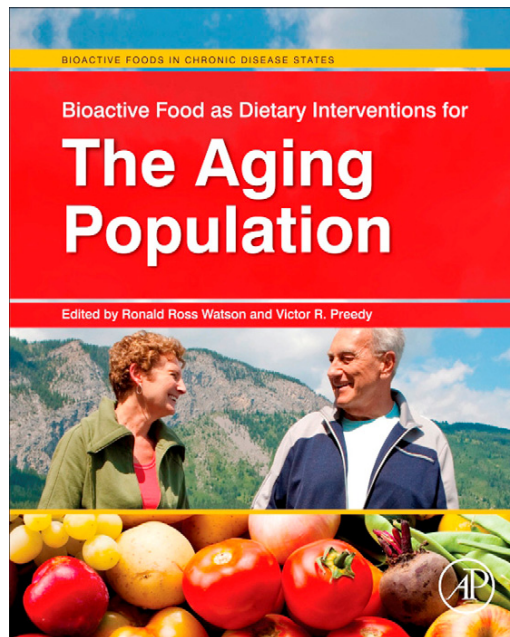


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CHAPTER 16

Nutritional Hormetins and Aging

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ABBREVIATIONS

- ARE** Antioxidant response element
ELS Essential lifespan
HSR Heat shock response
Keap Kelch-like ECH-associated protein
Nrf2 Nuclear factor erythroid-2-related factor
SR Stress response

1. INTRODUCTION

Modulation of human health and longevity through nutrition is one of the longest running themes in the history of anti-aging. While dreams of the perfect food for eternal youth and immortality may still occupy the minds of some, modern scientific knowledge has opened up novel approaches toward understanding and utilizing nutrition in a more realistic and rational way. One such modern approach is hormesis and hormetins for healthy aging and longevity, which is based on the observations that low levels of potentially toxic substances can have health beneficial effects by the induction and stimulation of maintenance and repair systems. Such a phenomenon of mild stress-induced health benefits is known as physiological hormesis (Calabrese, 2004; Mattson and Calabrese, 2010), and any condition which causes physiological hormesis is termed as a hormetin (Rattan, 2008). Nutritional hormetins are the hormesis-inducing components of the food, which bring about their beneficial effects by activating one or multiple pathways of stress response (SR) (Rattan, 2012a).

However, in order to fully appreciate the application of nutritional hormetins to modulate aging and longevity, it is important first to have a brief overview of the current status of one's understanding of the biological basis of aging, which will be followed by the discussion of nutritional hormetins in aging research and interventions.

2. UNDERSTANDING THE BIOLOGICAL PRINCIPLES OF AGING

The biological bases of aging are well understood, and a distinctive framework has been established, which can be the basis for developing effective interventions. There are four major biological principles of aging and longevity:

1. *Evolutionary life history principle*: Aging is an emergent phenomenon seen primarily in the period of survival beyond the natural lifespan of a species, termed 'essential life-span' (ELS) (Rattan, 2000, 2006).
2. *Non-genetic principle*: There is no fixed and rigid genetic program, which determines the exact duration of survival of an organism, and there are no real gerontogenes whose sole function is to cause aging (Rattan, 2006).
3. *Differential principle*: The progression and rate of aging are different in different species, organisms within a species, organs and tissues within an organism, cell types within a tissue, sub-cellular compartments within a cell type, and macromolecules within a cell (Rattan, 2006).
4. *Molecular mechanistic principle*: Aging is characterized by a stochastic occurrence, accumulation, and heterogeneity of damage in macromolecules, leading to the shrinkage of the homeodynamic space and the failure of maintenance and repair pathways (Rattan, 2006, 2007; Holliday and Rattan, 2010; Rattan, 2012b).

Thus, aging is an emergent and epigenetic meta-phenomenon beyond ELS, which is not controlled by a single mechanism. Although, individually, no tissue, organ, or system becomes functionally exhausted even in very old organisms, it is their combined interaction and interdependence that determines the survival of the whole. All living systems have the intrinsic homeodynamic ability to respond, to counteract, and to adapt to the external and internal sources of disturbance. A wide range of molecular, cellular, and physiological pathways of repair are well known, and these range from multiple pathways of nuclear and mitochondrial DNA repair to free radical counteracting mechanisms, protein turnover and repair, detoxification mechanisms, and other processes including immune responses and stress responses. All these processes involve numerous genes whose products and their interactions give rise to a "homeodynamic space" or the "buffering capacity", which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state. Aging, senescence, and death are the final manifestations of a progressive shrinking of the homeodynamic space (Holliday and Rattan, 2010, Rattan, 2006, 2007).

3. FROM UNDERSTANDING TO INTERVENTION

As a biomedical issue, the biological process of aging underlies all major human diseases. Although the optimal treatment of each and every disease, irrespective of age, is a social and moral necessity, preventing the onset of age-related diseases by intervening in the

basic process of aging is the best solution for improving the quality of human life in old age. According to the principles of aging and longevity described above, therapeutic interventions against aging need to be primarily preventive in terms of slowing down the rate and extent of shrinkage of the homeodynamic space.

A critical component of the homeodynamic property of living systems is their capacity to respond to stress. In this context, the term “stress” is defined as a signal generated by any physical, chemical, or biological factor (stressor), which, in a living system, initiates a series of events in order to counteract, adapt, and survive. [Table 16.1](#) gives a list of main molecular SRs, their potential stressors, and various effectors, which are integral to the organismic property of homeodynamics.

Based on the involvement of one or more molecular SRs, higher-order (cellular, organ, and body level) SRs are manifested, which include apoptosis, inflammation, and hyperadrenocorticism leading to increased levels of circulating corticosterones in the body. Not all pathways of the SR respond to every stressor, and although there may be some overlap, generally, SR pathways are quite specific. The specificity of the response is mostly determined by the nature of the damage induced by the stressor and the variety of downstream effectors involved. For example, cytoplasmic induction of protein denaturation by heat, heavy metals, and antibiotics will initiate the so-called heat shock response (HSR) by inducing the synthesis of heat shock proteins (HSP) followed by the activation of proteasome-mediated protein degradation ([Liberek et al., 2008](#); [Verbeke et al., 2001](#)). However, unfolded proteins in the endoplasmic reticulum (ER) will induce unfolded protein response (UPR) and will initiate the induction of synthesis of a totally different set of proteins and their downstream effectors ([Banhegyi et al., 2007](#); [Yoshida, 2007](#)). Similarly, whereas oxidative damage to proteins will generally initiate Nrf2-mediated antioxidant response, damage to DNA by free radicals or other agents will result in the activation

Table 16.1 Major Pathways of Stress Response in Human Cells

Stress response	Stressors	Effectors
Heat shock response (HSR)	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome, and other proteins
Unfolded protein response (UPR)	Unfolded and misfolded proteins in endoplasmic reticulum	Chaperones and co-chaperones
Autophagic response	Food limitation, hypoxia, damaged organelles	Lysosomes
DNA-repair response	Radiation, oxidants, free radicals	DNA-repair enzymes
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme oxygenase, FOXO
Sirtuin response	Energy depletion	Sirtuins
NFκB inflammatory response	Pathogens, allergens, damaged macromolecules	Cytokines, nitric oxide synthase

of DNA repair enzymes. In the same vein, whereas nutritional deprivation and low energy levels will activate autophagy and FOXO-sirtuin pathways, infections and antigenic challenge will generally initiate pro-inflammatory NF κ B response.

However, often, the source of activation (stressor) cannot be easily identified and may involve more than one stressor and their effectors. Examples of such SR include early inflammatory SR and neuroendocrinal SR, which lead to the synthesis and release of interleukins and corticoid hormones, respectively. Similarly, pathways involving NF- κ B, Nrf2, FOXO, sirtuins, and heme-oxygenase (HO) activation may involve more than one type of stressors and stress signals, including pro-oxidants, free radicals, reactive oxygen species (ROS), and nutritional components. But most importantly, an appropriate and optimal SR is an essential aspect of successful homeodynamics and continued survival.

4. STRESS, HORMESIS, AND HORMETINS

The consequences of SR can be both harmful and beneficial depending on the intensity, duration, and frequency of the stress and on the price paid in terms of energy utilization and other metabolic disturbances. But the most important aspect of SR is that it is not monotonic with respect to the dose of the stressor; rather, it is almost always characterized by a non-linear biphasic relationship. Several meta-analyses performed on a large number of papers published in the fields of toxicology, pharmacology, medicine, and radiation biology have led to the conclusion that the most fundamental shape of the dose response is neither threshold nor linear but is U- or inverted U-shaped depending on the endpoint being measured (Calabrese, 2008; Calabrese et al., 2007). This phenomenon of biphasic dose response was termed as hormesis (Southam and Ehrlich, 1943), and the science and study of hormesis is now termed as hormetics (Rattan, 2012a).

The key conceptual features of hormesis are the disruption of homeodynamics, the modest overcompensation, the re-establishment of homeodynamics, and the adaptive nature of the process. An example of stress-induced hormesis is the well-documented beneficial effects of moderate exercise as a hormetic agent, which initially increases the production of free radicals, acids, and aldehydes (Radak et al., 2008). Another frequent observation in studies of hormesis is that a single hormetic agent, such as heat shock or physical activity, can improve the overall homeodynamics of cells and enhance other activities such as tolerance to other stresses, by initiating a cascade of processes resulting in a biological amplification and eventual beneficial effects (Mattson, 2008; Rattan, 2008).

Hormesis in aging is defined as the life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress. Various mild stresses that have been reported to delay aging and prolong longevity in cells and animals include temperature shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise, and food restriction. All such compounds, which bring about biologically beneficial effects by causing mild stress and thus stimulating defense

pathways, are termed as hormetins (Rattan, 2008; Rattan and Demirovic, 2010; Rattan et al., 2009). Hormetins may be categorized as: (1) physical hormetins, such as exercise, heat, and radiation; (2) psychological hormetins, such as mental challenge and focused attention or meditation; and (3) biological and nutritional hormetins, such as infections, micronutrients, spices, and other sources.

5. NUTRITIONAL HORMETINS

Among different types of hormetins, nutritional hormetins, and especially those derived from plant sources, have generated much scientific interest for their health beneficial effects. This is because of the realization that not all chemicals found in plants are beneficial for animals in a simple and straightforward manner, but rather they cause molecular damage by virtue of their electrochemical properties and have a typical biphasic hormetic dose response (Balstad et al., 2011). Although the exact nature of the initial molecular damage caused by such compounds may not be easily identified, an activation of one or more SRs, as listed in the Table 16.1, is a good indicator of the primary action of the compound.

For example, the antioxidant response by the activation of Nrf2 transcription factor follows the electrophilic modification/damage of its inhibitor protein Keap1, which then leads to the accumulation, heterodimerization, nuclear translocation, and DNA binding of Nrf2 at the antioxidant response element (ARE), resulting in the downstream expression of a large number of the so-called antioxidant genes, such as heme oxygenase HO-1, superoxide dismutase, glutathione, and catalase (Balstad et al., 2011; Calabrese et al., 2008, 2010). Some well-known phytochemicals, which strongly induce Nrf2-mediated SR, include curcumin, quercetin, genistein, and eugenol (Balstad et al., 2011; Lima et al., 2011). A similar induction of SR involving Nrf2 has also been reported for various food extracts, such as coffee, turmeric, rosemary, broccoli, thyme, clove, and oregano (Balstad et al., 2011; Demirovic and Rattan, 2011). Screening for other inducers of Nrf2 SR in natural compounds isolated from nutritional sources, or synthetic compounds with nutritional utility, and in complex and multiple food extracts will discover novel hormetins useful for healthy aging and longevity.

Another SR pathway, which has been studied in detail and can be the basis for identifying novel nutritional hormetins, is the so-called HSR. Induction of proteotoxic stress, such as protein misfolding and denaturation, initiates HSR by the intracellular release of the heat shock transcription factor (HSF) from their captor-proteins, followed by its nuclear translocation, trimerization, and DNA binding for the expression of several heat shock proteins – HSPs (Liberek et al., 2008; Verbeke et al., 2001). A wide range of biological effects then occur which involve HSPs and include protein repair, refolding, and selective degradation of abnormal proteins leading to the cleaning up and an overall improvement in the structure and function of the cells. Various phytochemicals and

nutritional components have been shown to induce HSR and have health beneficial effects, including anti-aging and longevity-promoting effects. Some examples of nutritional hormetins involving HSR are phenolic acids, polyphenols, flavanoids, ferulic acid (Barone et al., 2009; Son et al., 2008), geranylgeranyl, rosmarinic acid, kinetin, zinc (Berge et al., 2008; Son et al., 2008; Sonneborn, 2010), and the extracts of tea, dark chocolate, saffron, and spinach (Wieten et al., 2010). Further screening of animal and plant components, for their ability to induce HSR, will identify other potential hormetins.

Other pathways of SR, which are involved in initiating hormetic effects of nutritional components, are the NF κ B, FOXO, sirtuins, DNA repair response, and autophagy pathways. Resveratrol and some other mimetics of calorie restriction work by the induction of one or more of these SR pathways (Longo, 2009; Sonneborn, 2010). Hormesis may also be an explanation for the health beneficial effects of numerous other foods and food components, such as berries, garlic, Gingko, and other fruits and vegetables. Discovering novel nutritional hormetins, by putting potential candidates through a screening process for their ability to induce one or more SR pathways in cells and organisms, can be a promising strategy. Finally, understanding the hormetic and interactive mode of action of natural and processed foods is a challenging field of research and has great potential in developing nutritional and other lifestyle modifications for aging intervention and therapies.

REFERENCES

- Balstad, T.R., Carlsen, H., Myhrstad, M.C., et al., 2011. Coffee, broccoli and spices are strong inducers of electrophile response element-dependent transcription in vitro and in vivo – studies in electrophile response element transgenic mice. *Molecular Nutrition & Food Research* 55, 185–197.
- Banhegyi, G., Baumeister, P., Benedetti, A., et al., 2007. Endoplasmic reticulum stress. *Annals of the New York Academy of Sciences* 1113, 58–71.
- Barone, E., Calabrese, V., Mancuso, C., 2009. Ferulic acid and its therapeutic potential as a hormetin for age-related diseases. *Biogerontology* 10, 97–108.
- Berge, U., Kristensen, P., Rattan, S.I.S., 2008. Hormetic modulation of differentiation of normal human epidermal keratinocytes undergoing replicative senescence in vitro. *Experimental Gerontology* 43, 658–662.
- Calabrese, E.J., 2004. Hormesis: from marginalization to mainstream: a case for hormesis as the default dose-response model in risk assessment. *Toxicology and Applied Pharmacology* 197, 125–136.
- Calabrese, E.J., 2008. Hormesis and medicine. *British Journal of Clinical Pharmacology* 66, 594–617.
- Calabrese, E.J., Bachmann, K.A., Bailer, A.J., et al., 2007. Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. *Toxicology and Applied Pharmacology* 222, 122–128.
- Calabrese, V., Cornelius, C., Mancuso, C., et al., 2008. Cellular stress response: a novel target for chemoprevention and nutritional neuroprotection in aging, neurodegenerative disorders and longevity. *Neurochemical Research* 33, 2444–2471.
- Calabrese, V., Cornelius, C., Dinkova-Kostova, A.T., Calabrese, E.J., Mattson, M.P., 2010. Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxidants & Redox Signaling* 13, 1763–1811.
- Demirovic, D., Rattan, S.I.S., 2011. Curcumin induces stress response and hormetically modulates wound healing ability of human skin fibroblasts undergoing ageing in vitro. *Biogerontology* 12, 437–444.

- Holliday, R., Rattan, S.I.S., 2010. Longevity mutants do not establish any “new science” of ageing. *Biogerontology* 11, 507–511.
- Liberek, K., Lewandowska, A., Zietkiewicz, S., 2008. Chaperones in control of protein disaggregation. *EMBO Journal* 27, 328–335.
- Lima, C.F., Pereira-Wilson, C., Rattan, S.I., 2011. Curcumin induces heme oxygenase-1 in normal human skin fibroblasts through redox signaling: Relevance for anti-aging intervention. *Molecular Nutrition & Food Research* 55, 430–442.
- Longo, V.D., 2009. Linking sirtuins, IGF-I signaling, and starvation. *Experimental Gerontology* 44, 70–74.
- Mattson, M.P., 2008. Hormesis defined. *Ageing Research Reviews* 7, 1–7.
- Mattson, M.P., Calabrese, E. (Eds.), 2010. *Hormesis – a revolution in biology, toxicology and medicine*. Springer, New York.
- Radak, Z., Chung, H.Y., Koltai, E., Taylor, A.W., Goto, S., 2008. Exercise, oxidative stress and hormesis. *Ageing Research Reviews* 7, 34–42.
- Rattan, S.I.S., 2000. Biogerontology: the next step. *Annals of the New York Academy of Sciences* 908, 282–290.
- Rattan, S.I.S., 2006. Theories of biological aging: genes, proteins and free radicals. *Free Radical Research* 40, 1230–1238.
- Rattan, S.I.S., 2007. Homeostasis, homeodynamics, and aging. In: Birren, J. (Ed.), *Encyclopedia of Gerontology*. 2nd edn. UK, Elsevier Inc.
- Rattan, S.I.S., 2008. Hormesis in aging. *Ageing Research Reviews* 7, 63–78.
- Rattan, S.I.S., 2012a. Rationale and methods of discovering hormetins as drugs for healthy ageing. *Expert Opinion on Drug Discovery* 7, 439–448.
- Rattan, S.I.S., 2012b. Biogerontology – from here to where? The Lord Cohen Medal lecture–2011. *Biogerontology* 13, 83–91.
- Rattan, S.I.S., Demirovic, D., 2010. Hormesis can and does work in humans. *Dose-Response* 8, 58–63.
- Rattan, S.I.S., Fernandes, R.A., Demirovic, D., Dymek, B., Lima, C.F., 2009. Heat stress and hormetin-induced hormesis in human cells: effects on aging, wound healing, angiogenesis and differentiation. *Dose-Response* 7, 93–103.
- Son, T.G., Camandola, S., Mattson, M.P., 2008. Hormetic dietary phytochemicals. *Neuromolecular Medicine* 10, 236–246.
- Sonneborn, J.S., 2010. Mimetics of hormetic agents: stress-resistance triggers. *Dose-Response* 8, 97–121.
- Southam, C.M., Ehrlich, J., 1943. Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture. *Phytopathology* 33, 517–524.
- Verbeke, P., Fonager, J., Clark, B.F.C., Rattan, S.I.S., 2001. Heat shock response and ageing: mechanisms and applications. *Cell Biology International* 25, 845–857.
- Wieten, L., van der Zee, R., Goedemans, R., et al., 2010. Hsp70 expression and induction as a readout for detection of immune modulatory components in food. *Cell Stress & Chaperones* 15, 25–37.
- Yoshida, H., 2007. ER stress and diseases. *FEBS Journal* 274, 630–658.