Cosmetics **2015**, *2*, 11-20; doi:10.3390/cosmetics2010011

OPEN ACCESS

cosmetics

ISSN 2079-9284

www.mdpi.com/journal/cosmetics

Review

Hormetins as Novel Components of Cosmeceuticals and Aging Interventions

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Academic Editor: Enzo Berardesca

Received: 29 October 2014 / Accepted: 22 December 2014 / Published: 6 January 2015

Abstract: A promising strategy for maintaining a healthy and youthful phenotype during aging is that of mild stress-induced beneficial hormesis. The basis of hormesis lies in the molecular pathways of stress response, which are essential for the survival of a biological system by activation of maintenance and repair mechanisms in response to stress. Moderate physical exercise is the best example of a hormetin that brings about a wide range of health beneficial hormesis by first challenging the system. Similarly, other natural and synthetic hormetins can be incorporated in cosmeceutical formulations, and can help achieve benefits including maintenance of the skin structure and function. Several polyphenols, flavonoids and other components from spices, algae and other sources are potential hormetins that may act via hormesis. Stress response pathways that can be analyzed for screening potential hormetins for use in cosmetics and cosmeceuticals include heat shock response, autophagy, DNA damage response, sirtuin response, inflammatory response and oxidative stress response.

Keywords: aging; anti-aging; homeodynamics; hormetics; hormesis; stress

1. Introduction

Cosmetics and cosmeceuticals fulfill an important psycho-social-biological need of human beings in feeling good about themselves and in trying to maintain the structural and functional integrity of the body, especially that of the skin. Scientific research on understanding the biological basis of aging has

made tremendous advances, and a general framework about aging, age-related changes and strategies for intervention, has been developed [1–6]. Most importantly, biological aging is now viewed as an emergent phenotype due to the failure of maintenance and not due to the execution of any programme involving the so-called gerontogenes [2,7–10]. This understanding can change our approach towards aging interventions from anti-aging reversion to achieving healthy aging by preserving the function and enhancing robustness and resilience.

The aim of this article is to provide a brief overview of the biogerontological understanding of aging, to present the phenomenon of stress-induced beneficial hormesis, and to discuss the potential use of hormesis-inducing natural and synthetic hormetins as novel components of cosmeceuticals.

2. Biogerontology in a Nutshell

Research on the biology of aging has established a framework for understanding aging in the context of imperfect survival mechanisms. It is known that the survival of a biological system is a constant struggle between the occurrence of molecular damage and the mechanisms of maintenance and repair. There are three major sources of damages to molecules within a cell: (1) reactive chemical species, including free radicals, formed as a consequence of intra-cellular metabolism involving oxygen, metals and other metabolites, and external inducers of damage, such as radiation and pollutants; (2) nutritional components such as glucose and its metabolites; and (3) spontaneous errors in biochemical processes, such as in DNA duplication, transcription, post-transcriptional processing, translation, and post-translational modifications. Millions of damaging events occur in cells constantly, and in the absence of a wide range of complex molecular, cellular and physiological pathways of maintenance and repair the survival of a system will be impossible. All these processes and their interactions give rise to a network of maintenance and repair systems, which are the ultimate determinants of an individual's chance and ability to survive and to maintain a healthy state [8,11–14].

Living systems have the intrinsic ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional conceptual model to describe this property is homeostasis, which has dominated biology, physiology and medicine since 1930s, but is incomplete and outdated. The main reason for the incompleteness of the homeostasis model is its defining principle of "stability through constancy", which does not take into account the dynamic and interacting nature of the living systems. Instead, the term homeodynamics is being increasingly used to account for the fact that the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is in a dynamic regulation and interaction among various levels of organization [15]. Thus, homeodynamics is the property of living systems that enables them to counteract stress, adapt, survive and maintain health. Homeodynamics is characterized by three main components: (i) stress response (SR); (ii) damage repair and removal processes; and (iii) constant remodeling and adaptation [12]. These components of homeodynamics involve hundreds of genes and their interacting networks of gene-products, which are essential for survival.

With respect to aging and longevity, evolutionary processes have shaped, sharpened and determined the extent and size of the homeodynamic space of a species in order to assure its survival until, at least, reproduction and continuation of generations. This duration of life is known as the essential lifespan (ELS) [16,17]. Of course, numerous genes and their products are involved in the regulation and

determination of ELS, and such genes are known as the longevity assurance genes. Although molecular damage occurs and even accumulates right from the time of birth, it is after the period of ELS that an exponential accumulation of molecular damage can be observed clearly. Biologically, it is this period of survival beyond ELS, which is considered to represent the process of aging, and which happens due to the progressive failure of homeodynamics, but without any specific geronto-genetic program to cause it [17–20]. The process of aging is the basis of all changes in all parts of the body, and lead to structural and functional impairment, to senescence, to increased probability of emergence of various age-related diseases and to eventual death.

3. Modulation of Aging through Hormesis

Although a wide variety of approaches to intervene in the process of aging are being tested and developed, a promising and novel biotechnological strategy for modulating aging is that of mild stress-induced hormesis [21]. The consequences of stress can be both harmful and beneficial depending on the intensity, duration and frequency of the stress, and on its cost in terms of energy utilization and other metabolic disturbances. However, the most important aspect of biological SR is that it is not monotonic with respect to the dose of the stressor. SR is almost always characterized by a nonlinear 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-shaped or inverted U-shaped, depending on the endpoint being measured [22–24]. This phenomenon of biphasic dose response, in which exposures to low levels of potentially toxic compounds had opposite or non-toxic and even beneficial effects, was termed as hormesis [25]. The terminology for hormesis has been further refined to specify the nature of the hormetic responses, such as physiological hormesis, pre-conditioning hormesis, and post-exposure conditioning hormesis [26]. It should be pointed out that hormesis is distinct from the claims made by homeopathy which does not show any biphasic dose response [24].

The best example of hormesis is moderate physical exercise, which is biochemically a stressor, but leads to biologically health beneficial effects much beyond the local target of exercise. Hormesis has now been shown to have numerous practical applications in slowing down aging, strengthening the homeodynamics, increasing the longevity and improving the overall health [27–29]. The conditions or hormetic agents which initially cause slight disruption of homeodynamics, but which then lead to achieving physiologically beneficial effects, are known as hormetins [29–33].

There is a large body of evidence demonstrating successful applications of mild stress-induced hormesis in experimental model animals and in humans [27,29,34]. These stresses are versatile and include physical exercise, nutritional components, fasting, micronutrients, irradiation, heat, ischemia, and even mental challenge. The biologically beneficial effects achieved through such hormetin-based interventions include slowing down cellular aging and senescence *in vitro*, extension of cellular and organismic lifespan, enhancement of stress tolerance, improved maintenance, repair and removal of macromolecular damage, and overall strengthening of the homeodynamics [27,29,34]. Recently, novel hormetins, especially those derived from plant sources, have generated much scientific interest for their beneficial effects. Some examples of such hormetins are phenolic acids, polyphenols, flavonoids,

ferulic acid, geranylgeranyl, rosmarinic acid, resveratrol, kinetin, and the extracts of tea, dark chocolate, saffron and spinach [29–33].

The basis of hormesis lies in the biological property of homeodynamics, of which a crucial component is the SR. Early detection of damage or disturbance by a stressor is followed by the activation of one or more series of biochemical processes including the activation of repair, removal and maintenance mechanisms. Major SR pathways identified in mammalian cells and tissues, including in the skin, are depicted in Figure 1. In addition to these, stress-induced kinases [35] and the response to hypoxia [36] are other important pathways, which are not discussed here. For each pathway, there is detailed information available with respect to the immediate and delayed steps, such as transcriptional factor translocation, specific gene-expression activation, and synthesis of hundreds of protective enzymes, chaperones and other proteins involved in macromolecular degradation of damaged macromolecules and organelles [37,38].

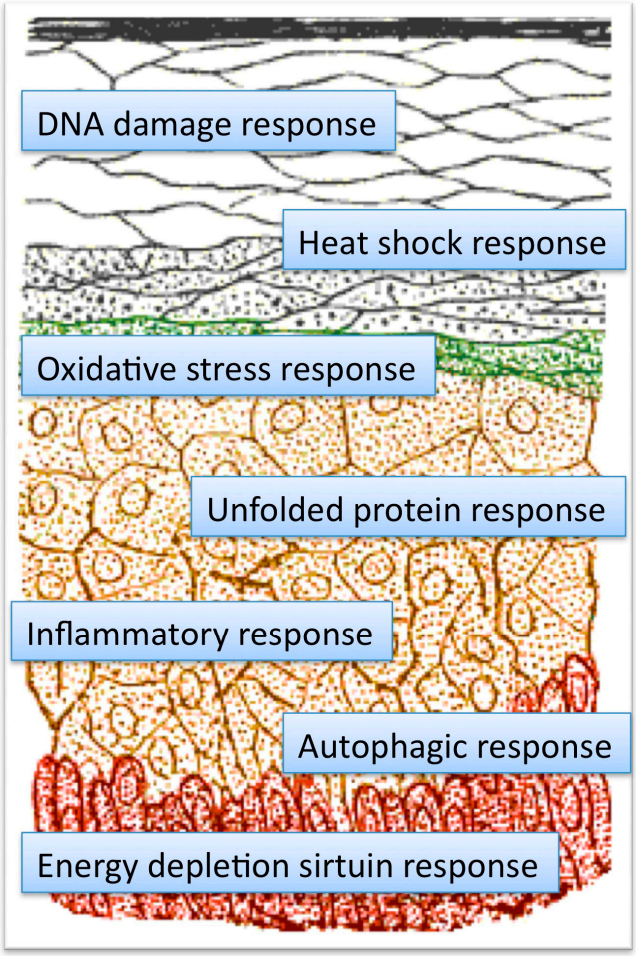

Figure 1. Major stress response pathways in the skin, which detect disruption of the homeodynamics and initiate a series of maintenance and repair processes, with eventual health beneficial effects.

4. Hormesis and Hormetins in Cosmetics

As discussed above, conditions that bring about biologically beneficial effects by initially causing molecular damage, which then leads to the activation of one or more SR pathways and thereby

strengthens the homeodynamics, are termed as hormetins. These may be further categorized as: (1) physical hormetins, such as exercise, thermal shock and irradiation; (2) psychological hormetins, such as mental challenge and focused attention or meditation; and (3) biological and nutritional hormetins, such as micronutrients, spices and other interventions including calorie restriction and fasting.

Discovering novel 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. Previously, a general scheme for screening natural and synthetic compounds or complex extracts for potential hormetic use for human beings was put forward [33]. A modified version of this scheme is presented in Figure 2 in the context of the skin and cosmeceuticals. For example, monotypic or mixed-cultures of keratinocytes, fibroblasts and melanocytes, and/or 3D-*in vitro* skin model systems may be most appropriate for screening for potential hormetins as components of cosmetics and cosmeceuticals. The screening scheme, as presented here, may appear to be quite complex and not feasible in its entirety. However, further refinement of the scheme within the limitations of the available techniques can easily be done for practical purposes. Furthermore, the choice of early and late markers of stress-induced pathways can also be modified according to the need of the screening protocol.

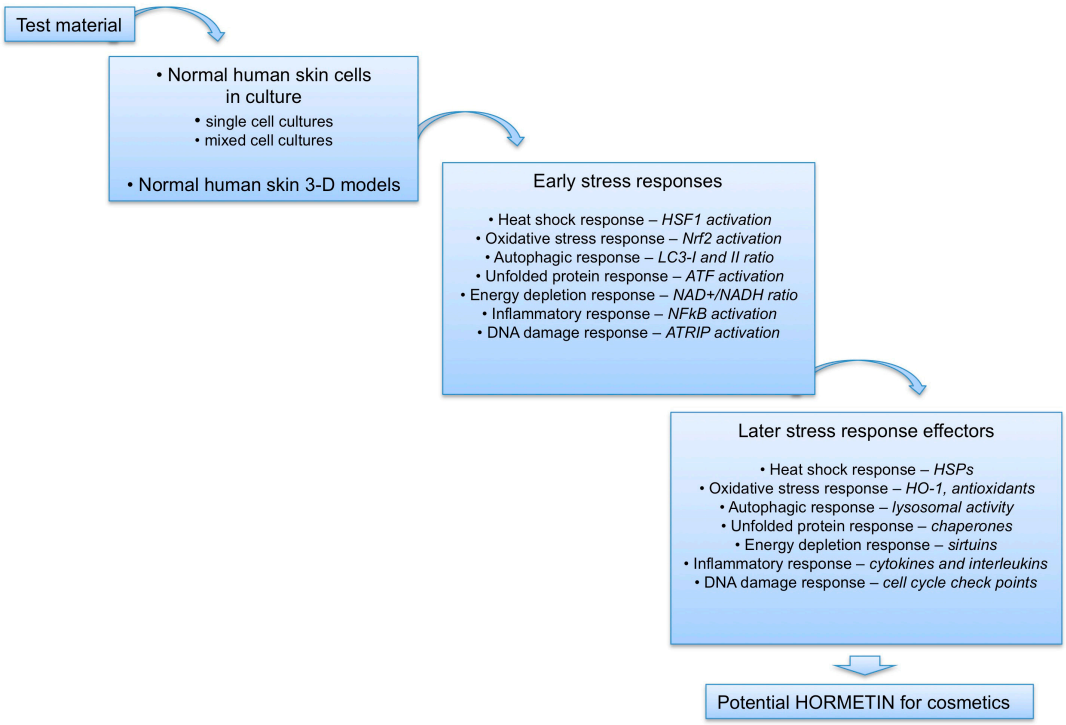

Figure 2. A scheme for the screening of potential hormetins for cosmeceuticals by analyzing the immediate stress response markers and late effector molecules for the maintenance and repair in cell cultures and 3D skin models.

Analysing SR pathways for their immediate response, followed by the determination of amounts and activities of downstream effector molecules will be the first screen for identifying potential hormetins. Although the exact nature of the initial molecular event caused by a compound may not be easily identified, activation of one or more SR pathways is a good indicator of the primary action of a potential hormetin. It should be pointed out that the specificity of a potential hormetin is mostly determined by the nature of the molecular change induced by the test material and the variety of

downstream effectors involved. For example, while protein denaturation initiates heat shock response followed by the activation of proteasome-mediated protein degradation [39–42], unfolded proteins in the endoplasmic reticulum (ER) induce unfolded protein response (UPR) [43]. Similarly, DNA damage induces the DNA repair response; oxidants induce the Nrf2-mediated antioxidant response; food restriction and calorie restriction (CR) induce autophagy [44,45]; energy limitation induces the sirtuin response [46]; and inflammatory agents induce the NF-kB response [47]. Modulation of all these pathways by mild stress-induced hormesis has been shown to have health maintaining, therapeutic and longevity promoting effects in a wide range of biological systems, including humans [29–31]. However, one significant aspect of hormesis is that although the starting point or the initial target of a stressor, such as exercise, may be specific and the immediately observable effects could be quite small, repeated hormetic exposures lead to a biological amplification of effects at the whole body level [29–31].

An example of a successful skin care cosmetic product developed by incorporating the ideas of hormesis is based on the studies to analyse the molecular effects of active ingredients extracted from the roots of the Chinese herb Sanchi *(Panax notoginseng)* on gene expression at the level of mRNAs and proteins in human skin cells [48] The results showed that the ginsenosides extracted from Sanchi induced the transcription of stress genes and increased the synthesis of stress proteins, especially the heat shock protein HSP1A1 or Hsp70, in normal human keratinocytes and dermal fibroblasts. Furthermore, this extract also has significant positive effects against facial wrinkles and other symptoms of facial skin aging as tested clinically, which may be due to its hormetic mode of action by stress-induced synthesis of chaperones involved in protein repair and removal of abnormal proteins [48]. (also see: http://www.givenchybeauty.com/en/skincare/vaxin-for-youth/inspiration).

5. Conclusions and Perspectives

Applying the ideas from the science of hormetics can discover and develop potentially useful compounds with specific targets for structural and functional maintenance of the skin. Hormetins can strengthen the homeodynamics, increase robustness of the system and enhance resilience [29]. Just as in the case of exercise-induced hormetic benefits via heat shock protein synthesis, hormetins such as ginsenosides in the cosmeceutical formulations [48] may be considered as performing a kind of intracellular molecular exercise. Certain CR mimetics may prove to be effective hormetins acting via autophagic and sirtuin-dependent SR pathways [49–53]. Other pro-oxidants which induce Nrf2-based SR pathways, such as curcumin, quercetin, polyphenols and flavonoids [54–56], and mildly proinflammatory compounds acting through NFkB pathways [57] can also be investigated as potential hormetins. Other compounds and conditions such as those inducing DNA damage response [58] and hypoxia may be potential hormetins [59]

Of course, there are several issues with respect to the vehicles, topical applications, and transdermal penetration of hormetins that need to be resolved [60]. Furthermore, it is also important to know whether several hormetins can be combined or not, and what other effects of hormetins may emerge. All these issues and concerns can be addressed by undertaking systematic scientific research. In principle, hormetins from natural and synthetic sources can be a highly successful strategy to develop novel cosmetics and cosmeceuticals.

Conflicts of Interest

The author declares no conflict of interest.

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