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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 má-fěisàn 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.

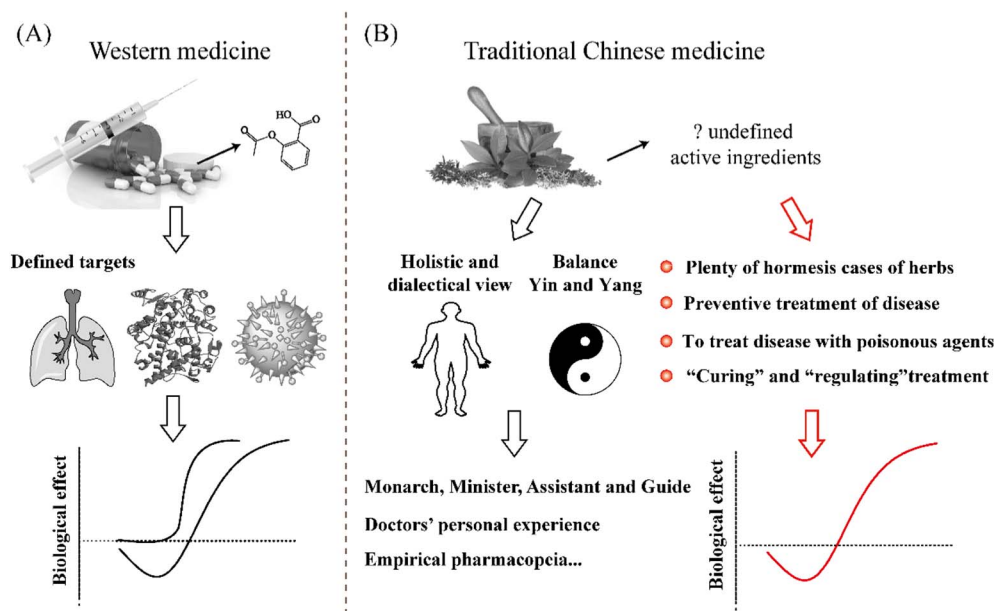


Fig. 1. Comparison of Western medicine and TCM in terms of the dose determination in clinical practices. (A) In Western medicine, the active components of a medicine and their action targets (organs, proteins, or pathogens) are usually defined. The doses of medicines are based on dose-response curves that are supported by abundant experimental and clinical data. (B) TCM treats the disease from a holistic and dialectical view and aims to restore a balance between Yin and Yang. The active ingredients in the herbs are usually undefined. The doses of the herbs are generally based on empirical rules, doctors' personal experience, and empirical pharmacopeia. On the basis of studies of both a range of hormetic cases in TCM and the hormetic mechanisms that are involved in actions and effects of various herbal medicines, it is proposed that hormesis can provide a guide to interpret the mechanisms and functions of the herbal medicines.

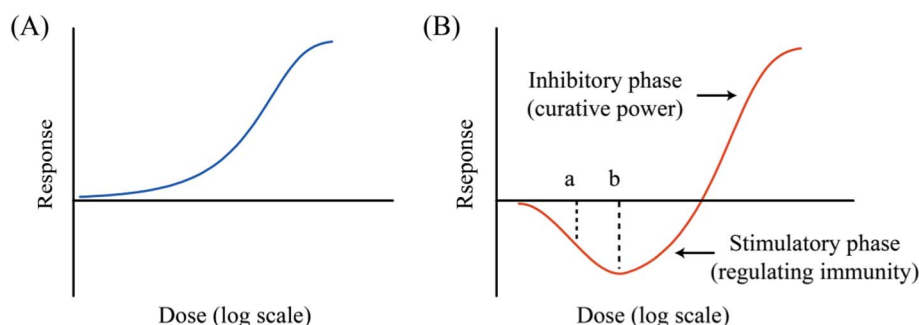


Fig. 2. Dose-response curves. (A) The traditional dose-response model displays an S-shaped curve. According to this S-shaped curve, a functional threshold exists, below which no response can be reliably observed, and the response increases monotonically with dose until a ceiling/maximum response is achieved. (B) The hormetic dose-response model displays a "J-shaped" curve, with both the stimulatory and inhibitory phases.

treatments upon hormetic principles (Calabrese, 2015a). It was not until recently that these historical impediments were addressed and rectified (Calabrese, 2015b; Calabrese & Jonas, 2010). With the steady growth of reported hormetic phenomena in the literature (Calabrese & Blain, 2011), the hormesis concept has become more broadly accepted within both the scientific and regulatory communities and is now included in leading textbooks in toxicological and pharmacological sciences (Calabrese, 2009; Calabrese & Hayes, 2014; Eaton & Klaassen, 2003).

A large body of evidence has indicated that the medicines used in Western clinical treatment may have the potential to induce hormesis (Calabrese, 2008d). For medicines that are designed for killing harmful organisms or tumor cells, the hormetic effects are undesired and could cause harm in patient treatment. While in other cases, the hormetic effects could be beneficial and are utilized for disease treatment. For example, anxiolytic drugs, anti-seizure drugs, and drugs for Alzheimer's disease manifest the hormetic dose-response modes, with the low dose stimulation being key to their curative effects.

3. Hormesis in TCM treatment

3.1. Hormesis of TCM herbs in various in vitro models

Hormetic dose-responses are common to the TCM field. The extracts of many herbs, either individually or combined, can induce hormetic responses in various models including animal and human cells (see Table 2 and supporting information). In general, hormetic responses often result in effects that can be important to a mechanistic understanding of certain TCM herbal medicines. For instance, several herbs,

including *Drynaria fortunei*, *Eupolyphaga sinensis*, *Carthamus tinctorius*, and *Pheretima aspergillum*, are beneficial to human bone cells at low concentrations, with stimulatory effects on osteoblast proliferation (Fu, Chen, Chen, & Yao, 2014; Fu, Sheu, Chen, Chen, & Yao, 2015; Lin et al., 2002; Sun, Thériault, & Anderson, 2004; Wang et al., 2014). In addition, Schisandrin B, extracted from *Fructus Schisandrae* showed cytoprotective effects against oxidative stress at low concentrations (Lam & Ko, 2012), and quercetin extracted from *Levisticum officinale* can prevent the formation of cancer cells at low doses (1–40 μ M) (Vargas & Burd, 2010). However, hormetic responses can also be harmful. As reported by Bao et al. (2015), berberine extracted from *Rhizoma coptidis* at low doses (1.25–5 μ M) can stimulate tumor cell proliferation, which can have undesirable implications and consequences in the clinical treatment of cancer.

Herb-induced hormetic responses can also occur within a preconditioning model (Calabrese et al., 2007). As reported by Qi, Han, and Rong (2012), the preconditioning effect(s) of mild Z-ligustilide from *Rhizoma chuanxiong* and *Angelica sinensis* protect PC12 cells from oxygen/glucose deprivation-induced cell death (i.e., in an in vitro model of stroke-related cell insult). Westerheide et al. (2004) also demonstrated that celastrol extracted from *Tripterygium wilfordii* protects HeLa and SH-SY5Y neuronal cells from subsequent exposure to lethal heat stress, decreased apoptotic cell death, and a resulting decrease in total cell death.

3.2. "Preventive treatment of disease" through hormetic mechanisms

An important aspect of TCM practice is known as "preventive treatment of disease" or "casual treatment" (Liang & Yin, 2010; Yin,

Table 2*In vitro* hormesis cases of TCM herbal medicines.

Herbal medicines	Active ingredients	Findings	Reference
<i>Fructus schisandrae</i>	Schisandrin B	Schisandrin B showed cytoprotective effects at low concentrations and cytotoxicity at high concentrations.	(Lam & Ko, 2012)
<i>Rhizoma coptidis</i>	Berberine	Berberine at low doses (1.25–5 μ M) promoted cell proliferation, while higher doses (10–80 μ M) inhibited cell proliferation.	(Bao et al., 2015)
<i>Levisticum officinale</i> , <i>Anethum graveolens</i> , etc.	Quercetin	Quercetin was beneficial in cancer prevention in the concentration range of 1–40 mM while showing beneficial anti-tumor effects at higher doses by exerting cytotoxic effects at concentrations > 40 mM.	(Vargas & Burd, 2010)
<i>Prunus</i> , <i>Carthami Tinctorii</i> , <i>Paeoniae rubra</i> , <i>Angelicae sinensis</i> , <i>Ligustici chuanxiong</i> , <i>Rehmanniae praeparata</i>	NA	The herb mixtures protected rat brain against ischemia and reperfusion-induced injury in an inverted U-shaped mode.	(Li et al., 2014)
<i>Rhizoma chuanxiong</i> , and <i>Angelicae sinensis</i>	Z-ligustilide	Mild Z-ligustilide preconditioning protected cells by stimulating moderate ROS production, but higher concentrations of Z-ligustilide could be toxic over a prolonged period of time due to massive ROS production.	(Qi et al., 2012)
<i>Genista tinctoria</i>	Genistein	Genistein presented a biphasic regulation of prostate cancer growth and metastasis.	(Touny & Banerjee, 2009)
<i>Drynaria baronii</i> , <i>Angelica sinensis</i> , <i>Cornus officinalis</i>	NA	The three herbal extracts at lower concentrations induced low level (0–37.2% of the maximum response) growth stimulation on both normal and tumor cells and exerted hormetic effect against RAW264.7 cells.	(Chu et al., 2009; Chu, Hashimoto, Satoh, Wang, & Sakagami, 2009)
<i>Tripterygium wilfordii</i>	Celastrrol	Celastrrol exerted cytoprotective hormetic actions against subsequent exposures to lethal stress in HeLa cells and SH-SY5Y neuronal cells by activating the expression of heat shock proteins.	(Westerheide et al., 2004)
<i>Hypericum perforatum</i>	Hypericin	Hypericin can promote neuronal plasticity and stress resistance by a hormesis-based mechanism.	(Mattson & Cheng, 2006)
<i>Rhizoma cyperi</i> , <i>Poria coccus</i> , <i>Pericarpium aurantii</i> , <i>Radix Polygalae</i> , <i>Fructus Schisandrae</i> , <i>Radix Glycyrrhizae</i> , etc.	NA	Pretreatment with the extracts of these herbs prevented H ₂ O ₂ - and ZnCl ₂ -induced cell damage in H9c2 cardiomyocytes, which seems to act through a hormetic mechanism.	(Kim, Kwon, Cho, & Lee, 2006)
<i>Curcuma longa</i>	Curcumin	Curcumin exerted hormetic effects on proteasome activity and heat-shock protein synthesis in human keratinocytes.	(Ali & Rattan, 2006)
<i>Rhodiola rosea</i> , <i>Eleutherococcus senticosus</i> , <i>Schisandra chinensis</i> , etc.	NA	These herb extracts induce stress protection mechanisms, which is likely a type of hormesis.	(Panossian & Wikman, 2009)
<i>Soybean</i>	Glyceollin I	Glyceollin I extends yeast life span at low (nM) doses, while reducing life span and inhibiting yeast cell proliferation at higher (μ M) doses.	(Liu, Wu, Feng, Yang, & Huang, 2014)
<i>Panax notoginseng</i>	Ginsenosides	Ginsenosides induced the transcription of stress genes and increased the synthesis of stress proteins in normal human keratinocytes and dermal fibroblasts.	(Rattan, Kryzch, Schnebert, Perrier, & Nizard, 2013)
<i>Corydalis yanhusuo</i>	dl-Tetrahydropalmatine	dl-Tetrahydropalmatine at low dosages acts as an anxiolytic in mice (0.5–10 mg/kg), while causing anxiety at high(er) doses (30 and 50 mg/kg).	(Leung, Zheng, Huen, Law, & Xue, 2003)
<i>Pheretima aspergillum</i>	NA	The extracts at 500 μ g/mL–6 mg/mL significantly enhanced osteoblast proliferation, while at > 6 mg/L significantly inhibited osteoblast proliferation.	(Fu et al., 2014)
<i>Radix Astragali</i> and <i>Radix Angelicae Sinensis</i>	NA	The two herbs mixed at 5:1 and at 1000 μ g/mL significantly increased the number of osteoblasts, intracellular ALP levels, and nodule numbers.	(W. Wang et al., 2014)
<i>Drynaria fortunei</i> (Kunze) J. Sm	propinqualin	Lower concentrations of the herb extract had positive effects on osteoclast proliferation, survival, and resorptive activity, but higher doses of extract proved detrimental to osteoclast and osteoblast survival.	(Sun et al., 2004)
<i>Geriforte</i>	NA	Pretreatment with 10 mg/kg of Geriforte (about 1/475th of the LD ₅₀ dose) can protect the mice from γ -radiation-induced injuries.	(Jageti & Baliga, 2004)
<i>Plantago major</i> and <i>Plantago asiatica</i>	NA	<i>P. major</i> and <i>P. asiatica</i> at low concentrations (< 50 μ g/mL) showed beneficial effects on immunomodulatory activity, enhancing lymphocyte proliferation and secretion of interferon- γ , while at high concentrations (> 50 μ g/mL) presented the opposite effects.	(Chiang, Chiang, Chang, & Lin, 2003)
<i>Naringin</i>	NA	The naringin (100 ng/mL–50 mg/mL) exhibited stimulatory effects on the proliferation of osteoblasts, osteoclast activity, and nodule formation.	(Chen et al., 2013)
<i>Erxian</i> Decoction: <i>Rhizome Curculiginis</i> , <i>Herba Epimedii</i> , <i>Radix Morindae officinalis</i> , <i>Rhizome Anemarrhenae</i> , <i>Cortex Phellodendri</i> , and <i>Radix Angelicae sinensis</i>	NA	<i>Erxian</i> Decoction stimulated proliferation of osteoblasts and osteoprotegerin secretion.	(Sze et al., 2012)

2007). The goal of preventive treatment is to protect humans from disease by “dealing with premorbid conditions” (Liang & Yin, 2010) or “handling diseases in their germination and preventing them from exacerbating” (Xu, Luo, & Xia, 2009). In TCM, “preventive treatment of disease” is deemed to be a better orientation to human health than curing disease after the occurrence of clinical signs and/or symptoms. Various methods have been developed for facilitating “preventive treatment of disease”; for example, the major *bupleurum* decoction, as well as *lignum dalbergiae odoriferae*, and *Santalum album* may reverse impaired glucose tolerance in pre-diabetic conditions, thus preventing the onset of this condition at an early stage (Pan, Zhou, & Tong, 2008). Another example is the use of herbal plasters that contain *Semen brassicae*, *Rhizoma corydalis*, *Euphorbia kansui*, and *Asarum sieboldii* for the prevention of bronchial asthma through the enhancement of immune function, e.g., activation of the hypothalamic-pituitary-adrenal axis or regulation of T-lymphocyte subsets and serum IgE level (Zang, Xuan, & Feng, 2009).

The “preventive treatment of disease” concept appears similar to ischemic preconditioning (Hua & Sun, 2008), in which a prior ischemic exposure to a herbal mixture can protect cells from subsequent, more massive ischemic injury, e.g., ischemic stroke. Many forms of preconditioning are likely to act through hormesis-based mechanisms (Calabrese, 2016a, 2016b), and the hormetic concept may be instrumental to many of the effects of herbal medicines used in TCM treatment (see Table 2).

4. Stimulatory and inhibitory aspects of hormesis correspond to “regulating” and “curing” in TCM

4.1. Curing and regulating treatment in TCM

“Curing” and “regulating” aspects of interventions are deemed to be equally important in TCM. Specifically, a “curing” treatment aims to alleviate or remove the symptoms of a disease, whereas a “regulating” treatment means to enhance the immunity against disease and restore the normal physiological functions. The classical theory of, and approach to, TCM was developed two thousand years ago, and while more recent developments under the Mao government altered certain constructs, even the current form of TCM remains distinct from much of the regnant Western biomedical view of, and orientation to, human bodily function, the nature of health and diseases, and the role and activities of medicine as a profession and practice (Giordano, Boatwright, Stapleton, & Huff, 2002; Giordano & Jonas, 2007). TCM sees the human body as an integrated whole, which experiences functional fluctuations that reflect a dynamic balance of the internal and external environments, and the illness is deemed as a manifestation of underlying disharmony. Regulating treatments aim at balancing “Yin and Yang,” normalizing the activity of Zang-fu organs, and stabilizing Qi (see Table 1). All of these treatments aim at restoring a balance in and between physiological systems toward the end of promoting, sustaining, and/or restoring normal function (Zhang & Li, 2015). TCM places considerable emphasis upon both “regulating” and “curing,” and “regulating” treatments can be considered both preventive and synergistic to more curative approaches.

4.2. Relationship between hormesis and the curing and regulating treatment

In TCM, there is a well-known construct: “to treat the malignant disease with poisonous agents (Yi Du Gong Du).” As noted by the classical TCM volume *Huangdi Neijing* (Yellow Emperor's Inner Canon), practitioners are advised “to cure a disease, one should use a poison.” Toward these ends, herbs with toxic effects are frequently employed in TCM treatments. For instance, *Leigongteng* (*Tripterygium wilfordii* Hook F.), historically recognized as a toxic herb, has been used in TCM to “dispel pathogenic wind” (Table 1), “remove dampness,” and relieve arthritis.

In some cases, herbal medicines with toxic potentials are capable of inhibiting pathogenic factors and thereby the development of diseases. For instance, herbal medicines with active components that show direct killing effects on tumor cells are employed for anticancer treatment (Hsiao & Liu, 2010). For the purpose of “curing,” these herbal medicines should be given at high doses that induce inhibitory effects. Therefore, the “curing” treatment in TCM is associated with the inhibitory phase of the hormetic model (Fig. 2B). While in other cases, herbal medicines with toxic potential at low doses could exert stimulatory actions on various physiological functions through which the “regulatory” effect is achieved. This is analogous to the hormetic concept that a substance that is beneficial at low doses can be harmful at high doses, and re-iteratively, the stimulatory and inhibitory aspects of the hormetic dose response appear to correspond to “regulating” and “curing” effects, respectively, of herbal medicines that are used in TCM (Fig. 2B).

The relationship of hormesis to TCM concepts of “regulating” and “curing” treatments for a diverse set of diseases is likely to be complex and relatively specific, especially if and when considered within the “Monarch, Minister, Assistant, and Guide” system. For example, administration of a low(er) dose of an herbal medicine (i.e., a Minister that is usually given at low doses) may be useful in upregulating adaptive mechanisms, such as immune surveillance. In this situation, excessive dosing of the Minister treatment could cause harm/damage. In contrast, a high dose of a toxic chemotherapeutic agent that destroys tumor cells could serve as a Monarch. Moreover, it is possible that a Monarch herb might be immunostimulatory at lower doses. It is still uncertain how other TCM herbal treatments employed under the “Monarch, Minister, Assistant, and Guide” framework (e.g., Assistant, Guide) act to exert effect(s). This remains speculative, yet we claim that this perspective may allow for further research on hormetic mechanisms of TCM herbal medicines and their use in practice, which could foster improved assessment, understanding, and integration of TCM approaches within medical care.

5. Quantifying doses in TCM treatment based on hormesis

5.1. Current method for quantifying doses in TCM

The effectiveness of a TCM formula is dependent upon the doses of the herbal medicines. At present, the doses of herbal medicines that are clinically used are prescribed according to the “doctors' personal understanding on the pharmacopeia” (Huang et al., 2011; Li et al., 2012; Song, Yang, & Chen, 2013), a combination of empirically objective and subjective decision-making that is illustrated in Fig. 1B. However, this process relies heavily upon the doctors' personal experience and can reflect varying degrees of ambiguity, uncertainty, and lack of experimental data. Thus, to date, a scientific method for determining dose response parameters and effect(s) of various TCM herbal medicines is lacking.

5.2. Hormesis is a scientific basis to determine herb doses

Herein, we propose that hormetic mechanisms may provide a scientific basis both to explain the effects of TCM herbal treatments and determine doses of the herbal medicines used in TCM. The hormetic dose response has two phases, stimulation and inhibition, that correspond to the “regulating” and “curing” aspects of TCM treatment, respectively. Thus, we argue that clinically used herbal doses should be determined by fully considering hormetic effects.

In clinical practice, TCM treatment may use low(er) doses of herbal medicines to sustain wellness and prevent the onset of certain diseases and conditions. However, with the onset of disease, high(er) doses of herbal medicines are often employed to elicit a “curing” effect and then low(er) doses of herbal medicines for “regulating” functions through the upregulation of adaptive responses (Feng, Pang, & Ye, 2008; Tong, Dong, Chen, & Zhen, 2012).

In “regulating” treatments, herbal medicines are commonly given at relatively low doses. However, the active ingredients in many herbs are in low concentrations and in some cases may be too low to affect maximum stimulatory effects (S. Wang et al., 2012). As shown in Fig. 2B, the herbs at dosage *a* can induce beneficial effects through hormesis but are not at concentrations that induce maximum effects. The doses of the herbal medicines should be somewhat higher (i.e., given at dosage *b*) to achieve an optimized stimulatory/regulation effect (Fig. 2B). This “optimal” dosage *b* is called a “superhigh” dose in TCM as it is notably higher than the doses routinely used in clinical treatments. The TCM literature provides examples of the effectiveness of using such “super high”/optimal dosages of herbal medicines (see Chen & Yang, 2010; Liu & Zhang, 2016; Yang et al., 2011; Zhang, 2016 for specific cases).

5.3. Herb doses should be adjusted according to diseases

An herbal medicine may exert differing effects (i.e., inhibition and stimulation) at high and low dosages because of its hormetic potential. Moreover, the active ingredients in a certain herbal medicine may be differentially effective in the treatment of certain diseases. Therefore, a dose of an herbal medicine may induce inhibition in treating one disease and induce stimulation in treating another. Simply put, an herbal medicine may play different roles in treating different diseases. As noted by the TCM practitioner Xu Lingtai (1693–1771), “there must be a main prescription for a disease, and one prescription must have a main herb” (Li, Wang, Zhang, Zhang, & Yan, 2014).

Each TCM formula is composed of several (or even dozens of) herbal medicines, and as noted, the components in an herbal medicine may have diverse biological activities and potencies and can induce varying (and sometimes opposite) effects. Those that are abundant and have high bioactivity may be effective at relatively lower doses, while those that are at low concentration and have low bioactivity may only be effective at higher doses. Hence, at a given dose, some of the components in the herbs may not necessarily be effective. Furthermore, the components in an herbal medicine or herbal formula may have synergistic effects in the hormetic zone (Calabrese, 2008b). However, synergy within a hormetic zone may not evoke a maximum response. The hormetic response is modest, and thus, synergistic effects usually will not induce a response > 60% of control but instead will enable a lower dose of the mixture(s) that cause the maximum response.

5.4. Herb doses should be based on syndrome differentiation

One characteristic of TCM is that the treatment is based on a system of syndrome differentiation known as *Bian Zheng Lun Zhi*. The TCM syndrome represents the manifestations of diseases at particular stages, which implies that as the disease develops, the syndrome(s) may, and often will, change from one type to another (Kou, Zou, & Chen, 2013), and accordingly, various methods may be required and involved at different stages of a disease.

Treatments based on syndrome differentiation utilize a multi-step process that employs different herbal medicines (doses) to engage adaptive and/or healing/restorative mechanisms. Hormetic processes may act to mediate such healing/restoration processes. For instance, the dose of astragalus in an herbal formula is usually 30 g during the early period of a disease, while it turns to 15 g after using high doses for a certain time (usually a course of treatment), or in some other cases, it is replaced by other herbs that have the similar (but weaker) function. The decrease in the doses of astragalus can change its effects from inhibition (at high doses) to stimulation (at low doses) and results in enhancement on the immunity of the human body, which further controls the disease and benefit the human health.

The use of changing treatments over a distinct time, as in TCM approaches that are based on syndrome differentiation, suggests the possibility that a timed treatment process could facilitate multiple/

sequential stages of physiological process that are involved in the sustenance or recovery of normal function. However, it is important to note that hormetic responses can be elicited, and often occur, as part of multiple stage processes of physiological regulation and repair. Therefore, we opine that this (at least theoretically) prompts consideration of hormesis as being viable and of value to both explain and elicit putative mechanisms of TCM treatments that are based on syndrome differentiation.

There is considerable published experimental data elucidating hormesis-mediated/enhanced processes and clinical data demonstrating effects of particular TCM herbal medicines, and we assert that in some instances, such findings could—and should—be framed within a dose-response and temporally oriented framework. In this light, we herein posit a limited but functional framing and integration of hormetic mechanisms and syndrome differentiation-based herbal treatments, which, while speculative, could provide a basis and plan for future research.

5.5. Herb doses are affected by inter-individual variability

In addition, a number of biological factors, including age, sex, genetic composition, nutritional status, and preexisting disease conditions, may influence susceptibility to hormetic effects of various chemicals, with inter-individual variation ranging up to two to three orders of magnitude (Calabrese, 1985). For example, drugs used in Western medicine to treat hypertension vary widely based upon these factors: effective doses of reserpine vary by 8-fold, ranging from 0.125 mg to 1.0 mg per day, while the effective doses of guanethidine vary by 50-fold, ranging from 10 mg to 500 mg per day (Xu, 1995). Given such variation, doses used in Western medicine treatment are routinely adjusted according to the weight, sex, and age of individual patients.

In TCM, “individualization” of patient treatment is also emphasized. Herbal doses are determined in consideration of each patient's particular condition(s) and syndrome differentiation. Important to any such consideration is that the width of the hormetic zone (stimulatory phase) can be quite variable, ranging from 1/20th to 1/1000th of the traditional threshold (Calabrese, 2015b), and it is difficult (if not impossible) to estimate the concentration of a chemical (or herb) that induces the greatest stimulation solely by the four main diagnostic TCM methods: observation, listening, interrogation, and pulse analysis. Additional methods are needed to more accurately evaluate individual variability in the response to herbal medicines and to more effectively prescribe doses of TCM herbal medicines so as to operate within the hormetic zone. Toward such ends, we propose the need to establish guidelines for herbal dosing according to (1) evaluation and explication of the active ingredients in specific herbal medicines; (2) fuller elucidation of the mechanisms, actions and effects of these chemical components, both alone and in combination; and (3) clinical data that enable more thorough consideration of individual patient factors that can affect pharmacokinetic and pharmacodynamics functions and hormetic properties of the various chemical components of herbal medicines used in TCM.

6. Discussion

TCM herbal treatment is frequently questioned for lack of rigorous scientific evidence of its effectiveness, so significant effort is required for the popularization of TCM applications. However, the study on TCM is currently challenging for researchers because the treatments are usually complex, and the TCM theories are vastly different from those of modern Western medicine. This paper has attempted to reconcile and integrate TCM with modern Western medicine by proposing that hormetic mechanisms may be (at least partly) involved in and/or subserve the actions and effects of many of the herbal medicines used in TCM practice. Our approach is premised upon studies of both a range of chemical constituents and patterns of effects of herbal medicines used

in TCM and those of hormetic mechanisms that are involved in actions and effects of various chemicals.

These experiments have often included endpoints of potential biomedical and/or clinical relevance. Such studies of TCM herbal medicines and hormetic processes have often included several concentrations, permitting an assessment of a very broad range of dose-response relationships, including concentrations/doses below estimated traditional threshold responses. Although a number of TCM herbal medicines exhibit biphasic hormetic dose responses, it will be important to repeatedly and reliably demonstrate these effects during both pre-clinical and clinical studies as has been done with several (classes of) agents in the Western pharmacopeia (Calabrese, 2008a, 2008b, 2008c).

At present, a lot of work has been done to recognize and separate the active components in herbal medicines. Many of the mechanistic studies have been based on these single agents. However, it must be noticed that the compounds in herbal medicines often modulate and modify the effects of the active ingredient in the herb, so an extracted active ingredient from the herb alone may not ensure the therapeutic effect in clinic. Therefore, a complete evaluation of putative hormetic mechanisms and processes that may be operative in TCM will require significant investment of research time and effort, given the considerable heterogeneity of chemical constituents present in TCM herbal medicines and the use of such herbs in combination and in differing protocols for differing stages of particular diseases.

To be sure, numerous patterns of hormetic mechanisms and effects are possible and probable for TCM herbal medicines and their chemical components, and therefore, their use in and against specific pathologies may each and all require distinct evaluation. It may be that mechanisms and effects are peculiar to select agents acting at defined doses in individuals of particular genotypes and/or phenotypes, under distinct physiological and environmental conditions. Arguably, acquiring such information will be ever more important, given the recent calls for both precision medicine (<https://www.whitehouse.gov/precision-medicine>) and enhanced appreciation of traditional, culturally relevant healthcare practices (https://www.who.int/medicines/publication/traditional/trm_strategy). It is in this light that the elucidation and understanding of hormetic mechanisms may provide something of a “Rosetta Stone” with which to gain insight to the pharmacological actions and effects of various chemicals of TCM herbal medicines. In addition, like the Rosetta Stone, hormesis may provide a guide with which to interpret these agents' mechanisms and functions and, in this way, enable relation and translation of this knowledge to principles, perspectives, and practices that can be used in a more truly “integrative” medicine.

Conflict of interest statement

The authors declared that they have no conflicts of interest to this work. We have no financial and personal relationships with other people or organizations that can inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled “Hormesis as a Mechanistic Approach to Understanding Herbal Treatments in Traditional Chinese Medicine”.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pharmthera.2017.10.013>.

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