



Implication of hormetic effect in traditional Chinese medicine

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Traditional Chinese medicine (TCM) is one of the most systematically documented and developed traditional medicine systems in the world, which still increasingly benefits large populations worldwide nowadays. TCM is rooted in traditional Chinese philosophies, mainly Taoism. Its major theories include *tian ren he yi* (a concept that human and nature are an integral unity), *yin and yang*, *five elements* (symbolically refer to fire, earth, wood, metal and water), *qi* (vital energy flows in the body), *meridians and collaterals*, *zang fu* (similarly refer to organs), etc. Along with the development of Chinese civilization, TCM has been continuously evolved over thousands of years and clinically proven to be efficacious for the treatment or prevention of various symptoms or diseases. However, TCM is inherently different from modern Western medicine in most, if not all aspects of philosophy and theories and tactics of diagnosis and treatment of diseases. In a modern era of globalization and advanced science and technology, TCM has to be extensively developed to meet the basic requirements of modern science, such as consistency, observability, predictability, testability, etc. Indeed, substantial progress has been made in the research of TCM herbal medicine by using cutting-edge separation and analysis technologies (1,2). However, rare significant achievements have been reached in the studies on theories and practices of TCM. The review article “*Hormesis as a mechanistic approach to understanding herbal treatments in traditional Chinese medicine*” by Wang *et al.* (3) was such a meritorious attempt to bring a new insight into the “black box” of TCM.

The term hormesis describes a biphasic dose response to an environmental factor (physical, chemical or biological) characterized by a low dose stimulation or

beneficial effect and a high dose inhibitory or toxic effect on the cell or organism (4,5). Plenty of evidence suggests that hormetic dose response is a general biological phenomenon, which is independent of stimulus type, experiment model, and endpoint of observation (6). Hormetic effect of organisms can be considered as an evolutionarily conserved adaptive protection mechanism to a moderate stress induced by environmental factors (7,8). Over hundreds of millions of years’ evolution, organisms have developed a set of elaborate mechanisms to respond adaptively to various hazardous factors to increase their ability to survive and reproduce in harsh competitive environments. The concept of hormesis is supposed to be a theoretical framework for quantitative understanding (at least partially) the cellular and molecular mechanisms underlying the theory of biological evolution (7). In this regard, hormesis is far beyond a dose response in toxicology and pharmacology. It could have a broad impact on life sciences and related areas, such as genetics, immunology, neurology, nutrition, health, aging, cancer, and clinical medicine (9-11). Obviously, TCM should also be within the scope. Increasing evidence indicated that TCM herb extracts and phytochemicals generally induced hormetic dose response (3,12). Phytochemicals, such as polysaccharides, saponins, isoflavones and polyphenols, which are enriched in TCM herbs, usually show beneficial activities, including anti-oxidation (13), anti-inflammation (14), immunoregulation (15), etc. Moreover, in our observations and others, phytochemicals commonly do not target specific molecules, but non-specifically activate many cellular stress-related signaling pathways (8,16-19), e.g., MAPKs, Nrf2/ARE, Sirtuins,

HSF1, NF- κ B, FOXOs, PI3K/Akt and autophagic response pathways, at relatively low doses. It is reasonable to speculate that the health beneficial effects of dietary and herbal phytochemicals could be generally attributable to the activation of stress responses and then hormetic protective effects and consequently enhancement of cell or organ functions. This is in line with the principle of TCM that treatment of diseases can be through enhancing physiological functions (particularly digestion, hematopoiesis, immunity, and so on), as discussed in the article by Wang *et al.* (3). Given many phytochemicals in TCM herbs only exhibit mild activities and their circulatory concentrations are relatively low due to poor absorption, low bioavailability and low content in herbs, the pharmacological efficacy of TCM herbal medicine may somewhat attribute to a certain profile of hormetic effects induced by a distinct group of chemical components. It is interesting and important to investigate the details of TCM herbal medicine-induced hormetic effects in various types of cells/organs and their roles in the therapeutic or preventive activities of TCM treatment in the future. However, it is nevertheless still too simplified and ambiguous to uncover the mechanisms underlying TCM only in the frame of hormetic concept, as TCM treatment involves complicated and delicate theories and schemes for diagnosis and treatment of diseases based on individual patient's signs and syndrome and the natures and flavors of TCM medicinal materials (herbs, minerals, etc.). Notably, TCM is a systematic, holistic and personalized medicine, which employs a set of "language" and dialectical way of thinking essentially different from Western medicine as mentioned previously. There might be some connections rather than equivalences between these two systems. Therefore, interpretation of TCM theories using conventional biomedical sciences and technologies is inevitably superficial and insufficient. TCM should be kept in its own entity and developed in its own way. Biomedical approaches can be employed to qualitatively and quantitatively characterize TCM, such as symptom differentiation, evaluation of therapeutic efficacy, toxicity and quality of TCM medicinal materials, to make TCM consistently observable, predictable and testable. To this end, strategies and technologies of systems biology, such as omics (e.g., genomics, proteomics, metabolomics, etc.), bioinformatics and chemometrics, could be more feasible and practicable tools that may holistically bridge TCM and Western medicine (20,21).

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Footnote

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References

1. Xu QH, Bauer R, Hendry BM, et al. The quest for modernisation of traditional Chinese medicine. *BMC Complement Altern Med* 2013;13:132.
2. Guo DA, Lu AP, Liu L. Modernization of traditional Chinese medicine. *J Ethnopharmacol* 2012;141:547-8.
3. Wang D, Calabrese EJ, Lian B, et al. Hormesis as a mechanistic approach to understanding herbal treatments in traditional Chinese medicine. *Pharmacol Ther* 2018;184:42-50.
4. Calabrese EJ, Bachmann KA, Bailer AJ, et al. Biological stress response terminology: Integrating the concepts

- of adaptive response and preconditioning stress within a hormetic dose-response framework. *Toxicol Appl Pharmacol* 2007;222:122-8.
5. Mattson MP. Hormesis defined. *Ageing Res Rev* 2008;7:1-7.
 6. Calabrese EJ. Hormesis: a fundamental concept in biology. *Microbial cell* 2014;1:145-9.
 7. Calabrese EJ, Mattson MP. Hormesis provides a generalized quantitative estimate of biological plasticity. *J Cell Commun Signal* 2011;5:25-38.
 8. Mattson MP, Calabrese EJ. *Hormesis: A Revolution in Biology, Toxicology and Medicine*. Totowa, NJ: Humana Press, 2010.
 9. Calabrese EJ, Iavicoli I, Calabrese V. Hormesis: its impact on medicine and health. *Hum Exp Toxicol* 2013;32:120-52.
 10. Calabrese EJ, Mattson MP. How does hormesis impact biology, toxicology, and medicine? *NPJ Aging Mech Dis* 2017;3:13.
 11. Calabrese EJ. Hormesis: a revolution in toxicology, risk assessment and medicine. *EMBO Rep* 2004;5:S37-40.
 12. Calabrese V, Cornelius C, Dinkova-Kostova AT, et al. Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity. *Biochim Biophys Acta* 2012;1822:753-83.
 13. Malireddy S, Kotha SR, Secor JD, et al. Phytochemical Antioxidants Modulate Mammalian Cellular Epigenome: Implications in Health and Disease. *Antioxid Redox Signal* 2012;17:327-39.
 14. Jia XJ, Ma LS, Li P, et al. Prospects of *Poria cocos* polysaccharides: Isolation process, structural features and bioactivities. *Trends Food Sci Tech* 2016;54:52-62.
 15. Ferreira SS, Passos CP, Madureira P, et al. Structure function relationships of immunostimulatory polysaccharides: A review. *Carbohydr Polym* 2015;132:378-96.
 16. Gezer C. Stress Response of Dietary Phytochemicals in a Hormetic Manner for Health and Longevity. In: Fumiaki Uchiumi. Editor. *Gene Expression and Regulation in Mammalian Cells*. London: IntechOpen, 2018.
 17. Bao JL, Huang BR, Zou LD, et al. Hormetic Effect of Berberine Attenuates the Anticancer Activity of Chemotherapeutic Agents. *Plos One* 2015;10:e0139298.
 18. Zhang C, Li C, Chen S, et al. Berberine protects against 6-OHDA-induced neurotoxicity in PC12 cells and zebrafish through hormetic mechanisms involving PI3K/AKT/Bcl-2 and Nrf2/HO-1 pathways. *Redox Biol* 2017;11:1-11.
 19. Zhang C, Li C, Chen S, et al. Hormetic effect of panaxatriol saponins confers neuroprotection in PC12 cells and zebrafish through PI3K/AKT/mTOR and AMPK/SIRT1/FOXO3 pathways. *Sci Rep* 2017;7:41082.
 20. Lu AP, Bian ZX, Chen KJ. Bridging the Traditional Chinese Medicine Pattern Classification and Biomedical Disease Diagnosis with Systems Biology. *Chin J Integr Med* 2012;18:883-90.
 21. Buriani A, Garcia-Bermejo ML, Bosisio E, et al. Omic techniques in systems biology approaches to traditional Chinese medicine research: Present and future. *J Ethnopharmacol* 2012;140:535-44.

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