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Opinion

Similarities between the Yin/Yang Doctrine and Hormesis in Toxicology and Pharmacology

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Hormesis is a generalizable dose–response relationship characterized by low-dose stimulation and high-dose inhibition. Despite debate over this biphasic dose–response curve, hormesis is challenging central beliefs in the evaluation of chemicals or drugs and has influenced biological model selection, concentration range, study design, and hypothesis testing. We integrate the traditional Chinese philosophy – Yin/Yang doctrine – into the representation of the Western hormetic dose–response relationship and review the Yin/Yang historical philosophy contained in the hormesis concept, aiming to promote general acceptance and wider applications of hormesis. We suggest that the Yin/Yang doctrine embodies the hormetic dose–response, including the relationship between the opposing components, curve shape, and time-dependence, and may afford insights that clarify the hormetic dose–response relationship in toxicology and pharmacology.

Highlights

Hormesis is a dose–response relationship characterized by stimulation at low dose and inhibition at high dose, and which is typically represented as a J-shaped or an inverted U-shaped curve.

Hormesis exhibits generalizable features and has mechanistic explanations, but there is still much debate over this biphasic dose–response curve.

However, hormesis is changing central beliefs in toxicology and pharmacology.

To guide the debate on hormesis and further promote its acceptance and application, an improved biological framework to understand and interpret hormesis is needed.

Yin/Yang doctrine, a traditional Chinese philosophy that has sound scientific foundations, can provide new insights into diverse biomedical problems, and provides an opportunity to re-recognize hormesis.

Yin/Yang Doctrine as a Means to Re-Recognize Hormetic Dose–Response Phenomena

Hormesis is a dose–response relationship characterized by stimulation at low dose and inhibition at high dose, and is typically represented as a J-shaped or inverted U-shaped curve (Figure 1A) [1]. Hormetic dose–response phenomena have generated considerable interest in the scientific community over several decades, and a large body of literature regarding hormetic phenomena has been published not only in toxicology and pharmacology but also in many other areas of biology (e.g., plant biology, microbiology, biogerontology) [2,3]. Hormetic dose–responses have been reported for a wide range of agents (e.g., antibiotics, persistent organic pollutants, heavy metals, ionic liquids, macromolecules, nanomaterials, and radiation) and in a diverse set of organisms (bacteria, algae, worms, flies, rodents, humans, and many others), which reflect the generality of the phenomenon [4–7]. In addition, numerous explanations for different hormetic dose–response curves have been proposed based on the two classical hormetic mechanisms, namely overcompensation (where hormesis represents overcompensation in response to disrupted homeostasis) and direct stimulation (where hormesis reflects the action of an agent on two receptor subtypes that respectively affect stimulatory and inhibitory pathways) [8,9]. Although hormesis is usually used to describe the response of an organism to drugs or environmental factors, it should also be recognized that hormesis is integral to normal physiological function [10,11].

Although hormetic phenomena exhibit generalizable features and usually have scientific explanations, there is still much debate regarding the biphasic hormetic dose–response curve, particularly its general acceptance and application in toxicology and pharmacology. Some suggest that the concept of hormesis is based largely on empirical observations and does not adequately consider the underlying mechanisms [12,13]. In general, the dispute regarding hormetic dose–response relationships probably results from the following issues: inadequate study designs with respect to the number and spacing of doses, lack of a time component, how to assess

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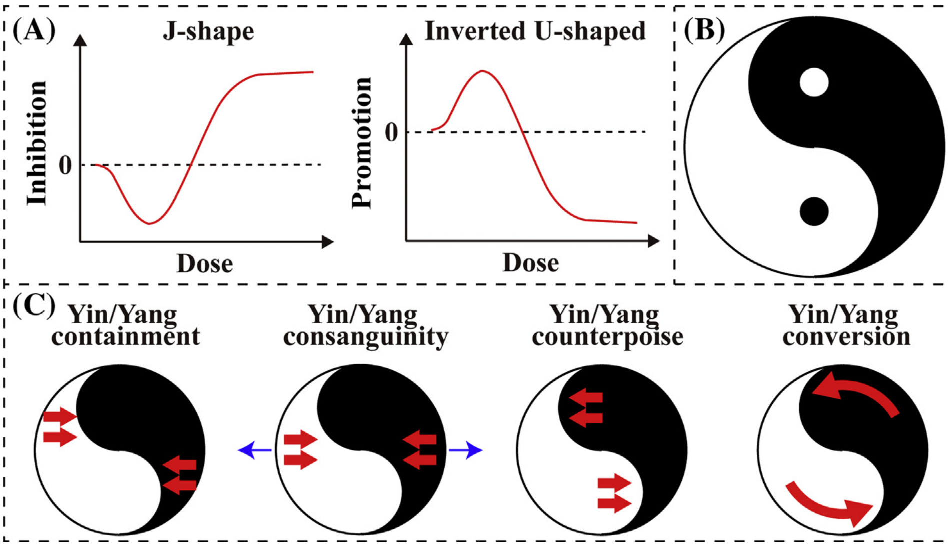

Figure 1. Consistency between Hormetic Dose–Response and '4C' (Containment, Consanguinity, Counterpoise, and Conversion) Laws in Yin/Yang Doctrine. (A) The typical J-shaped and inverted U-shaped hormetic dose–response curve. (B) The classical symbol for Yin/Yang. (C) Four types of relationships between Yin and Yang in Yin/Yang doctrine (4C laws): Yin/Yang containment is used to describe how Yin and Yang restrain and suppress each other to form everything in the universe; Yin/Yang consanguinity means that Yin and Yang originate from the same root and represent the same object in different ways, and neither can exist in the absence of its counterpart; Yin/Yang counterpoise indicates that Yin and Yang move or change in opposite directions to generate a dynamic equilibrium; Yin/Yang conversion clarifies that Yin can transform into Yang under some circumstances, and vice versa, and this change into the reverse qualitatively starts from the aforementioned quantitative movements (Yin/Yang counterpoise), and thus generates the diversity of the whole world.

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the quantitative features of hormetic dose–response, and a lack of unified mechanistic explanations. The application of hormetic dose–response in risk assessment is also disputed because the hormetic model affects not only how regulatory and public health agencies act but also how professionals frame their thoughts and strategies for studying dose–response relationships. Despite ongoing debate, a growing number of experiments are being designed to investigate the hormetic phenomenon. In addition, hormesis is increasingly recommended as a fundamental model because it more accurately reflects the actual dose–response at both low and high doses than do traditional threshold and linear non-threshold models [14–17]. The hormetic responses of organisms to drugs mean that one dose of the drug may be clinically effective to treat disease but another dose may be harmful or ineffective [18,19]. For example, suramin can inhibit the proliferation of cancer cells at high doses, and thus is used as the anticancer agent in the clinic; however, the drug can enhance cancer cell proliferation at low doses by acting as a partial agonist [20]. In the COVID-19 epidemic, low-dose chest irradiation has been recommended for treating patients based on hormetic mechanisms [21]. Therefore, it could be said that hormesis is challenging the central beliefs of toxicology and pharmacology [22–24] in terms of biological model selection, concentration range, study design, and hypothesis testing [25,26]. To guide the debate on hormesis and further promote its acceptance and application, it is necessary to deeply explore and unify the theories of hormesis.

Yin/Yang doctrine, based on two archetypical or universal polarities, is not only a profoundly ancient Chinese philosophy but also a holistic, dynamic, and dialectical world view [27,28] that has sound scientific foundations and wide applicability in exploring diverse biomedical problems [29–36]. Therefore, Yin/Yang doctrine has potential to provide an improved biological framework for understanding and interpreting hormesis. We introduce Yin/Yang doctrine into the re-exploration of hormesis, and establish the scientific concordance between hormesis and Yin/Yang doctrine by reviewing published hormetic dose–responses, including the stimulation/inhibition relationship, the time-dependent feature, and the fundamental meaning of the biphasic dose–response curve.

The Yin/Yang Doctrine, an Ancient Chinese Philosophy but an Important Scientific Concept in Modern Biomedicine

The Core Concept of the Yin/Yang Doctrine

Yin and Yang are two opposing but complementary parts (polarities or forces) [27,37]. Ancient Chinese philosophy suggests that Yin and Yang work together to produce all things in the universe, where there are an infinite number of Yin/Yang pairs – such as Heaven and Earth, man and woman, hot and cool, high and low, large and small, and so on [27]. Figure 1B depicts the classical Yin/Yang symbol. In general, whereas Yin refers to the essence and relatively immobile aspect of an entity, Yang represents its appearance and dynamic state. There are four types of relationships between Yin and Yang (Figure 1C), namely Yin/Yang containment, Yin/Yang consanguinity, Yin/Yang counterpoise, and Yin/Yang conversion; these so-called '4C' laws reflect the core concept of Yin/Yang doctrine [38]. The 4C laws will be discussed later in more detail in the context of hormesis.

Applications of Yin/Yang Doctrine in Biomedicine

Yin/Yang doctrine is a fundamental concept in traditional Chinese medicine (TCM) [39], and this could be regarded as its earliest application in the biomedical field. TCM correlates the living system with health and disease using Yin/Yang [37]. Regarding the human body, the inner part is Yin whereas the outer part is Yang; for the trunk, the abdomen is Yin whereas the back is Yang; for the internal organs, the viscera are Yin and the bowels are Yang; the heart, liver, spleen, lung, and kidney are Yin, whereas the gallbladder, stomach, intestines, bladder, and *San Jiao* ('triple burner', a functional organ that does not have a physical structure) are Yang.

In modern biomedicine, Yin/Yang doctrine was first used in 1975 to describe the antagonistic action between cAMP and cGMP in cellular regulation [40]. Subsequently, Yin/Yang was used to describe the opposing stimulatory and inhibitory influences that regulate cellular activities [41]. In 1991, Shi *et al.* named an important transcriptional factor Yin Yang 1 (YY1) because its target site is responsible for dual mediation of transcriptional activation and repression [42]. With increasing acceptance of the core concept of Yin/Yang doctrine, some western biologists and physicians have recognized that, compared with common pairs of opposites (e.g., plus/minus, increase/decrease, inhibition/stimulation), Yin/Yang better describes opposing biological responses because Yin and Yang not only oppose each other but can also act coordinately. Since the beginning of the 21st century, Yin/Yang doctrine has been frequently applied to human disease research, including immunology, inflammation, cancer, and diabetes [43–55]. Hence, Yin/Yang doctrine may promote and repurpose the generalizable dose–response curve of hormesis in toxicology and pharmacology.

Concordance between Yin/Yang Doctrine and Hormesis

The Yin/Yang Doctrine Clarifies the Relationship between Stimulation and Inhibition in Hormesis

In hormesis, stimulation and inhibition represent opposite and correlated polarities that make up the biphasic dose–response curve – that reflects the dual beneficial and adverse effects of an agent. Hence, stimulation/inhibition may be regarded as a typical Yin/Yang pair, and their relationship follows the 4C laws of Yin/Yang doctrine (Box 1 for an example), as summarized later.

(i) Yin/Yang containment: based on the definition of hormesis, stimulation and inhibition in a biological context represent opposite endpoints induced by an agent relative to controls.

Box 1. An Example Where the Yin/Yang Doctrine Reflects Time-Dependent Hormesis

Sun *et al.* found that sulfapyridine (SPY) triggers time-dependent hormesis in the bioluminescence of *Aliivibrio fischeri* (*A. fischeri*) over a period of 24 h (Figure I) [56]. (i) In the first stage (1–4 h), SPY has no influence on bioluminescence. (ii) In the second stage (5–9 h), there is only stimulation of bioluminescence, and the hourly maximum stimulatory rate first increases and then decreases. (iii) In the third stage (10–16 h), SPY begins to inhibit the bioluminescence at high doses, and the hourly maximum inhibitory rate increases while the hourly maximum stimulatory rate continues to decrease. (iv) In the fourth stage (17–24 h), the hourly maximum stimulatory and inhibitory rates both tend to stabilize.

The changing feature of this typical time-dependent hormetic phenomenon conforms to the 4C laws of the Yin/Yang relationship.

(i) In the first stage (1–4 h), SPY does not yet enter the cells and thus does not affect bioluminescence. The dose–response curve is a flat line (equivalent to Yin/Yang counterpoise).
(ii) In the second and third stages (5–16 h), SPY acts on stimulatory and inhibitory signaling pathways to trigger stimulation and inhibition of bioluminescence, and these stimulatory and inhibitory actions are distinct in the different growth phases of *A. fischeri*; thus, SPY begins to trigger hermetic effects on the bioluminescence, and the basic parameters of dose–response curve vary with the increase of exposure time (equivalent to Yin/Yang containment and conversion).
(iii) In the fourth stage (17–24 h), *A. fischeri* growth enters stationary phase in which the stimulatory and inhibitory actions of SPY on the bioluminescence stabilize (equivalent to Yin/Yang consanguinity and counterpoise).

It should be noted that Yin/Yang is an integrated concept that describes all pairs of contrary and unified polarities. Specifically, Yin is not necessarily stimulation, and Yang is not necessarily inhibition: in some cases Yin may be inhibition and Yang may be stimulation.

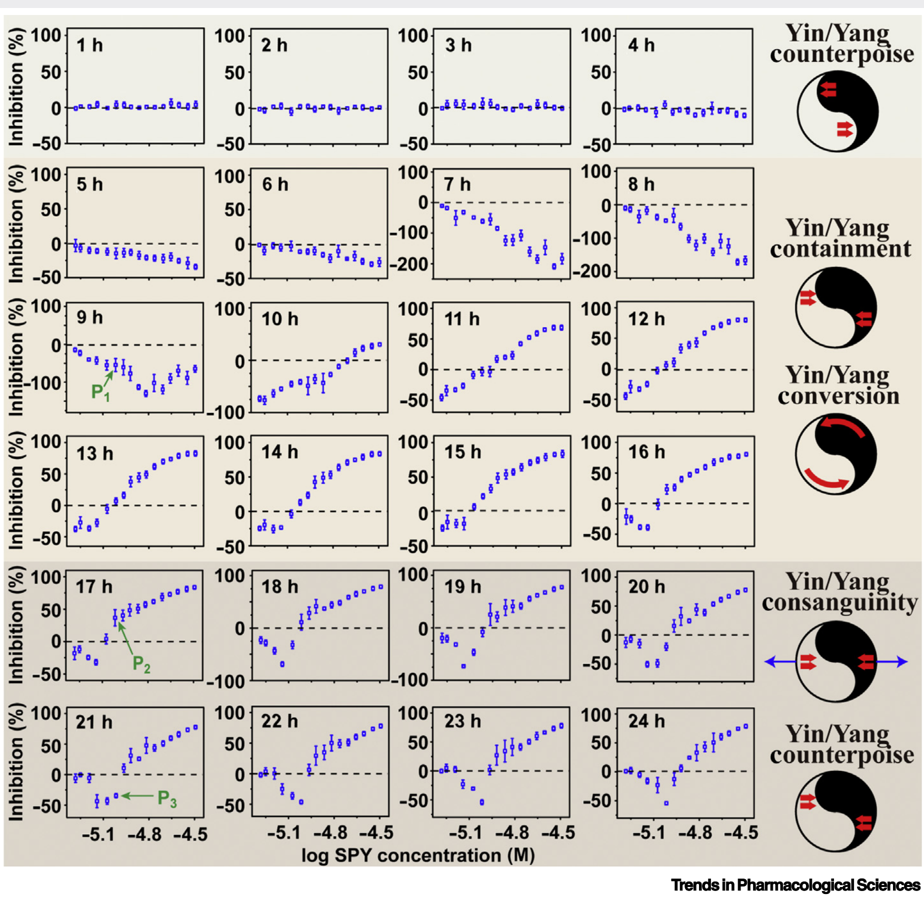

Figure I. Time-Dependent Hormetic Effects of Sulfapyridine (SPY) on the Bioluminescence of *A. fischeri* over a 24 h Period [55], and Correspondence to the 4C Laws of the Yin/Yang Relationship. In each scatter diagram, the x axis represents the logarithm of SPY concentration, and the y axis represents SPY-mediated inhibition of bioluminescence. P_1, P_2, and P_3 represent the inhibitory effects of SPY (9.63×10^{-6} M) on bioluminescence at 9, 17, and 21 h.

(ii) Yin/Yang consanguinity: although stimulation and inhibition are opposing effects, they both derive from a biological response in which both stimulation and inhibition originate from the same root, and both stimulation and inhibition are indispensable components of the hormetic dose–response relationship.
(iii) Yin/Yang counterpoise: Yin and Yang wax and wane with time before they finally achieve an equilibrium; in time-dependent hormesis, stimulation and inhibition always tend to be stable at the end of exposure time.
(iv) Yin/Yang conversion: in time-dependent hormesis, the stimulatory effect (or inhibitory effect) of an agent at a given dose may change into an inhibitory effect (or stimulatory effect) with increased exposure time (points 'P' in Figure I in Box 1).

Yin/Yang Doctrine Reveals the Shape of the Hormetic Dose–Response Curve

Yin/Yang doctrine also casts light on the dose-dependence of stimulation/inhibition, namely the shape of the hormetic dose–response curve. If we plot the concentration or dose of an agent on the x axis, and the extent of inhibition on a test endpoint on the y axis, the hormetic dose–response (i.e., dose–inhibition) relationship inevitably exhibits a biphasic J-shaped curve (Figure 1A). It is intriguing that when the curve of the demarcation between Yin and Yan (in the classical Yin/Yang symbol) is rotated through 90° clockwise or anticlockwise, it strongly resembles the characteristic J-shaped hormetic dose–response curve (Figure 2A). Indeed, some parameters quantitively follow the Yin/Yang demarcation curve – areas A and B in Figure 2B (left) represent the first and second regions delineated by the Yin/Yang curve and the x axis; m and n refer to the widths of areas A and B, respectively; and p and q are the heights of areas A and B, respectively. These parameters can have corresponding meanings in the hormetic dose–response curve (right): A and B then represent areas of stimulation and inhibition, respectively; m and n denote the stimulatory and inhibitory concentration ranges, respectively; and p and q denote the maximum and minimum extents of stimulation and inhibition, respectively (Figure 2B, right). Based on the opposing but complementary relationship between Yin and Yang, the area of region A should be equal to the area of region B; furthermore, m should be equal to n, and p should be equal to q. However, in actual J-shaped hormetic dose–response curves the stimulatory region usually differs from the inhibitory region in width, height, and area [57–59], although this depends on the test organism, endpoint, concentration range, timepoint, and other parameters that influence the extent of both stimulation and inhibition.

Moreover, the typical J-shaped hormetic dose–response curve is not exactly equivalent to the Yin/Yang curve: in detail, the extent of inhibition in the hormetic dose–response curve first decreases and then increases to a stable value (often approaching 100%, Figure 1A). We suggest that this depends on the test endpoint. The most commonly used endpoints in toxicology and pharmacology are qualitative, such as cell proliferation, cell vitality, or cell death [60–62], which do not reflect the response of organism once the extent of inhibition reaches a maximum. We opine that the ideal J-shaped hormetic dose–response curve may display variations that themselves are similar to the Yin/Yang demarcation curve (Figure 2C), notably when the test endpoints reflect complex biological activities (e.g., bacterial bioluminescence; Box 1) rather than qualitative measures (e.g., cell proliferation), and when the organisms are exposed to wide dose range of agent (theoretically extending to an infinite dose). In such cases we speculate that the hormetic dose–response relationship may display undulations that reflect several successive Yin/Yang curves (Figure 2C).

The Yin/Yang Doctrine Reflects the Time-Dependent Features of Hormesis

When the toxicity of an agent is tested at different time-points following exposure, the hormetic effects often vary with time, exhibiting time-dependent features [56,63]. In typical time-

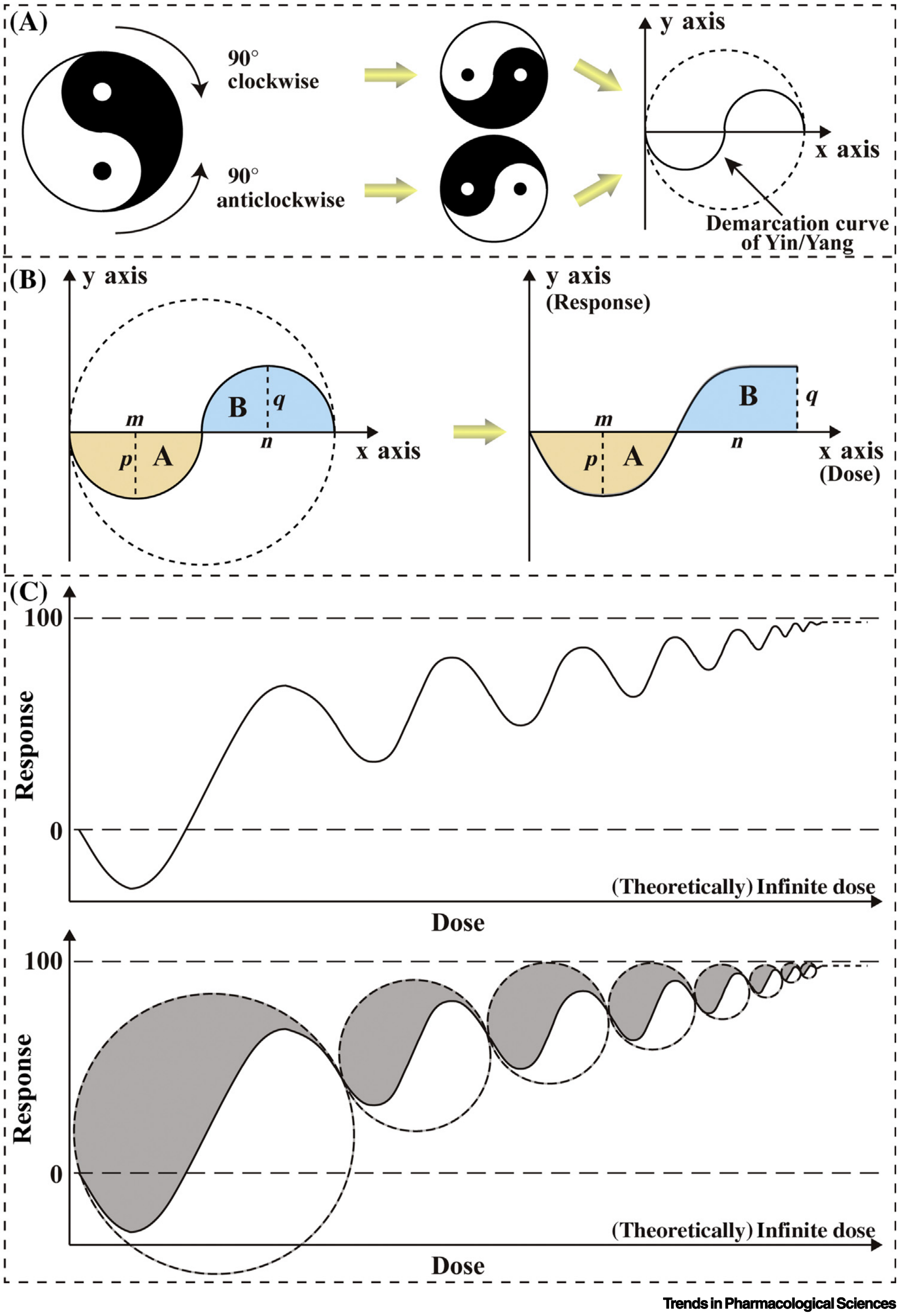

Figure 2. Similarities between the Yin/Yang Symbol and the Hormetic Curve. (A) Rotated through 90° clockwise or anticlockwise, the Yin/Yang demarcation curve can be envisaged as depicting the J-shaped hormetic dose–response curve. (B) Likewise, similarities can be drawn between the Yin/Yang demarcation curve and a hormetic dose–response curve. In the Ying/Yang symbol, A and B represent the areas of the first and the second regions delineated by the Yin/Yang demarcation line and the x axis, *m* and *n* are the widths of areas A and B respectively, and *p* and *q* are the heights of areas A and B, respectively. These parameters can also have corresponding meanings in the hormetic dose–response curve where A and

(Figure legend continued at the bottom of the next page.)

dependent hormesis, the basic parameters of the hormetic dose–response curve vary with exposure time, and these include magnitude of stimulation, concentration range of stimulation, magnitude of inhibition, and concentration range of inhibition [64,65]. Because the relationship between stimulation and inhibition in hormesis is proposed to follow the 4C laws of Yin/Yang, the time-dependent feature of hormesis could reflect Yin/Yang doctrine. All things in the universe are held to move in a consistent way: from Yin/Yang consanguinity and counterpoise to Yin/Yang containment and conversion, and then back to Yin/Yang consanguinity and counterpoise [38]. Hence, time-dependent hormesis may follow variations in the Yin/Yang relationship (Box 1).

The Yin/Yang Doctrine Can Be Used to Explore the 'Opposing and Constrained' Regulatory Factors in Hormesis

Analyzing the 'Opposing and Constrained' Components of a Hormetic Curve

The question of how to model hormetic dose–response data has received wide attention from toxicologists and pharmacologists [66,67]. Over recent decades several representative hormetic models have been developed, among which the model based on Yin/Yang doctrine seems to best embody the biphasic features of hormesis [68,69].

In constructing this hormetic fitting model, Deng *et al.* drew on the 4C laws of the Yin/Yang relationship and suggested that the J-shaped hormetic dose–response relationship can be regarded as the combination of two 'opposing and constrained' virtual S-shaped dose–response relationships [70]. The fitting model for the hormetic dose–response curve is based on a bilogistic function that exhibits typical biphasic dose–response features (Figure 3A, black line) in which the response at each dose is treated as the summation of stimulation and inhibition at seven specific and significant points in the curve: A (NEP, no effect point), B (half-maximum stimulation point at lower concentration), C (maximum stimulation point), D (half-maximum stimulation point at higher concentration), E (ZEP, zero equivalence point), F (half-maximum inhibition point), and G (maximum inhibition point). Inhibition then can be depicted as a S-shaped dose–response curve above the x axis (Figure 3A, blue dashed line) and stimulation can be depicted by an inverted S-shaped dose–response relationship below the x axis (Figure 3A, yellow dashed line) [70]. The two curves thus appear to be 'opposing' (above vs below the x axis; negative vs positive) and 'constrained' (interplay generates the fitting model) elements of the hormetic model, which resemble the relationship of Yin and Yang. The corresponding virtual stimulatory and inhibitory dose–response curves could therefore be deemed to represent the 'opposing and constrained' components of a hormetic curve. This novel model, combined with Yin/Yang doctrine, has been successfully used to fit the hormetic dose–response data, reflecting the applicability of the Yin/Yang doctrine to hormetic phenomena [56,71,72].

Identifying the 'Opposing and Constrained' Factors That Produce Hormesis

In addition to analyzing hormesis, Yin/Yang doctrine has also enhanced exploration of the underlying mechanisms. In the two hormetic mechanisms – direct stimulation and overcompensation – direct stimulation based on receptor/signaling pathways (Box 2) seems to better reveal the wisdom of Yin/Yang doctrine than does overcompensation. Direct stimulation theory suggests that an agent has two different receptors in an organism, and that these influence the corresponding signaling pathways to trigger stimulatory and inhibitory effects on the test endpoint [9,75]. The relationship between these two opposing actions follows the 4C laws of Yin and

B represent stimulatory and inhibitory areas, respectively; *m* and *n* denote the stimulatory and inhibitory concentration ranges, respectively; and *p* and *q* denote the maximum stimulatory and maximum inhibitory rates, respectively. (C) When the test endpoint reflects complex biological activities, and the organism is exposed to a wide dose range of agent (theoretically extending to infinite dose), the hormetic dose–response relationship can be presented as a wave-like increasing curve that is composed of several successive Yin/Yang demarcation curves.

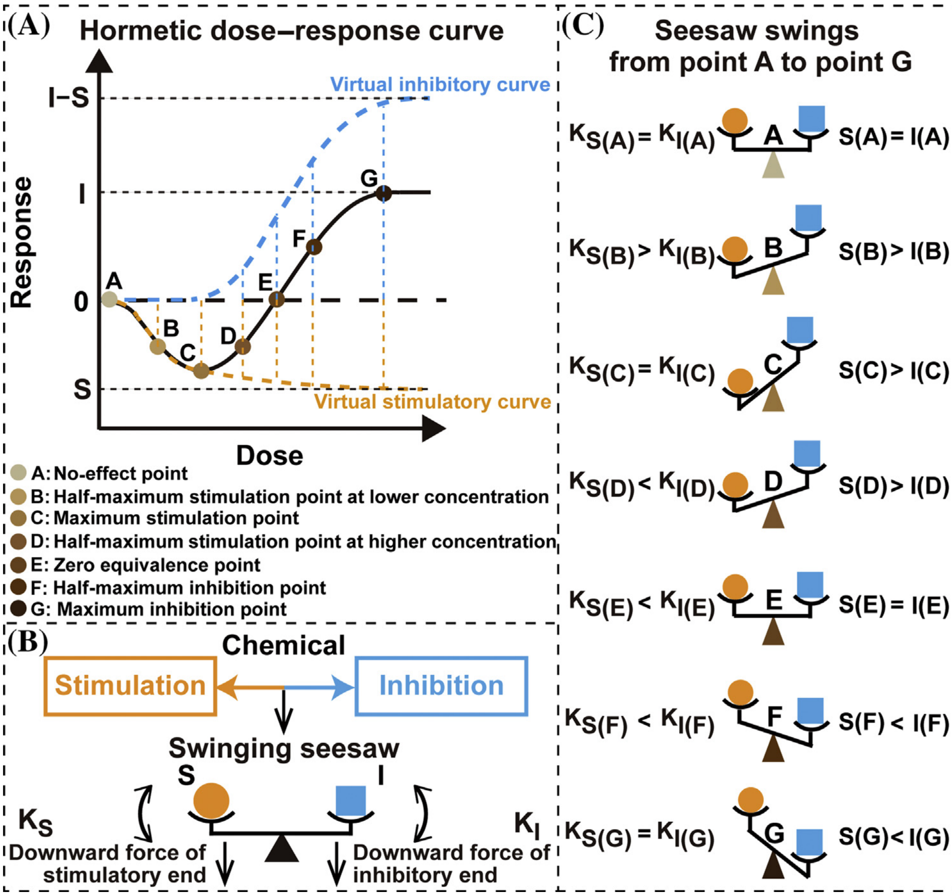

Figure 3. The 'Yin/Yang Doctrine' Contained in Hormesis. (A) The graph shows the fitting model for hormetic dose–response curve (in black) with seven specific and significant points on the curve (A–G). These points are detailed in the accompanying key. S represents the maximum stimulation and I represents the maximum inhibition. The S-shaped dose–response relationship (blue dashed line) represents inhibition, and the inverted S-shaped dose–response relationship (yellow dashed line) refers to stimulation. (B) The swinging seesaw model: stimulation (S) and inhibition (I) at each end generate the seesaw; the downward force of the stimulatory end of the curve (K_S) equals the absolute value of the gradient of the virtual stimulatory curve and represents the increasing rate of stimulatory effects, whereas the downward force at the inhibitory end of the curve (K_I) equals the absolute value of the gradient of the virtual inhibitory curve and represents the increasing rate of inhibitory effects; when the incline of the seesaw is at the stimulatory end, S > I; when the seesaw is in balance, S = I; and when the seesaw is at the inhibitory end, S < I. (C) The schematic shows how the seesaw swings regularly between the stimulatory and inhibitory ends from point A to point G in a hormetic dose–response curve.

Yang, which indicate that the stimulatory and inhibitory effects can be seen as the two polarities – Yin and Yang in hormesis – and represent the 'opposing and constrained' factors of Yin/Yang.

Yin/Yang Doctrine Can Describe the Balance Contained in Hormesis

The Dynamic Balance of Stimulation and Inhibition in Hormesis

Yin/Yang doctrine indicates that stimulation and inhibition are the 'opposing and constrained' regulatory factors in hormesis. However, stimulation and inhibition may also be created through Yin/Yang counterpoise and conversion. When exploring the hormetic mechanism underlying the dose-dependent effects of sulfapyridine (SPY) on the bioluminescence of *A. fischeri* (Box 1), Sun *et al.* drew on Yin/Yang doctrine to develop a swinging seesaw model to explain the typical pattern of hormesis (where stimulation and inhibition occupy the two ends of the

Box 2. 'Opposing and Constrained' Factors Contained in Hormetic Mechanisms

Numerous hormetic mechanisms based on receptors and signaling pathways have been published over the past two decades which embody the applicability of Yin/Yang doctrine, and provide a mechanistic explanation for the hormetic phenomenon. Calabrese recently summarized the receptor systems that display biphasic dose–response relationships; their ligands include many classes of compounds, such as adenosine, dopamine, estrogen, nitric oxide, prolactin, and some growth factors [8,9]. For example, administration of dopamine (a catecholamine in the pathway of synthesis of the neurotransmitter norepinephrine) to rats, mice, dogs, monkeys, and humans can trigger hormetic effects on diverse endpoints – including locomotion, pain sensitivity, blood pressure, prolactin secretion, oxytocin release, heart rate, memory, and neuronal adenylate cyclase activity [73]. Mechanistic studies indicate that the stimulatory and inhibitory effects of dopamine are mediated by different receptors or receptor subtypes that have opposite actions and different ligand affinities: dopamine has a small number of high-affinity receptors in the stimulatory pathway, but a diverse range of low-affinity receptors in the inhibitory pathway [74], ultimately resulting in the hormetic dose–response relationship. In addition, Sun *et al.* suggest that an agent must have more than one receptor in the stimulatory and inhibitory pathways to induce hormetic effects on the endpoint, such as the bioluminescence of *A. fischeri* [7]. Yin/Yang doctrine can classify receptors into those that stimulate the endpoint and those that inhibit, and ultimately disclose the 'opposing and constrained' factors that underpin hormetic phenomena.

seesaw) (Figure 3B) [56]. Because the virtual stimulatory and inhibitory curves are both logical dose–response relationships, the downward forces at the two ends of the seesaw have similar variations, namely from zero to maximum and then back to zero. Thus, in the response of *A. fischeri* bioluminescence to SPY exposure (Box 1), an increase in SPY concentration leads to swinging of the seesaw regularly between stimulation and inhibition (from point A to point G, Figure 3A), momentarily reaching a steady-state balance between the two, and ultimately resulting in a biphasic dose–response (Figure 3C).

Under this interpretation, hormesis reflects opposing and dynamic dose-dependent stimulatory and inhibitory effects that reflect both the ‘opposing and constrained’ and ‘wax and wane’ features of Yin/Yang doctrine that are embodied in the swinging seesaw model.

Hormesis in Traditional Chinese Medicine

TCM has been practiced for thousands of years and is widely recognized as providing curative and/or healing treatments for diverse diseases and physiological conditions, including bone repair, Alzheimer’s disease, allergic disease, diabetic nephropathy, and hypertension [76–80]. In TCM, the multiple active ingredients of herbal medicines are often unknown, and the doses and combinations of herbal medicines are usually based on an empirical set of principles – referred as Monarch, Minister, Assistant, and Guide – whereas the components of Western medicine are well-characterized and their doses in clinical practice are typically based on published dose–response relationships [81,82]. Thus, compared with the highly quantitative and reproducible treatments of Western medicine, TCM treatments are potentially subjective and often non-quantitative, and are usually prescribed according to the pharmacopoeia and the personal experience of the physician [83]. This lack of a theoretical framework and objective criteria for TCM treatment often prompts serious concerns about the reproducibility of therapeutic treatments, and can negatively impact on dose, effect, and mechanism studies.

Wang *et al.* proposed a dose–response methodology based on Yin/Yang doctrine and hormesis to guide herbal medicine dosages in TCM treatment [84], as set out later.

(i) In light of Yin/Yang doctrine, TCM posits that disease reflects a disequilibrium of Yin and Yang. Thus, TCM treats the disease from a holistic and dialectical view and aims to restore a balance between Yin and Yang.
(ii) Extensive literature in regard to the hormetic dose–responses of herbal medicines indicate that the extracts of many herbs, either individually or combined, can trigger hormetic phenomena in

diverse models including animal and human cells *in vitro* [85,86]. Thus, herbal medicines may induce hormetic responses via physiological activities that are related to the disease.

(iii) TCM treatments act through hormetic dose–response mechanisms. Some herbal medications are given at high doses that exert inhibitory effects, which is used for ‘curing’ treatment. For example, medications that show direct inhibitory effects on tumor cells are used for anticancer treatment [87]. By contrast, some herbal medications are administered at low doses to induce stimulatory actions that aim at ‘regulatory’ effects. For example, low ‘regulatory’ doses of some herbal medications aim to promote adaptive responses [88]. Both ‘regulatory’ and ‘curing’ treatments aim to recover the disequilibrium between Yin and Yang.

Although the therapeutic effects of many herbal medicines used in TCM may be ascribed to hormesis, as is also increasingly recognized for several Western medicines, issues such as the lack of clearly defined clinical doses limit systematic clinical applications of TCM [89]. In addition, randomized clinical trials (RCTs), the gold standard for assessing the efficacy of agents, are constrained by hormetic dose–responses in TCM clinical research [89]. No more than 20% of TCM studies published in Chinese TCM journals have conducted credible RCTs [90]. Indeed, it is difficult to observe and identify the hormetic effects of herbal medications *in vivo*, and it is too early to state that hormetic dose–responses alone underlie clinical TCM treatment. Nevertheless, hormesis in conjunction with Yin/Yang doctrine provides an opportunity to explore the mechanistic principles of TCM in more depth.

Concluding Remarks and Future Perspectives

To sum up, the fundamental elements of hormesis, including the relationship between stimulation and inhibition, the shape of dose–response curve, and the time-dependence, all follow Yin/Yang doctrine. Furthermore, Yin/Yang doctrine also reveals the inherent connotations contained within hormesis, such as ‘opposing and constrained’ regulatory factors and balanced features, and incorporation of Yin/Yang doctrine is likely to promote further exploration of hormesis and its applications in several fields of biomedical science.

However, several problems remain (Box 3); based on the concordance between Yin/Yang doctrine and hormesis, in the following we provide a perspective on issues that remain to be addressed.

(i) Lack of quantitative parameters in a hormetic curve: the integrated areas of stimulatory and inhibitory responses between the Yin/Yang demarcation curve and the x axis (i.e., A + B in Figure 2B) may not be the most appropriate parameters to quantify both the vertical and horizontal variations of the hormetic curve.

(ii) Mechanistic explanations of hormetic phenomena: the Yin/Yang doctrine may help us to overcome the theoretical barriers between overcompensation and direct stimulation to establish a holistic mechanistic system for hormetic phenomena, including identification of the sources of stimulation and inhibition as well as their interactions.

(iii) Applications of hormesis in biomedicine: in view of the generality of hormetic responses in biomedicine, the clinical use of drugs should be guided based on the hormetic features of the dose–response relationship combined with the 'Yin/Yang' properties of drugs and target diseases.

(iv) Applications of hormesis in risk assessment: the holistic, dynamic, and dialectical world view – Yin/Yang doctrine – should be used in ecological or environmental risk assessments to establish correlations between the (lower-level) hormetic effects of chemicals on individual organisms, and the (higher-level) impact of chemicals on the whole ecological system. In brief, Yin/Yang doctrine may provide a macroscopic theoretical system from the ecological perspective that embraces the hormetic model.

Outstanding Questions

What is the best method to quantify the hormetic dose–response curve and accurately calculate the stimulatory/inhibitory areas as indicated by Yin/Yang doctrine?

Can we improve the detection of wave-like increasing hormetic dose–response curves by selecting the appropriate organism, test endpoint, and dose range of chemicals/drugs?

Can we put forward a Yin/Yang doctrine-based mechanism for hormesis that combines overcompensation and direct stimulation?

How can we utilize the stimulatory/inhibitory effects of a drug to treat a disease based on Yin/Yang doctrine?

Can we apply hormetic dose–response curves through Yin/Yang doctrine to explore TCM treatment indications, efficacy, and risks, as well as quality aspects of the herbal medications used?

Can we use Yin/Yang doctrine to classify the influence of chemicals on the environment into beneficial effects and harmful effects?

How can we establish the relationship between the hormetic effects of chemicals on individual organisms and their influence on the environment based on Yin/Yang doctrine?

Box 3. Current Problems in Hormesis and Its Applications

Quantitative Parameters in Hormetic Curves

Previously, multiple parameters such as zero equivalence point (ZEP), no-effect point (NEP), stimulatory concentration range (SCR), concentration with maximum stimulation (EC_m), maximum stimulation (E_m), concentration at half-maximum inhibition (EC_{50}) have been identified to quantitatively describe hormetic curves [91] (Figure IA). These parameters describe either the vertical variation (effect) or horizontal variation (dose/concentration). However, when two different dose–response curves have same E_m but different SCRs (Figure IB), or the same SCR but different E_m values (Figure IC) [92], a single distinguishing parameter is unable to accurately quantify the hormetic effect [93].

Mechanistic Explanation of the Hormetic Phenomenon

Overcompensation and direct stimulation have been the classical mechanistic explanations for hormetic phenomena over the past century [8,9]. However, it is unfortunate that these two key mechanistic concepts did not merge into a single unifying principle. Furthermore, nearly all the available examples based on these two approaches are partial explanations [94,95] – they demonstrate that an agent mediates both stimulation and inhibition, but they do not clarify how stimulation and inhibition interplay to induce a biphasic response.

Applications of Hormesis in Biomedicine

Most, if not all, drugs used in biomedicine can exhibit hormetic dose–response curves in terms of their effects on disease symptoms. For example, some anticancer agents (such as suramin and toremifene) have clear inhibitory effects on cancer cells at specific doses (useful or beneficial effects) but can increase the proliferation or viability of cancer cells at lower doses [96,97]. Thus, how to guide the clinical use of drugs based on hormesis remains a challenge.

Applications of Hormesis in Risk Assessment

Although hormesis is recommended as a default model, one of the biggest puzzles in ecological or environmental risk assessment is that it is difficult to establish the correlation between the hormetic (lower-level) effects on an individual organism, and the (higher-level) impact on the whole ecological system. Hormetic responses are generally explored at the individual or group levels [7,98], and few studies have been performed on multiple populations, multispecies communities, or even the whole ecological system.

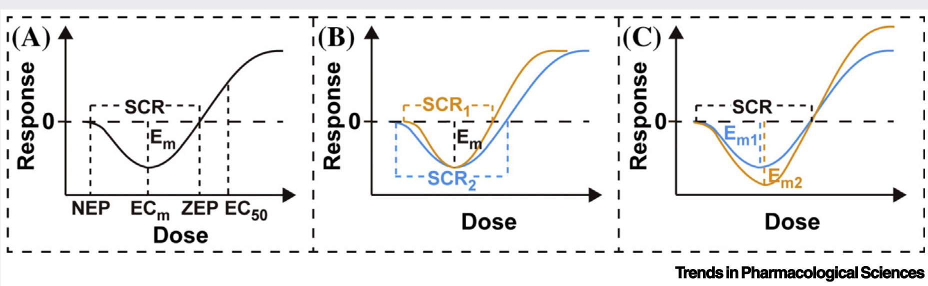

Figure I. Components of the Hormetic Dose–Response Curve. (A) Schematic of a typical hormetic dose–response curve showing the classical parameters used to quantitatively describe it, where SCR is the stimulatory concentration range, NEP is the no-effect point, EC_m is the effective concentration at maximum stimulation, E_m is the effect at maximum stimulation, ZEP is the zero equivalence point, and EC_{50} is the concentration at 50% inhibition. (B) Two different dose–response curves (depicted in orange and blue) that have the same E_m values but different SCRs (SCR_1 and SCR_2). (C) Two different dose–response curves (depicted in orange and blue) that have the same SCR but different E_m values (E_{m1} and E_{m2}).

Ultimately, the greatest challenge in applying Yin/Yang doctrine in these fields will be in determining how to use the Yin/Yang doctrine to enhance the understanding and applications of hormesis, as well as to inform evolutionarily adaptive strategies and their wider implications (see Outstanding Questions). Addressing such questions would not only help to reveal the essence of hormesis but also benefit the further development of toxicology and pharmacology.

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