribed according to the pharmacopeia and doctor's personal experience (Zhong, Deng, Chen, Chuang, & He, 2013), which is potentially subjective and often non-quantitative, and this can create considerable uncertainty. This lack of theoretical guidance and objective criteria for herb doses in TCM treatment often prompts serious concerns about the reproducibility of therapeutic treatments and can negatively impact dose, effect, and mechanism studies.

Unlike TCM, Western medicine is typically highly quantitative, and treatments tend to be more reproducible, at least to some extent, because the components of medicines used are identified and their doses in clinical practice are defined and stipulated (Fig. 1A). In addition, these treatment doses are typically related to published dose-response relationships, which quantitatively describe the effectiveness of differing amounts of an administered medicine. Western medicine has become the mainstream therapeutic practice worldwide because it is supported by these objective and reproducible research methods (Fig. 1A).

With growing interest in and the use of TCM within Western clinical practices, it becomes important to develop a more salient framework for characterizing which components of certain TCM herbal medicines are active and the doses and mechanisms that subserve such activity (Giordano, Boatwright, Stapleton, & Huff, 2004). Toward this end, we propose a dose-response methodology to guide herbal doses in TCM treatment that is based on hormesis. On the basis of both extensive literature in hormesis and dose-effect patterns of herbal medicines, we posit that hormesis may mediate the therapeutic effects of many herbal medicines used in TCM in ways similar to which hormetic effects have been shown to be operative in the effects of a variety of Western medicines (Calabrese, 2008a, 2008b, 2008c, 2008d).

2. Hormesis has been widely implemented in Western medicine

Hormesis is a biphasic dose-response model that has received increased interest in the biological, biomedical, and therapeutic sciences in recent years (Calabrese, 2013; Calabrese, Dhawan, Kapoor, Iavicoli, & Calabrese, 2016; Calabrese, Iavicoli, & Calabrese, 2013). While the traditional dose-response model displays an S-shaped curve (Fig. 2A), the hormetic model often displays a “J-shaped” (or inverted “U-shaped”) curve, depending on the endpoint graphed, with both stimulatory and inhibitory phases (Fig. 2B).

As emphasized nearly a century ago by Alfred J. Clark (Waddell, 2010), the dose-response relationship has been and remains a central risk assessment concept and tool in Western biomedicine's approach to determining the “safe” and “hazardous” dosages and levels of pharmacological agents and toxic substances (Calabrese & Hayes, 2014). The core concept underlying the dose-response properties that became known as hormesis was first established by Schultz (1888), based upon studies of several disinfecting agents using a yeast-based model (Schultz, 1888). Similar findings were reported in other microbiological models and in plant and insect models over the next several decades (Heald, 1896; Hotchkiss, 1923; Jensen, 1907). The term hormesis was first introduced in 1943 by Southam and Ehrlich to describe the capacity of extracts of the red cedar tree to stimulate the growth and metabolism of multiple fungi strains (Southam & Ehrlich, 1943). The expansion and acceptance of the hormesis concept within the biomedical and medical literature was initially impeded because of an (inappropriate) attempt by Schulz to base putative effects of homeopathic

Table 1
Interpretations of some terms.

Terms	Interpretation
Channels and collaterals	A network of passages, through which energy, Qi and blood putatively circulate.
Dampness	Dampness is an abnormal state of the body's energy that leads to a pathological accumulation of fluid-type stuff
Dryness	Dryness is a pernicious influence that has deleterious effects on the body's moistures, with syndromes including constipation, thirst, headaches, and excessive sweating.
Fire	One of the six pernicious influences in TCM, which causes syndromes such as high fever, burning heat sensation of the skin, irritability, and forceful and rapid pulse.
Monarch, Minister, Assistant and Guide	An empirical rule to determine the combination of different herbs in TCM treatment procedure. According to this rule, a typical TCM formula (multi-herb prescription) contains at least four herbs that play differing roles as the Monarch, Minister, Assistant, and Guide, respectively. The Monarch is primarily responsible for the therapeutic effect, and the Minister is used to enhance the therapeutic effect of the Monarch, while the role of the Assistant is to neutralize the side effects of the Monarch and Minister, and the role of Guide is to enhance the capacity of the other herbs to reach sites of effect. According to TCM practice, the Monarch herbs are usually administered in large(r) doses, while the other herbs are administered in small doses.
Perpetual motion	TCM holds that all matters, including the whole of nature, are dynamic. The human body is an integral whole, within which various tissues and organs are in perpetual motion and working together to keep the body functioning.
Qi	The vital substance that comprises the human body and maintains life activities and physiological functions of the viscera.
Wind	Wind is a pathogenic factor that causes a common cold, with symptoms of headache, nasal obstruction, itching or sore throat, *etc.*
Yin and Yang	Descriptions of complementary, interconnected, and interdependent forces in the natural world. TCM maintains that Yin and Yang in the human body are kept in balance under normal conditions, which reflects a dynamic equilibrium of physiological processes. The imbalance between Yin and Yang, *e.g.*, excess or deficiency of Yin (and/or Yang), may cause disease.
Zang-Fu	Zang and fu are Chinese terms for the human organs. In the human body, there are five zang organs, namely the heart, lung, spleen, liver, and kidney, and six fu organs, namely the gall bladder, stomach, large intestine, small intestine, urinary bladder, and sanjiao (three areas of the body cavity). Brain functions in TCM are dispersed and maintained between the five zang organs. As a consequence, brain diseases are considered as systematic disease, and their treatments suggest a normalization of activity and the functional interactions between the five zang organs, which reproduces a biological model based on chaos theory.