Role of Phytochemicals in Eliciting Longevity Genes

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Abstract

Phytochemicals are diverse secondary metabolites derived from plants, and it has been proven that phytochemicals can extend longevity by evolutionarily conserved mechanisms. The positive impact of dietary phytochemicals on overall health and longevity has been studied extensively over the past decade. The emerging role of phytochemicals as an effector of metabolic and longevity signals offers new therapeutic perspectives. In this regard, we will discuss the role of phytochemicals in eliciting the longevity genes and also the various mechanisms involved. This review will give a broad outline of how different phytochemicals modulate signaling pathways that modulate the expression of specific set of genes. This review will also highlight the most exciting perspective for research in the future in this rapidly developing field of signaling pathways which include the genes encoding heat shock protein, genes responsible for the antioxidant response, genes involved in metabolism, etc. and are crucial for the phytochemicals to elicit longevity.

Despite various beneficial biological functions, phytochemicals might have adverse side effects like carcinogenicity and genotoxicity at high doses or concentrations. Hence, the future research challenge is to determine the optimal dose range and to perform intervention studies in order to improve longevity.

Keywords

Aging · Phytochemicals · Longevity · Oxidative stress

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17.1 Introduction

Life expectancy is defined as the average total number of years that a species is expected to live. Differently, life span is the duration of time that one individual lives from birth till death. Maximum life span is an inherent characteristic of each and every species and remains relatively unaltered through generations, while it may be increased or decreased over generations that needs a number of biological pathways to be altered, rewired, or reprogrammed (Ma et al. 2015). Even though human life span has been unaltered for the past million years at approximately 125 years, life expectancy has gradually increased (~27 years during the last century), especially in Western countries (Hayflick 2000). This increase might be mainly due to the control of many communicable diseases by the invention of antibiotics and preventive measures like vaccination that had ultimately resulted in population aging (Elavarasan et al. 2012), which reflects a human success story of increased longevity. In the current global scenario, living up to the age of 70 or 80 is common in many parts of the world. Human population in the world had reached 7 billion in 2012, among which 562 million (or 8.0%) were aged 65 and above. In 2015, 3 years later, the elderly population rose by 55 million, and it reached 8.5% of the total population of the world (World Population Aging 2015). Among the various continents, Asia is referred to as the population giant, in terms of size of its older population (617.1 million in 2015), which is more than half of the world's aging population. By the year 2050, nearly 1000 million older people are projected to live in Asia, accounting for about two-thirds (62.3%) of the world's total older population even though the estimated speed of aging for Asia and Latin America remain the same (World Population Aging 2015).

Aging or senescence is the decline in the ability of the organism to withstand stress of any kind resulting in the increased risk for mortality and morbidity. "Senescence" is derived from the Latin word *senex*, meaning "old age." The analysis that many animals living in a natural environment generally die earlier because of natural causes like disease, predation, starvation, or drought (Holliday 2006)] suggests that aging is a unique phenomenon applicable to the highly evolved human species (Hayflick 2000).

Many gerontologists accept that aging is an adaptive process, caused by factors of multiple etiologies, and these factors tend to get modulated by the genetic and environmental factors (Holliday 1995). The detrimental effects of aging are best observed in postmitotic tissues, where cells that are irreversibly damaged or lost cannot be replaced by mitosis of intact ones (Murali et al. 2008).

Increasing life span without proper health is deleterious. Survival with good health and physiological functions has been termed as "successful aging," "healthy aging," or "exceptional aging." Research with supercentenarians have revealed that people with longevity have the onset of disease with disability and decline in physical and cognitive function at older ages; thereby their health span approaches life span (Andersen et al. 2012). Nearly 30% of centenarians and 70% of supercentenarians escape many of the major age-related diseases including dementia, or many of the centenarians and supercentenarians have exhibited a delay on the onset of major age-related disease until age ≥80 years. Even though women have the greater

probability of survival, male centenarians have better cognitive and physical functional status (Newman and Murabito 2013).

Many different molecular players have been identified to be responsible for longevity: Apo E (Schächter et al. 1994), cholesteryl ester transfer protein (CETP) (Koropatnick et al. 2008), Forkhead box protein O3 (FOXO3A) (Willcox et al. 2008), insulin-like growth factor 1 (IGF-1), mammalian target of rapamycin (mTOR) (Kenyon 2010), RAC-alpha serine/threonine-protein kinase (AKT1) (Pawlikowska et al. 2009), sirtuins (Lin et al. 2000), and mitochondrial DNA haplotypes 9 (Alexe et al. 2007).

The exact mechanisms by which these longevity genes are shown to modulate the aging process are still unknown except for few genes. However, it is clear that these genes are involved in pathways of lipid metabolism and DNA repair which delay the onset of age-associated diseases like cardiovascular disease, dementia, and Alzheimer's disease. Meta-analysis of all compiled human genome-wide association study (GWAS) conducted to broadly examine the genetics of resistance to age-associated disease by Jeck et al. (2012) identified ten different locations across the genome which are shown to be associated with the susceptibility to multiple age-related diseases. These locations have genes associated with cellular senescence or inflammation pathways, portraying the significance of these pathways in influencing the human health span. Even though a number of genes have been identified, it is undeniable that many genetic variants combine to influence human life span: no single gene variant is found to be responsible.

Healthy longevity has been an unrelenting quest of human from ancient times. Exceptional longevity is a complex trait which is not only determined by genetic factors but also by external and environmental factors (Christensen et al. 2006). The major external factors that affect longevity include dietary patterns, stress, and sedentary lifestyle. The environmental factors include exposure to toxicants and pollutants that interfere with normal metabolic and physiological processes leading to mutations or decline of organ functions.

Even though the complex relationship among dietary habits/intervention and aging has not been fully explored, research from animals and human data suggest that dietary intervention can retard aging process, preventing or protecting them from various age-associated diseases and their pro-inflammatory status, the inflammaging (Fontana and Partridge 2015). Healthy diets with less concentrations of refined sugars and proteins from animal sources can substantially decrease the risk of age-related diseases, thereby favoring successful aging and longevity (Longo et al. 2015). On the contrary, a bad dietary lifestyle is shown to accelerate the aging process by modulating the pathways and mitogenic stimuli, finally accelerating aging phenotype (Verburgh 2015).

Moreover, effective interventions have to be developed to sustain or enhance longevity as the younger generations are having a lifestyle that leads to obesity, which makes them less healthy, and even they tend to have shorter lives than their parents. Dietary and pharmacological interventions such as restriction of food or methionine (Flurkey et al. 2010) and administration of rapamycin, an inhibitor of mTORC1 (Miller et al. 2014), can retard aging by comprehensive interactions of multiple targets.

Phytochemicals called as nutraceuticals are defined as naturally derived bioactive compounds that are found in plant kingdom and have health benefits. Nutraceutical is a conjunction among nutrition and pharmaceutics, and it was coined in 1989 by Stephen De Felice (Gupta et al. 2010). However, many nutraceuticals have been referred to as agents that delay aging or age-related diseases; the translational gap between basic and clinical research has yet to be filled. Many in vitro and in vivo experimental evidences suggest that phytochemicals can influence the expression of numerous longevity genes, but the molecular interactions between phytochemicals and signaling pathways that modulate aging and age-related diseases are obscure. These dietary phytochemicals trigger a condition called hormesis (Verburgh 2015), which states their ability to induce the stress-protective gene expression and resist aging.

Many cellular proteins and signaling pathways have been identified as candidates that are indispensable for life span prolonging. We will discuss about the major cellular proteins that influence aging and few phytochemicals that modulate the expression of longevity genes.

17.2 Signaling Proteins and Aging

17.2.1 Proteins That Boost Antioxidant Status

The free radical theory of aging proposes that aging occurs as a consequence of the deleterious effects of free radicals produced during cellular metabolism (Harman 1981). Oxidative stress is caused due to the loss of balance between ROS production and antioxidant defenses affecting all the vital organs resulting in aging. Hence, circumventing oxidative stress is one of the key processes involved in delaying aging and age-associated diseases.

17.2.2 Key Proteins That Regulate Life Span

The key proteins and pathways that regulate life span directly or indirectly by reducing oxidative stress include Nrf2 (Kensler et al. 2007), insulin/IGF1 signal transduction pathway (Kenyon 2010), DAF 16/FOXO (Kwon et al. 2010), sirtuins (Imai et al. 2000), and heat shock factor 1 (HSF-1) (Shemesh et al. 2017).

17.3 Phytochemicals and Antiaging

The dream of longevity is not new, and a multitude of reviews have been written to address the process of aging in an elaborate fashion (Murphy and Partridge 2008). Identification and isolation of long-lived *C. elegans* mutants have triggered an array of research activities to identify many life span-modulating genes, and *C. elegans* mutant has been the organism for studying anti-aging strategies.

17.3.1 Garlic

Allium vegetables including garlic and onion have been reported to have health benefits from ancient times (Rivlin 2001). Epidemiological studies have identified that diets rich in *Allium* vegetables are associated with lowered risk of cancer (Tanaka et al. 2004 and other age-associated diseases like diabetes, neurological diseases (Powolny and Singh 2008), and cardiovascular disease (Ried et al. 2008).

Different forms of garlic including raw garlic, garlic oil, garlic powder, oil-extracted garlic macerates, aged garlic extract (AGE), and individual garlic-derived compounds such as ajoene, *S*-allyl cysteine, diallyl thiosulfinate (allicin), diallyl disulfide (DADS), and diallyl trisulfide (DATS) have been tested (Charron et al. 2016) for cardiovascular benefits and antiaging potential. S-Allyl-L-cysteine (SAC) is the primary thio-allyl compound in aged garlic extract (AGE), and the antiaging effects of SAC were extensively studied by Moriguchi et al. (1997). His studies have shown that chronic intake of a low dosage of SAC in the diet improved the deficit in learning performance in SAMP8 mice and memory consolidation in SAMP10 mice. These findings have substantiated that SAC helps in reducing age-related learning disabilities and cognitive disorders.

Chronic administration of S-allyl cysteine is also shown to activate Nrf2 factor, one of the longevity genes, and enhance the activity of antioxidant enzymes in the striatum, frontal cortex, and hippocampus in Wistar rat (Franco-Enzástiga et al. 2017). The protective effect of garlic extract on ROS formation, MMP-1 protein and mRNA expressions, cytokines such as interleukin (IL)-1β and IL-6, senescence-associated β-galactosidase activity, and SIRT1 activity in UVB-irradiated HaCaT cells is an added evidence for garlic to act as a potent antiaging agent (Kim 2016).

17.3.2 Coffee

Coffee use dates back to the Stone Age and is one of the three most-popular beverages in the world (alongside water and tea) that is rich in antioxidants and caffeine. In the recent past, coffee has been recognized as a potent beverage for healthful aging, with special emphasis by its ability to protect from cardiovascular diseases (Ding et al. 2014) and mild cognitive impairment (Takahashi and Ishigami 2017). Caffeine, a secondary metabolite with pesticide activity, which paralyzes and kills certain insects is a xanthine alkaloid compound. It acts as a stimulant that fends off drowsiness in humans and is mostly distributed through drinks including tea, coffee, soft drinks, and chocolate.

Park et al. (2017) have studied the association of coffee consumption with total and cause-specific mortality among nonwhite populations and found that increased coffee consumption was associated with a significantly low risk for death in Latinos, Japanese Americans, African Americans, and whites. Similarly Ding et al. (2014) have identified that regular coffee drinking in moderate amounts is associated with a decreased incidence of death from cardiovascular disease, neurological diseases, and

suicide. Moreover, habitual coffee drinking following acute myocardial infarction was shown to be associated with a reduced risk of mortality (Brown et al. 2016).

Sutphin et al. (2012) have reported that caffeine is capable of extending life span and improving health span in *C. elegans*. Life span extension by caffeine might be due to its epistatic interaction with dietary restriction and reduced insulin signaling. Studies by Lublin et al. (2011) have shown that caffeine significantly decreased the age-dependent acceleration of mortality rate which was dependent on DAF- 16.

Studies with worms have been carried out to study the influences from caffeine and non-caffeine sources of coffee with respect to longevity. Dostal et al. (2010) identified SKN-1 as a major downstream signaling molecule involved in the caffeine-independent delay in amyloid beta toxicity using coffee extract. Lublin et al. (2011) identified IIS as an important player in life span extension by caffeine. Moreover, the polyphenol chlorogenic acid present in coffee has lipid-lowering effect in diet-induced obese mice by downregulating sterol regulatory element-binding protein 1 (Takahashi and Ishigami 2017). Studies by Sutphin et al. (2012) have clearly shown that caffeine appears to act, at least in part, by activating the FOXO transcription factor DAF-16 as it could not extend longevity in Daf 16 mutants, but it extended the life span of Sir-2, Hif-1, and Cep-1 mutants to some extent, although the magnitude of effect of caffeine was comparatively lesser in wild type. Hence, it is evident that the life span-extending effects of caffeine may be mediated by several genetic pathways.

17.3.3 Curcumin

A myriad of health benefits have been attributed to curcumin, which was first isolated as "yellow coloring matter" from *Curcuma longa* by Vogel and Pelletier in 1815 (Bandyopadhyay 2014). Curcumin, a known powerful antioxidant, has the capacity to mitigate age-associated cellular damage induced by the production of reactive oxygen species (ROS) (Queen and Tollefsbol 2010). Lee et al. (2010) have reported that curcumin extends life span of different strains of *Drosophila melanogaster* and attributed this effect to its ability to afford protection against improvement in locomotion, oxidative stress, and chemopreventive effects. Extension of life span was also found to be gender as well as genotype specific. Curcumin also is shown to modulate the expression of a plethora of aging-related genes, including the insulin, JNK, and methuselah signaling pathways.

Motterlini et al. (2000) reported that curcumin reduced oxidative stress by upregulating the expression of HO-1 in bovine aortic endothelial cells. In addition, curcumin is also shown to inhibit NF-κB, which is the main mediator of inflammation, to activate the expression of many pro-inflammatory cytokines. Furthermore, curcumin decreases or blocks the mTOR, which integrates the input from multiple signaling pathways and acts as a sensor of cellular nutrient and energy levels and redox status in cells (Sikora et al. 2010). Shen et al. (2013) have shown that curcumin-enriched diets increase antioxidant enzyme activity and mean life span in

Drosophila. A 75% improved life span and activity for curcumin-fed flies in Ab1–42-expressing transgenic *Drosophila* was observed by Caeser et al. (2012).

17.3.4 Quercetin

Quercetin, the major flavonol found in several fruits and vegetables including broccoli, apples, onions, cherries, blueberries, and red grapes, is a natural antioxidant with potential anticancer and antiaging activities. Quercetin is shown to have putative health beneficial effects with special reference to its ability to boost antioxidant status (Belinha et al. 2007). Many studies have identified that quercetin increases the ability of the organism to resist stress and extend life span. Mev-1 mutant, which is characterized by an increased accumulation of endogenous ROS (provides a special test system to prove the antioxidative capacity), exhibited a significant quercetin-mediated gain in life span (Ishii et al. 1998). It is thereby conceivable that the antioxidative property of quercetin may have impacted life span extension in mev-1 mutants. On the other hand, Saul et al. (2008) established that quercetin-mediated longevity is observed in a daf-16(mgDf50) loss-of-function mutant. These finding dictates that the reduction of internal oxidative stress is not the exclusive role of quercetin. Quercetin-induced longevity and stress resistance have been described in three different studies that identified the antioxidant properties and the UNC-43/SEK-1 pathway as the major mechanism behind its life span extension (Pietsch et al. 2009). The other genes that might be tentatively involved in quercetin's ability to increase life span might be age-1 and daf-2, which are central players in IIS to inhibit DAF-16 activity.

17.3.5 Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a polyphenolic phytoalexin which is found in red wine and the skin and seeds of grapes, has been reported to possess a wide range of biological and pharmacological activities including antiaging effects. It increases longevity in the short-lived invertebrates *C. elegans* and *Drosophila* (Howitz et al. 2003) and prolongs life span and retards the onset of age-related markers in a short-lived vertebrate fish *Nothobranchius furzeri* (Valenzano et al. 2006). Resveratrol is shown to affect gustatory responsiveness to a significant extent and is shown to prolong life span in honey bees (wild type) under normal oxygen conditions. Moreover, resveratrol is shown to have a satiety effect on honey bees and further reduce food intake (Rascón et al. 2012). Cidea, a gene which regulates energy balance in brown fat, was upregulated on high-cholesterol diet feeding, and it was downregulated by resveratrol supplementation. This clearly indicates the ability of resveratrol to prevent the deleterious effects of excess caloric intake and modulate known longevity pathways. The life-prolonging ability of resveratrol is caused by influencing the insulin sensitivity, PGC 1 alpha, and sirtuins similar to that of calorie restriction in honey bees (Baur et al. 2006). The knockdown or

knockout of Sirt-1 prevented the autophagy induction by resveratrol in human cells, and it is suggested that autophagy is required for the life span-prolonging ability of resveratrol, similar to that of calorie restriction (Morselli et al. 2010). These studies clearly indicate the ability of resveratrol to prevent the deleterious effect of excess calorie intake and modulate known longevity pathways by mimicking calorie restriction.

17.3.6 Green Tea Catechins

Green tea is obtained from the leaves of the plant *Camellia sinensis*, consumed primarily in China, Japan, and a few countries in North Africa and the Middle East, and is reported to contain 4000 biologically active compounds, one-third of which are polyphenols (Weisburger 2002). Tea and tea flavonoid consumption has been linked to lower incidences of chronic diseases such as cardiovascular disease and cancer (Pandey and Rizvi 2009). The health benefits associated with tea consumption have been attributed in part to the antioxidant and free radical scavenging activity (Rice-Evans 1999). Green tea and its catechins, namely, gallocatechin, (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), (-)-epigallocatechin-3-gallate (EGCG), and catechin and (-)-epicatechin (EC), are best known for their antioxidant properties (Yang et al. 1999).

EGCG treatment increases the mean life span of *C. elegans* and reduces its susceptibility to lethal oxidative stress. Studies by Abbas and Wink (2009) show that EGCG pretreatment suppresses hsp-16.2 expression under oxidative stress and increases the life span.

EGCG is shown to safeguard the aged rats when challenged with hypercholesterolemic diet (Senthil Kumaran et al. 2009). EGCG brought about an augmentation in the activities of enzymic antioxidants like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase and improved the nonenzymic antioxidants like tocopherol, ascorbic acid, and glutathione. EGCG ameliorated the malondialdehyde and protein carbonyl levels and emerged out as a good antioxidant neutraceutical and a neuroprotective agent in alleviating the age-associated oxidative damage in aged rat brain (Srividhya et al. 2009). EGCG is shown to mediate the downregulation of NF-AT and thereby macrophage infiltration in experimental hepatic steatosis (Krishnan et al. 2014). These findings suggest the multifaceted role of EGCG in mitigating age-associated derangements.

17.3.7 Other Phytochemicals Reported as Longevity Agents

The other phytochemicals that have been reported to promote longevity in model organisms are glaucarubinone (Zarse et al. 2011), icariin and its derivative icariside II (Cai et al. 2011), arachidonic acid 5-lipoxygenase inhibitor nordihydroguaiaretic acid (West et al. 2004), aspirin (Strong et al. 2008), phloridzin (Xiang et al. 2011),

butein (Howitz et al. 2003), celastrol (Kiaei et al. 2005), crocin (Bakshi et al. 2009), ellagic acid (Saul et al. 2011), gallic acid (Saul et al. 2011), myricetin (Grünz et al. 2012), oleuropein (Katsiki et al. 2007), tocopherol (Sattler et al. 2004), coenzyme Q10 (Strachecka et al. 2014), tocotrienol (Aan et al. 2013), blueberry extract (Wilson et al. 2006), and tannic acid (Saul et al. 2010).

These studies indicate that even though genetics play a major role in determining the life span, dietary intervention by small molecules can influence many longevity. However, the mechanisms by which they influence the life span extension being still not absolutely identified. From the experimental evidences, it cannot be denied that these small molecular interventions have beneficial effect on healthy aging.

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