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Dietary antiaging phytochemicals and mechanisms associated with prolonged survival

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Abstract

Aging is well-known an inevitable process that is influenced by genetic, lifestyle and environmental factors. However, the exact mechanisms underlying the aging process are not well understood. Increasing evidence shows that aging is highly associated with chronic increase in reactive oxygen species (ROS), accumulation of a low-grade proinflammatory phenotype and reduction in age-related autophagy, suggesting that these factors may play important roles in promoting aging. Indeed, reduction of ROS and low-grade inflammation and promotion of autophagy by calorie restriction or other dietary manipulation can extend lifespan in a wide spectrum of model organisms. Interestingly, recent studies show that some food-derived small molecules, also called phytochemicals, can extend lifespan in various animal species. In this paper, we review several recently identified potential antiaging phytochemicals that have been studied in cells, animals and humans and further highlight the cellular and molecular mechanisms underlying the antiaging actions by these molecules.

Keywords

Aging; Phytochemicals; Calorie restriction; Reactive oxygen species; Inflammation; Autophagy

1. Introduction

Aging is one of the most familiar yet least well-understood biological sciences. It is physiologically characterized as a progressive, generalized systematic dysfunction of almost all organs, giving rise to the escalated vulnerability to environmental challenges and resulting in increased risks of disease and death. Indeed, aging in humans is associated with a greatly increased incidence of a number of degenerative diseases including cardiovascular disease, Type 2 diabetes, cancer and Alzheimer's disease, and these chronic diseases

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account for more than 70% deaths among Americans 65 years of age and older [1]. Therefore, preventing or delaying the pathogenesis of these chronic diseases is an essential strategy to promote healthy aging. Interestingly, both aging and chronic diseases are highly associated with increased metabolic and oxidative stress, elevated chronic, low-grade inflammation, and accumulated DNA mutations as well as increased levels of its damage [2–4]. It is well established that calorie restriction delays age-associated organ disorders and increases lifespan in a wide range of species, suggesting that targeting nutrient-sensing and energy metabolism pathways may be an effective approach to delay aging process and age-related diseases.

Emerging studies showed that some phytochemicals have potential in reducing risk of chronic diseases, although they are not considered essential nutrients. Most phytochemicals are secondary plant metabolites which are present in a large variety of foods including fruit, vegetables, cereals, nuts and cocoa/chocolate as well as in beverages including juice, tea, coffee and wine. More than 1 g of phytochemicals per day is commonly ingested with the diet [5]. There are seven main categories of phytochemicals, including phenolic compounds, terpenes, betalians, organosulfides, indoles/glucosinolates/sulfur compounds, protein inhibitors and other organic acids [6] (Table 1). Phenolic compounds, also known as polyphenols, are the largest, most studied group. For example, tea flavan-3-ols (epigallocatechin gallate, EGCG), berry anthocyanins, soy isoflavones, and grape stibenoids resveratrol are in this category [7–9]. Provitamin A carotenes from carrots and pumpkins, limonene from oils of citrus and cherries, saponins from legumes belong to terpenes [6]. Although tocopherol (vitamin E) and omega-3 fatty acids are included in terpenes as phytochemicals [6] and may have antiaging potential [10,11], these chemicals are not be discussed in this article because these essential nutrients are well known and their biological functions have been previously reviewed. Many phytochemicals have been well studied for their abilities to prevent or treat chronic diseases, and there are several reviews in terms of the actions of phytochemicals in prevention and treatment of cancer [12,13], cardiovascular disease [14,15], obesity [16,17], diabetes [18], as well as neurological dysfunctions [19]. Recently, emerging evidence shows that some food-derived bioactive compounds have antiaging capabilities, although studies in this field are still relatively limited. In this review, we summarize several major potential antiaging phytochemicals or “phytonutrients” that have been studied in cells, animals and humans and further highlight the possible mechanisms in delaying aging process by these molecules.

2. Antiaging phytochemicals

2.1. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic small molecule present in many plant-derived foods such as grapes, red wine [20], peanuts [21], various berries [22], cocoa [23], and hellebore [24]. About 20 years ago, there was a paradoxical epidemiological observation that French people who eat a diet high in saturated fat and drink red wine regularly have a lower incidence of coronary heart disease and longer lifespan, although it is well established that high intake of saturated fat is associated with high incidence of heart disease. Since the discovery that red wine contains significant amount of resveratrol, it has

drawn great interest in scientific community to explore its potential health benefits, leading to speculation that resveratrol might confer the health benefits of drinking red wine. For example, resveratrol in wine (up to 30 mg/L) [25] was found to inhibit the oxidation of low-density lipoproteins [26], a major step of the development of coronary heart diseases. In addition, a substantial body of evidence demonstrated that dietary resveratrol supplementation exerts beneficial effects on various other human chronic diseases and aging. It has been found that resveratrol can protect against diabetes, cancer and Alzheimer's disease [24,27,28]. In addition, resveratrol was reported to extend lifespan of yeast by 70% [9], a classic model in aging study. Further studies found that dietary intake of resveratrol can mimic calorie restriction in some ways and improve health and extend lifespan of *Caenorhabditis elegans* (*C. elegan*) [29], *Drosophila Melanogaster* (*Drosophila*) [30] and fish [31]. In concert with these findings, multiple studies using mouse models also demonstrated that dietary provision of moderate amount of resveratrol (0.01% or 0.04%) promoted health and increased lifespan of high-fat diet-induced obese male mice (C57B6) by 26 and 25%, respectively, when treatment started at about 1 year of age [32,33]. Consistently, resveratrol-treated obese mice displayed several physiological changes that are associated with healthier and longer life. Notably, resveratrol did not alter food intake or cause a significant reduction in body weight of obese mice, suggesting that the favorable effect of resveratrol on lifespan is not due to the secondary effect whereby it affects appetite or body weight. However, unlike high fat-fed mice, the same long-term resveratrol treatment (0.01% and 0.04%) did not extend lifespan of C57B6 mice fed a standard diet [33]. In addition, resveratrol (0.03%) also failed to exert such an effect in standard chow-diet-fed heterozygous mice [34,35]. Interestingly, it was also found that, even though the longevity was not increased in standard diet-fed mice, resveratrol treatment still exerted an array of other beneficial effects in mice that mimic some of physiological and transcriptional changes induced by calorie restriction, leading to overall healthier lives of these mice [33]. Based on these findings, it is very possible that resveratrol promotion of survival and extension of lifespan of the high-fat diet-fed mice is a secondary action whereby it favorably modulates high-fat feeding- or obesity-induced physiological and metabolic alterations in major organs and tissues, which could gradually lead to the pathogenesis of various chronic diseases. Indeed, resveratrol treatment reduces insulin resistance, oxidative stress, inflammation, vascular dysfunction, osteoporosis, cataracts, and the decline in motor coordination in high-fat diet-fed aged mice [33]. Specifically, resveratrol reduces the number of deaths caused by fatty changes in the liver combined with severe congestion and edema in the lungs [33], which are partially attributable to constant high-fat diet feeding. In humans, there is still no solid evidence that resveratrol intake can extend lifespan, but findings from several relatively short-term studies that resveratrol improved insulin resistance, blood flow, and various cardiovascular events, as well as decreased oxidative stress and inflammation may point to a promising antiaging action of this compound [36–39], given that cardiovascular disease is a major cause of age-related morbidity and mortality in humans. There are still several active clinical trials for assessing the potential beneficial effects of pure resveratrol or resveratrol containing products on various age-related health conditions, such as obesity, insulin resistance, impaired glucose tolerance, dyslipidaemia, inflammation, cognitive function, and Type 2 diabetes [40].

2.2. Epicatechin

(−)-epicatechin, a flavanol, can be found from various foods including apples, berries, chocolate, grapes, pears, and tea; however, cocoa bean has the highest levels of epicatechin (43,270 mg/kg fresh weight), far greater than that in the next highest epicatechin -containing product, green tea, which contains about 8,000 mg/kg [41–43]. Data from recent epidemiological studies indicate that people living on the San Blas Island, who are known to consume large amounts of cocoa beverage daily, have a considerable lower incidence of ischemic heart disease, stroke, diabetes, and a remarkably longer lifespan compared to those who live in the mainland of Panama [44,45]. Interestingly, these differences disappeared when people from San Blas Island migrated to Panama City where the amount of cocoa consumption was considerably reduced [46]. More recently, a study reported that dietary chocolate intake (4 kg chocolate/50 kg body weight) extended average life expectancy by as much as 4 years in humans [47]. While the underlying mechanism for this beneficial effect of dietary intake of cocoa products is unknown, recent human studies demonstrated that dietary intake of cocoa or chocolate can improve blood vessel function, insulin sensitivity, blood pressure, and inflammation [48], all of which could be associated with aging process. These data suggest that cocoa may exert health-promoting effects, although the specific cocoa components primarily responsible for these actions are not known.

It was recently reported that flavanol-rich cocoa beverage intake increased flow-mediated vasodilation in humans that was associated with increased plasma levels of nitric oxide, the major vasodilator in the circulation [49]. In line with this finding, another study found that intake of cocoa flavanols improved flow-mediated blood vessel dilatation in Type 2 diabetic patients [50], suggesting that the beneficial effects of cocoa on human vascular function may be at least partially attributable to flavanols such as epicatechin. While the various beneficial effects of cocoa epicatechin were primarily investigated using healthy humans or animals [44], there are only a few studies examining if epicatechin promotes lifespan.

It has been reported that long-term intake of cocoa polyphenolic extract increased lifespan in aged rats [51], and epicatechin was thought to partially contribute to this beneficial effect [52,53]. We recently reported that dietary intake of epicatechin (0.25% in drinking water) promoted survival of diabetic mice (50% mortality in diabetic control group vs. 8.4% in epicatechin group after 15 weeks of treatment). Interestingly, blood glucose, food intake and body weight gain were not altered by epicatechin treatment [54], suggesting that epicatechin promotion of mouse survival is not due to amelioration of hyperglycemia or modulation of calorie intake and metabolism, all of which are important factors affecting lifespan. Dietary intake of epicatechin (0.01–8 mmol/L in diet) also improved life span of *Drosophila* [54] and standard diet-fed aged mice (0.25% in drinking water, unpublished data). Consistently, it has been shown that dietary epicatechin extends lifespan of *C. elegans* [55]. We further found that extended lifespan by dietary epicatechin may be associated with reduced systematic inflammation markers and serum low-density lipoprotein cholesterol, increased hepatic antioxidant glutathione (GSH) concentration and total superoxide dismutase (SOD) activity, decreased circulating insulin-like growth factor-1 (IGF-1) and improved AMP-activated protein kinase-α (AMPKα) activity in the liver and skeletal muscle [54], all of which are established biomarkers that are associated with a longer and healthier lifespan.

Therefore, it is intriguing to speculate that epicatechin maybe a novel small food-derived molecule that is capable of prolonging healthy lifespan in humans.

2.3. Quercetin

Quercetin (3,3,4,5,7-pentahydroxyflavone) is a flavonoid abundant in many fruits and vegetables, including grapes, blueberries, cherries, onions, apples and broccoli [56,57]. It has been reported that dietary supplementation of quercetin at 200 mM extended the lifespan of *C. elegans* by 20%. Interestingly, recessive mutation of the gene *age-1* or *daf-2* (encoding for the IGF-1 receptor in C. *elegan*), two key players in the metabolic pathway to regulate the rate of aging, abolished the lifespan-extension effect of quercetin in *C. elegans* [58,59], suggesting that quercetin may prolong lifespan in the worms through inhibiting, either directly or indirectly, the age-1 and daf-2-mediated pathways. A recent study reported that quercetin and its derivative quercetin caprylate can rejuvenate senescent fibroblasts and increase their lifespan via activating proteasome [60]. Quercetin is reported as the most potent reactive oxygen species (ROS) scavenger of ROS in the flavonoid family and quercetin has over 6 times the antioxidant capacity than the reference antioxidant trolox or vitamin C [61–63]. Moreover, quercetin possesses strong antiinflammatory capacity by inhibiting lipopolysaccharides-induced production of cytokines interleulin-1α and tumor necrosis factor-α in immune cells [64,65]. These antioxidant and antiinflammatory properties may contribute to the antiaging effect of quercetin and its derivatives since chronic oxidative stress and inflammation are believed to play important roles in triggering the aging process (more detailed discussion on this topic is in second section of this paper).

2.4. Curcumin

Curcumin (diferuloylmethane) is a major curcuminoid that are present in 31 species of curcuma plants, including *Curcuma longa*, the rhizome of which provides the spice turmeric [66]. Curcumin is a lipophilic phenolic compound that constitutes as much as 5.4% of raw turmeric and is primarily responsible for the yellow color of turmeric [67]. Curcumin is comprised of curcumin I (94%), curcumin II (6%) and curcumin III (0.3%) [68]. Curcumin has been used for many centuries in traditional Chinese and Indian medicine as the treatment for several disorders including upset stomach, flatulence, dysentery, ulcers, jaundice, arthritis, sprains, wounds, acne and skin and eye infections [69]. Dietary intake of curcumin is considered safe, and it has been extensively studied for its potential beneficial effects on health. Accumulating evidence shows that curcumin supplementation extends lifespan of *Drosophila* [70–72] and *C. elegans* [73], and dietary intake (0.2%) of tetrahydrocurcumin, a metabolite of curcumin, significantly increased survival rate in mice [74]. Moreover, curcumin and piperine, an alkaloid present in black pepper, synergistically attenuated D-galactose-induced senescence in rats [75]. In addition, curcumin possesses antiinflammatory and antioxidant properties [76–78], which may also contribute to its potential antiaging effect.

2.5. Green tea extract and EGCG

Tea is the most consumed beverage in the world after water, and green tea extract is a rapidly growing dietary supplement in the United States because of its presumably

beneficial effects on cardiovascular disease [79], cancer [80], diabetes [81], obesity [82], and neurodegenerative disease [83]. The antiaging effect of green tea extract and its major bioactive component EGCG was not reported until recently, but all of these studies were performed with rodents or lower model organisms. Green tea extract reverses high-fat diet-induced mortality in *Drosophila* [84]. Consistently, EGCG increases lifespan of *C. elegans* maintained in normal or oxidative stress condition [85,86]. Green tea extract (80 mg/L containing 18.0% EGCG, 11.6% (−)-gallocatechin 3-*O*-gallate, 4.6% (−)-epicatechin 3-*O*-gallate, 15.0% (−)-epigallocatechin, 14.8% (+)-gallocatechin, 7.0% (−)-epicatechin, and 3.5% (+)-catechin), extends average lifespan of male C57BL/6 mice with normal diet from 801 days to 852 days [74]. Diet supplemented with the mix of 2% blueberry extract, 0.0115% EGCG and 0.3% pomegranate powder potentiated calorie restriction-induced longevity in aged male C57BL/6 mice [87]. However, the recent National Institute on Aging Interventions Testing Program reported that lifelong treatment of genetically heterogeneous male and female mice, beginning at 4 months of age, with 2% green tea extract, did not significantly extend their lifespan but diminished the risk of mid-life deaths in female mice [35]. Therefore, the antiaging effect of green tea extract and EGCG may depend on the mouse's genetic background and/or the presence of specific environmental factor such as nutritional stress. In addition, the treatment dose, duration and animal age at which the intervention begins may all affect the outcome. Studies assessing the antiaging action of green tea extracts in humans are scare, but interestingly, a cohort study shows that routine green tea drinking significantly decreased mortality rate in Japanese women [88]. This result is somewhat consistent with the finding from above stated rodent study. However, further study is needed to determine whether green tea extract has a gender-specific effect on longevity.

2.6. Other phytochemicals/plant-extracts

Aged garlic extract, which contains s-allycisteine, s-allymercaptocysteine, allicin and diallosulfides, has been reported to increase lifespan and learning in mice [89]. Fisetin and butein (10 mM), two phytochemicals from fruits and Chinese lacquer tree, extended lifespan of the yeast *Saccharomyces cerevisiae* by 33% and 5%, respectively [9]. Phloridzin, a dihydrochalcone with high concentration in apple, was reported to increase lifespan of yeast through regulating SOD and Sir2, a nicotinamide adenine dinucleotide (NAD)+ –dependent protein deacetylase [90]. Kaempferol, a flavonol present in ginko biloba, grapefruit, tea, broccoli and berries, also were found to extend lifespan of *C. elegans* by improving antioxidant potential and daf-16 translocation [91]. Glaucarubinone, a cytotoxic and antimalarial quassinoid known from different species of the plant family simaroubaceae, promotes mitochondria metabolism and extends lifespan of *C. elegans* [92]. Unlike many other natural compounds discussed in the paper, glaucarubinone appears to be a more potent antiaging agent, given that the effective doses are only 10–100 nM. Blueberry extracts were also found to increase longevity of *C. elegans* [93], which may be primarily ascribed to pro-anthocyanidins, a class of polyphenols or flavanols, as pure pro-anthocyanidins isolated from blueberry showed similar antiaging effect as whole blueberry extracts [93]. However, there have been no published studies, as to our knowledge, reporting the effect of these phytochemicals on aging in vertebrate animals.

3. Anti aging mechanisms of phytochemicals

3.1. ROS

While there is no unified mechanism underlying the aging process, a large body of evidence indicates that increased generation of ROS which are chemically reactive molecules with most of them containing oxygen and unpaired electrons is one of the major triggers of aging. Indeed, there is a strong correlation between chronological age and the levels of ROS generation and oxidative damage of tissues. ROS are primarily produced by mitochondrion during energy production (about 2% of total oxygen consumption was funneled to ROS) [94]. Access amount of ROS induces oxidation of fatty acids and proteins and causes oxidative damage of DNA that may lead to cellular senescence, functional alterations and pathological conditions [95,96]. Moreover, several age-related chronic diseases such as cardiovascular diseases, diabetes and cancer are associated with severe increases in oxidative stress [1,97]. Superoxide anion (O_{2-}), the major form of ROS produced in mitochondrion, is quickly converted to hydrogen peroxide by two intracellular enzymes, SOD1 in cytosol and SOD2 in the matrix of mitochondria. Hydrogen peroxide is further deactivated to become water and oxygen by catalase or glutathione peroxidases (GPx) [98]. Endogenous antioxidant GSH and exogenous antioxidants including vitamins C and E are also important ROS scavengers. Cells maintain redox balance and thus its normal function through generation and destruction of ROS. However, this balance can be interrupted by environmental factors and aging that leads to an excessive bioavailability of ROS. In fact, mitochondrial integrity declines as a function of age [99], and ROS is increased but, GPx is decreased during aging [100,101]. Given that ROS-induced oxidative stress plays a key role in driving the aging process, reducing ROS is proposed as a leading strategy to delay aging and related degenerative diseases. Some food-derived phytochemicals may play a significant role in maintaining the ROS-antioxidant balance. There are three major mechanisms by which phytochemicals defend ROS, which are discussed in more detail below.

3.1.1. Phytochemicals can directly scavenge ROS—Many phytochemicals are found to have antioxidant activity capable of scavenging ROS, a property that may be primarily attributable to their phenolic hydroxyl groups. Indeed, the ROS scavenge capacity depends on the number and position of the hydroxyl group and substituent, as well as glycosylation of phytochemical molecules [102–104]. Generally, phytochemicals with more hydroxyl groups may have a stronger antioxidant capacity. For instance, kaempherol-3,7,4′-trimethylether, kaempherol-3,4′-dimethylether, kaempherol-7-neohesperidoside and kaempherol, which have one (in the five position), two, three and four free hydroxyl substitutions, respectively, have 0, 1.0, 1.6 and 2.7 times of trolox equivalent antioxidant capacity, respectively, as determined by the peroxyl radical absorbance capacity ($ORAC_{ROO.}$) assay [105]. In addition, the 3′,4′ di-OH substitution is especially important to the antioxidant capacity, which is supported by findings that luteolin tetramethylether (without 3′,4′ di-OH structure), kaempherol (without 3′,4′ di-OH structure) and luteolin (with 3′,4′ di-OH structure) have 0, 2.67 and 3.57 times of trolox equivalent antioxidant capacity, respectively, although all these three compounds have four OH groups with the same basic structure flavones [105]. Moreover, substitution patterns in the B-ring and A-ring as well as the 2, 3-double bond (unsaturation) and the 4-oxo group in the C-ring also affect

antioxidant activity of phytochemicals [106,107]. Although how structural features confer the antioxidant capacity of phytochemicals is still not clear, it is generally believed that phytochemicals having at least one of these structural features such as 3′,4′-*o*-dihydroxyl group, a 2,3-double bond in conjugation with a 4-keto moiety, or a 3-hydroxyl group have high cellular antioxidant activity [105–107].

3.1.2. Phytochemicals can enhance the production of antioxidants—GSH is a ubiquitous water-soluble antioxidant and also an essential cofactor for antioxidant enzymes. It exists in two forms: the sulfhydryl form or the reduced GSH and the oxidized glutathione disulfide (GSSG). GSH plays a very important role in ROS defense system as it has potent electron donating capacity. Age-associated increase in ROS accumulation is partially due to the attenuations of *de novo* GSH synthesis, GSH recycling and the GSH/GSSG ratio. Indeed, it was found that total GSH levels were reduced by 50% in the livers of aged rats [108]. In addition, both the expression and activity of hepatic glutathione reductase, a central enzyme regulating GSH/GSSG ratio by reducing GSSG back to GSH, are also declined in aging rats [109]. Similarly, SOD activity in the heart of rats is greatly reduced with aging from 101.9 units/mg protein at 4 months of age to 44.7 units/mg protein at 22 months old [110]. SOD is detoxification enzyme critical in counteracting cellular and molecular damage by converting superoxide to hydrogen peroxide, which can then be neutralized to water and oxygen by catalase. It has been shown that deletion of either cytosolic or mitochondrial SOD results in shortened lifespan in yeast [111], fruit flies [112] and mice [113,114], which is likely the result of increased oxidative stress. Consistently, over expression of peroxisomal catalase can lead to about 20% lifespan extension in mice [115]. These results provide evidence supporting the oxidative theory of aging and thereby strengthening the antioxidant system may be able to extend healthy lifespan in animals. Interestingly, our recently study showed that dietary epicatechin extension of mouse lifespan is associated with increased SOD activity in the liver of diabetic mice [54]. However, it is unclear from this study how epicatechin treatment increases hepatic SOD activity. Interestingly, studies showed that other proposed antiaging phytochemicals are also able to induce SOD activity in various species. Dietary intake of curcumin (2-mg/g medium) increased SOD activity by (32% in *Drosophila* [70]. In mice, curcumin treatment (8 mg/kg, ip injection for 5 days) can restore X-ray-reduced hepatic SOD and GSH contents [116]. Similarly, resveratrol (50 μM) [117], EGCG (100 mg/kg, intradermal injection) [118] or quercetin (0.027% in the diet) [119] reversed oxidative stress-caused reduction of GSH and SOD levels in mice or rats. Combined, these results suggest that these antiaging compounds may facilitate healthy aging via promoting both the enzymatic (SOD) and non-enzymatic (GSH) antioxidant status, thereby attenuating the increased free radial formation and oxidative stress with aging, given that oxidative stress in aerobic cells is a major factor in aging process. However, there is possibility that maintenance of a better antioxidant capacity by these phytochemicals is a not a cause, but rather a consequence of their antiaging actions.

3.1.3. Phytocehmicals regulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway—Nrf2 is a transcriptional factor that plays a pivotal role in regulating various Phase II antioxidant enzymes and thereby detoxification process, including hemeoxygenase-1 (HO-1), NAD(P) H:quinoneoxidoredctase (NQO1) and GSH S-

transferase. Under normal condition, Nrf2 is associated with a Kelch-like ECH-associated protein1 (Keap-1) in cytoplasm. However, Nrf2 inducers such as ROS or electrophilic compounds cause dissociation of the Nrf2/Keap-1 complex by directly modifying the thiol group of Nrf2 and/or through kinase [*e.g.*, protein kinase C (PKC)]-dependent phosphorylation of Nrf2 Ser40 [120]. Dissociated Nrf2 then translocates into the nucleus where it induces the expression of several detoxifying enzymes, including SOD, GSH, NQO1 and HO-1, by binding to the antioxidant-response elements (AREs) in the promoter regions of the genes of these enzymes [121]. Thus, the Nrf2/ARE pathway plays an important role in transcriptional activation of various cellular defense mechanisms. Indeed, in Nrf2 gene-knockout mice, both basal and inducible levels of Phase II enzyme genes and proteins are greatly reduced that led to the increased sensitivity to chemical oxidants [122]. Therefore, search for agents that can activate Nrf2 may be an excellent strategy in protecting cells against oxidative stress and other environmental insults. The Keap1/Nrf2/ARE pathway can be activated by PKC, extracellular signal-regulated protein kinase (ERK), phosphatidylinositol-3-kinase (PI3K) and p38 MAP Kinase (MAPK) via phosphorylation of Nrf2 [123,124], suggesting that Nrf2 is not controlled only by a specific regulatory pathway. Some bioactive compounds, including sulforaphane [125,126], EGCG [127] and luteolin [128], have been shown to activate Nrf2 and induce HO1 and NQO1 production via the ERK- or PI3K-dependent mechanism. It was shown that activation of the Keap1/Nrf2/ARE pathway by curcumin is mediated via stimulation of the PKC [129] or MAPK [130] signaling pathway in human cells. A recent study reported that resveratrol promotes the survival of cerebellar granule neurons in rats by enhancing DNA-binding activity of Nrf2 and the expression of its downstream cytoprotective proteins NQO1 and SOD and also restoring the ethanol-reduced GSH by activation of the AMP-activated protein kinase (AMPK)/NAD-dependent deacetylase sirtuin-1 SIRT1 pathway [131,132]. Dietary intake of epicatechin was also shown to enhance Nrf2 protein expression and HO-1 accumulation in the nuclei of cortical neurons in mice [133]. This epicatechin action is not tissue specific, as it was also found that treatment of hepatocytes with epicatechin (10 μM) activates PI3K/Akt and ERK signaling, leading to Nrf2 phosphorylation, nuclear translocation and transcriptional activity [134]. These results suggest that the observed antioxidant activity or reduction of oxidative stress by these compounds *in vivo* may not entirely or even primarily due to their direct scavenging ROS. Rather, targeting the Nrf2-mediated pathway by these phenolic compounds could play a more important role in mediating the antioxidant action *in vivo*, given that many of polyphenolic phytochemicals have a poor bioavailability, with achievable circulating concentrations typically being less than 5 μM following dietary supplementation in both humans and animals [28,135]. However, the significant ROS scavenging activity can only be achieved *in vitro* at doses that are far beyond those attainable *in vivo* through dietary means.

3.2. Activation of AMPK and SIRT1 by phytochemicals

AMPK, an energy-sensing molecule highly conserved from yeast to mammals, is increasingly recognized as a master regulator of whole body energy homeostasis [136]. This heterotrimeric protein kinase, composed of a catalytic subunit (AMPKα) and two regulatory subunits (β and γ), senses low cellular energy levels by monitoring changes in the AMP:ATP ratio. AMP binding to the γ subunit induces a conformational change that allows

AMPKα to be phosphorylated at its threonine residue (Thr172) by the AMPK-activating protein kinase (LKB1). At whole body level, AMPK integrates stress responses, nutrient and hormonal signals to the control of food intake, energy expenditure and substrate utilization. At cellular level, activated AMPK inhibits hepatic gluconeogenesis [137], promotes fatty acid oxidation and insulin sensitivity [136] and regulates mitochondrial biogenesis [138]. To do so, AMPKα directly regulates the activity of acetyl-CoA carboxylase (ACC) and the peroxisome proliferator-activated receptor gamma coactivator-1-α (PGC-1α) [139–141], two of the most important metabolic regulators. Specifically, AMPKα phosphorylates and inhibits the activity of ACC, the rate limiting enzyme for fatty acid synthesis [139,140]. Meanwhile, it phosphorylates and activates PGC-1α, which controls the expression of many genes related to lipid oxidation and mitochondrial biogenesis [142,143]. Recently, several lines of evidence demonstrate that activation of AMPK increases lifespan and delays age-associated functional decline in various species [144–147]. Conversely, reduction of AMPK activity leads to age-associated dysfunction of skeletal muscle [148,149], blood vessel [150] and the liver [151,152]. Therefore, AMPK is emerging as an attractive target for developing strategies to extend healthy lifespan. Interestingly, all of above-discussed antiaging phytochemicals (resveratrol, EC, EGCG, quercetin and curcumin) have been found to activate AMPK. For instance, recent studies found that dietary resveratrol prevents Alzheimer's markers and increases lifespan of mice and *C. elegans* via activating the AMPK and SIRT1 pathways [9,32,153]. Resveratrol prevents renal lipotoxicity and inhibits mesangial cell glucotoxicity through activating AMPK-SIRT1-PGC1α axis in *db/db* mice [154]. Results from a more recent study showed that the beneficial effects of resveratrol on metabolism including improved insulin sensitivity, glucose tolerance, mitochondrial biogenesis and physical endurance were lost in AMPK-deficient mice [155], further confirming the critical role of AMPK in mediating the various beneficial actions of this compound. Similarly, beneficial actions of quercetin [156,157], EGCG [158], curcumin [159,160] and epicatechin [54] were also associated with activation of the AMPK pathway, suggesting that activation of AMPK may serve as a central mechanism for many observed biological effects of phytochemicals, even though their chemical structures are somewhat different. However, how these compounds are able to activate AMPK is an intriguing question.

Sirtuins are enzymes that function as NAD^+-dependent deacetylases and ribosyltransferases evolutionarily conserved from *Escherichia coli* to humans [161]. Sir2, one of sirtuins in *S. cerevisiae* yeast and *C. elegans*, mediate the life-extending effect of calorie restriction by increasing the ratio of NAD to its reduced form NADH [162,163]. In concert with these findings in microorganisms and invertebrate animals, the protein expression of SIRT1, homolog of the Sir2 gene in yeasts and worms and one of seven sirtuin members in vertebrate animals, is also increased in energy metabolism tissues in life-prolonged rats by calorie restriction [164]. Therefore, in addition to AMPK, SIRT1 also serves as a fuel-sensing molecule. Actually, recent studies show that these two enzymes share many common target molecules, suggesting that they may cross talk or on the same regulatory pathway in certain circumstances, which is not well understood. For instance, sirtuins promote deacetylation of several downstream molecules, including Ku70 [165] and p53 [166], two critical molecules for initiation of apoptosis, and LKB1 [167], a key molecule

upstream of AMPK. In this case, SIRT1 may be located at the upstream of AMPK. In addition, SIRT1 was shown to regulate the IGF-1 pathway through modulation of UCP2 expression [168,169]. SIRT1 also interacts with the forkhead/winged helix box gene, group O (FOXO), a crucial regulator of the IGF-1 signaling pathway. Specifically, SIRT1 was found to directly deacetylate and thereby activate FOXO1 [170] and FOXO3a [171], which play important roles in transducing insulin signaling downstream of serine/threoine protein kinase (Akt) [170]. In addition, Sir2 can directly bind to FOXO1-binding sites of some FOXO-targeted genes, such as antioxidant gene SOD, to enhance its expression through a deacetylase-activity-dependent manner in mammalian cells [170]. This finding suggest that, in addition to its function as a sensor of the energy status of cells, activation of sir2 and possibly other SIRTs may increase ability of scavenging ROS and therefore reduce oxidative stress.

Resveratrol was reported to directly activate SIRT1, which lead to improved mitochondrial biogenesis, energy metabolism, insulin sensitivity and survival of high-fat-fed mice [9]. However, whether these benefits of this compound are directly mediated via SIRT1 or through AMPK-mediated mechanism is still controversial. A recent study showed that mice fed a resveratrol (0.04%)-supplemented diet displayed the increased mitochondrial biogenesis and AMPK activation, whereas SIRT1-knockout mice displayed none of these benefits demonstrated in wild-type mice given resveratrol, suggesting that SIRT1 plays a critical role for AMPK activation and the subsequent beneficial effects of resveratrol on mitochondrial function [172]. However, results from some more recent studies indicated that resveratrol activates SIRT1 via stimulating the AMPK pathway, which is supported by observations that 1) resveratrol consistently increased SIRT1 and PGC-1α activity in mice [155,173] and SIRT1 activates PGC-1α, one of the major targets of AMPK signaling; 2) resveratrol cannot activate SIRT1 with native substrates *in vitro*, although it activates SIRT1 *in vivo* and deacetylate fluorophore-tagged substrates *in vitro* [174,175]; and 3) the abilities of resveratrol to activate SIRT1 and exert the beneficial metabolic effects in wild-type mice are lost in AMPK-deficient mice [155]. Interestingly, resveratrol treatment (oral gavage at 100 mg/kg body weight) was recently found to activate SIRT1 via cAMP phosphodiesterases-cAMP-Epac1-AMPK pathway both in C2C12 myotubes (50 μM) and in mice [176].

While mechanistic studies on the antiaging effects of other phytochemicals are limited, a recent study shows that quercetin intake may improve exercise performance, skeletal muscle and brain function, which are associated with activation of the SIRT1/PGC-1α pathway [156,157]. Similarly, EGCG was found to suppress oxidative stress that is mediated via the SIRT1/PGC-1α pathway [158]. However, several other studies found that EGCG and quercetin did not activate SIRT1 but inhibit SIRT1 in cellular system [177–179]. This may be due to the instability of EGCG and quercetin because EGCG becomes oxidized and subsequently produce ROS in the medium and quercetin and its metabolite generates SIRT1-inhibitory metabolites [177]. Several other phytochemicals including piceatannol, fisetin and butein were reported to activate SIRT1 and subsequently lead to prolonged lifespan of *C. elegans* [9]. However, how they activate SIRT1 is unclear.

3.3. Growth hormone (GH)/IGF-1 pathway

The GH/IGF-1 axis, evolutionarily conserved from invertebrates to mammals, has been extensively investigated in the regulation of the aging process [180,181]. IGF-1 axis directly regulates its downstream molecules such as PI3K, AKT and FOXO. It also interacts with other aging-relevant signals including SIRT1, AMPK and mammalian target of rapamycin (mTOR) signaling [182]. While the detailed mechanisms by which IGF-I regulates lifespan is not completely clear, it is well recognized that circulating IGF-I levels are inversely associated with lifespan in mammals [181,183]. Our study indicated that serum IGF-I levels were reduced by epicatechin treatment in diabetic mice without alternation in hepatic IGF-1mRNA expression [54]. One possible interpretation is that epicatechin may affect the binding of IGF-I and its carrier IGF binding proteins (IGFBPs) because as much as 99% of IGF-I in circulation is bound to one of the six IGFBPs [184], which can prevent the proteolysis of IGF-I, and therefore extend its half-life [185]. Another possibility is that epicatechin reduces IGF-I level through activation of AMPK, which inhibits IGF-I signaling and its protein synthesis through the phosphorylation of insulin receptor substrate-1 [186]. Interestingly, curcumin [187], resveratrol [188] and EGCG [189] inhibit IGF-1/IGF-1 receptor axis, although the underlying mechanism for this action by these phytochemicals are unknown. Nevertheless, these studies provide further evidence that epicatechin, curcumin, resveratrol and EGCG may be food-derived antiaging agents, given the important role of IGF-1 in regulating lifespan of various model organisms.

3.4. Antiinflammation

A large body of epidemiologic studies has shown that low-grade chronic inflammation plays a crucial role in the process of aging and age-related diseases in older adults. Chronic proinflammatory markers including IL-6, C-reactive protein (CRP) and TNF-α are consistently elevated with age in the absence of acute infection or other physiological stress [190], which are largely the results of chronically elevated levels of ROS [191], endocrinosenescence (reduction of growth hormone and dehydroepiandrosterone) [192] and the gradual decline in immune function (accumulation of proinflammatory CD8+/CD28− T cells, the decrease of naive T cells (CD95−) and the marked shrinkage of T cell repertoire) [193,194]. Consequently, the sustained increases in these proinflammatory molecules impair the function and integrity of various tissues and organs and thus accelerate aging and aging-related chronic diseases, although this increase is still in the sub-acute range [195]. Interestingly, calorie restriction significantly attenuates the increase of these proinflammatory markers while extending lifespan [195,196], suggesting that antiinflammatory agents may have potential to extend healthy lifespan. Resveratrol [197], EGCG [198], curcumin [197], quercetin [199] and epicatechin [54] have been shown to lower proinflammatory markers and decrease the adhesion of monocytes to other cells via inhibiting nuclear factor (NF)-kappa (NF-kB), the master regulator of the transcription of various proinflammatory molecules. For instance, studies found that EGCG decreases the adhesion of monocytes to vascular endothelial cells both *in vivo* and *in vitro*, which is accompanied by attenuation of proinflammatory chemokines such as IL-8 and monocyte chemotactic protein-1 (MCP-1), and vascular adhesion molecule-1 and intercellular adhesion molecule-1 through inhibiting NF-kB [198]. Dietary intake of epicatechin can also

diminish serum proinflammatory markers CRP, IL-1 and MCP-1 in mice while promoting their health and survival rate [54].

3.5. Autophagy

Autophagy is an evolutionarily conserved mechanism of lysosomal proteolysis in eukaryotes in response to nutrient deprivation. Apart from providing the starving cell with energy from degraded self-components, autophagy removes harmful proteins and damaged mitochondria. Therefore, autophagy is an essential cellular homeostasis mechanism. Declined autophagy, occurring during aging and the pathogenesis of age-related chronic diseases, leads to increased ROS production, inflammation, cell death, neurodegeneration, cancer, compromised immune response, diabetes and elevated aging process [200]. On the contrary, increased autophagy leads to longevity as shown in calorie-restricted mice [201,202], which may be mediated through down-regulating mTOR, the central autophagy regulator [196], via regulating multiple upstream molecules including SIRT1 and PI3K/AKT [182,203]. For instance, SIRT1 deficiency results in elevated mTOR signaling, and activation of SIRT1 by resveratrol reduces mTOR activity, whereas inhibition of SIRT1 using nicotin-amide enhances mTOR signaling [196]. These findings suggest that maintaining functional autophagy may delay aging. Interestingly, emerging evidence demonstrated that resveratrol [204], EGCG [205], epicatechin [206], quercetin [207] and curcumin [208,209] can induce autophagy in various types of cells via blocking mTOR activity. While the results from these *in vitro* studies may provide further evidence suggesting the antiaging action of these phytochemicals, it is presently unknown whether these compounds can activate autophagy *in vivo*.

4. Conclusions

Growing evidence shows that some phytochemicals (resveratrol, green tea extract, EGCG, epicatechin, quercetin and curcumin) present in the foods are antiaging molecules, and dietary intake of these compounds can promote health and extend lifespan in various animal models via multiple mechanisms, including reducing oxidative stress, suppressing low-grade chronic inflammation, inducing autophagy, as well as regulating several important molecules involved in promoting mitochondrial function and energy homeostasis (Fig. 1). Interestingly, it seems that these mechanisms mediating the proposed antiaging effects of phytochemicals are shared by calorie restriction, suggesting that nutritional intervention with these food components may be an alternative and more feasible strategy to promote healthy aging in humans. However, some of these compounds failed to extend lifespan of either normal diet-fed homozygous or genetically heterozygous mice. Therefore, it is possible that these agents may primarily act to correct the alterations of some metabolic pathways caused by chronically excessive calorie intake, thereby delaying the onset of age-related diseases that consequently lead to a healthier and longer lifespan. Alternatively, the antiaging potential of one or several of these molecules may depend on mouse genetic background, which may differ in energy regulatory mechanisms, resulting in different adaptation to nutritional or environmental stress and susceptibility to the pathogenesis of chronic diseases. If this is true, studies to determine these complex relationships and interactions among genetic background, nutrients and potential antiaging compounds may identify unique

modifier genes or metabolic pathways targeted by these phytochemicals and therefore could bring further insight into the mechanism of the antiaging action of these compounds.

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Abbreviations

ACC	acetyl-CoA carboxylase
AKT	serine/threonine protein kinase
AMPK	AMP-activated protein kinase
AREs	antioxidant-response elements
C. elegans	*Caenorhabditis elegan*
CRP	C-reactive protein
Drosophila	*Drosophila Melanogaster*
EGCG	epigallocatechin gallate
ERK	extracellular signal-regulated protein kinase
FOXO	forkhead/winged helix box gene, group O
GH	growth hormone
GPx	glutathione peroxidases
GSH	glutathione
GSSH	oxidized glutathione
HO-1	hemeoxygenase-1
IGF-1	insulin-like growth factor-1
IGFBPs	IGF binding proteins
IL	interleukin
LKB1	AMPK-activating protein kinase
Keap1	Kelch-like ECH-associated protein1
MAPK	p38 MAP Kinase
MCP-1	monocyte chemotactic protein-1
mTOR	mammalian target of rapamycin
NF-kB	nuclear factor (NF)-kappaB
NQO1	NAD(P)H:quinoneoxidoredctase
Nrf2	nuclear factor erythroid 2-related factor

ORAC	oxygen radical absorbance capacity
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator-1-α
PI3K	phosphatidylinositol-3-kinase
PKC	protein kinase C
ROS	reactive oxygen species
SOD	superoxide dismutase
TNFα	tumor necrosis factor-α

References

1. Ishizu T, Kajitani S, Tsutsumi H, Yamamoto H, Harano K. Diastereomeric difference of inclusion modes between (−)-epicatechin gallate, (−)-epigallocatechin gallate and (+)-gallocatechin gallate, with beta-cyclodextrin in aqueous solvent. Magn Reson Chem. 2008; 46:448–56. [PubMed: 18318450]
2. Heininger K. A unifying hypothesis of Alzheimer's disease. III. Risk factors Hum Psychopharmacol. 2000; 15:1–70.
3. Heininger K. A unifying hypothesis of Alzheimer's disease. IV. Causation and sequence of events. Rev Neurosci. 2000; 11(Spec No):213–328. [PubMed: 11065271]
4. Frisard M, Ravussin E. Energy metabolism and oxidative stress: impact on the metabolic syndrome and the aging process. Endocrine. 2006; 29:27–32. [PubMed: 16622290]
5. Ovaskainen ML, Torronen R, Koponen JM, Sinkko H, Hellstrom J, Reinivuo H, et al. Dietary intake and major food sources of polyphenols in Finnish adults. J Nutr. 2008; 138:562–6. [PubMed: 18287367]
6. Jane, Higdon; Drake, VJ. An evidence-based approach to phytochemicals and other dietary factors. 2. Vol. Chapter 8–19. New York: Thieme; 2013.
7. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004; 79:727–47. [PubMed: 15113710]
8. Wang Y, Chan FL, Chen S, Leung LK. The plant polyphenol butein inhibits testosterone-induced proliferation in breast cancer cells expressing aromatase. Life Sci. 2005; 77:39–51. [PubMed: 15848217]
9. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, et al. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature. 2003; 425:191–6. [PubMed: 12939617]
10. Zou S, Sinclair J, Wilson MA, Carey JR, Liedo P, Oropeza A, et al. Comparative approaches to facilitate the discovery of prolongevity interventions: effects of tocopherols on lifespan of three invertebrate species. Mech Ageing Dev. 2007; 128:222–6. [PubMed: 17169403]
11. Kiecolt-Glaser JK, Epel ES, Belury MA, Andridge R, Lin J, Glaser R, et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: a randomized controlled trial. Brain Behav Immun. 2012; 28:16–24. [PubMed: 23010452]
12. Miller PE, Snyder DC. Phytochemicals and cancer risk: a review of the epidemiological evidence. Nutr Clin Pract. 2012; 27:599–612. [PubMed: 22878362]
13. McCann SE, Freudenheim JL, Marshall JR, Graham S. Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. J Nutr. 2003; 133:1937–42. [PubMed: 12771342]
14. Vasanthi HR, ShriShriMal N, Das DK. Phytochemicals from plants to combat cardiovascular disease. Curr Med Chem. 2012; 19:2242–51. [PubMed: 22414106]
15. Bohn SK, Ward NC, Hodgson JM, Croft KD. Effects of tea and coffee on cardiovascular disease risk. Food Funct. 2012; 3:575–91. [PubMed: 22456725]

16. Gonzalez-Castejon M, Rodriguez-Casado A. Dietary phytochemicals and their potential effects on obesity: a review. Pharmacol Res. 2011; 64:438–55. [PubMed: 21798349]
17. Yun JW. Possible anti-obesity therapeutics from nature–a review. Phytochemistry. 2010; 71:1625–41. [PubMed: 20732701]
18. Sears B, Ricordi C. Role of fatty acids and polyphenols in inflammatory gene transcription and their impact on obesity, metabolic syndrome and diabetes. Eur Rev Med Pharmacol Sci. 2012; 16:1137–54. [PubMed: 23047497]
19. Youdim KA, Joseph JA. A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. Free Radic Biol Med. 2001; 30:583–94. [PubMed: 11295356]
20. Gu XL, Creasy L, Kester A, Zeece M. Capillary electrophoretic determination of resveratrol in wines. J Agricult Food Chem. 1999; 47:3223–7.
21. Wang KH, Lai YH, Chang JC, Ko TF, Shyu SL, Chiou RYY. Germination of peanut kernels to enhance resveratrol biosynthesis and prepare sprouts as a functional vegetable. J Agricult Food Chem. 2005; 53:242–6.
22. Ector BJ, Magee JB, Hegwood CP, Coign MJ. Resveratrol concentration in muscadine berries, juice, pomace, purees, seeds, and wines. Am J Enol Viticult. 1996; 47:57–62.
23. Hurst WJ, Glinski JA, Miller KB, Apgar J, Davey MH, Stuart DA. Survey of the trans-resveratrol and trans-piceid content of cocoa-containing and chocolate products. J Agricult Food Chem. 2008; 56:8374–8.
24. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006; 5:493–506. [PubMed: 16732220]
25. Stervbo U, Vang O, Bonnesen C. A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine. Food Chem. 2007; 101:449–57.
26. Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. Lancet. 1993; 341:1103–4. [PubMed: 8097009]
27. Jang MS, Cai EN, Udeani GO, Slowing KV, Thomas CF, Beecher CWW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997; 275:218–20. [PubMed: 8985016]
28. Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health–a comprehensive review of human clinical trials. Mol Nutr Food Res. 2011; 55:1129–41. [PubMed: 21688389]
29. Gruber J, Tang SY, Halliwell B. Evidence for a trade-off between survival and fitness caused by resveratrol treatment of Caenorhabditis elegans. Ann N Y Acad Sci. 2007; 1100:530–42. [PubMed: 17460219]
30. Bauer JH, Goupil S, Garber GB, Helfand SL. An accelerated assay for the identification of lifespan-extending interventions in Drosophila melanogaster. Proc Natl Acad Sci U S A. 2004; 101:12980–5. [PubMed: 15328413]
31. Valenzano DR, Terzibasi E, Genade T, Cattaneo A, Domenici L, Cellerino A. Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. Curr Biol. 2006; 16:296–300. [PubMed: 16461283]
32. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006; 444:337–42. [PubMed: 17086191]
33. Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, et al. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. Cell Metab. 2008; 8:157–68. [PubMed: 18599363]
34. Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci. 2011; 66:191–201. [PubMed: 20974732]
35. Strong R, Miller RA, Astle CM, Baur JA, de Cabo R, Fernandez E, et al. Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci. 2012; 68:6–16. [PubMed: 22451473]

36. Ghanim H, Sia CL, Abuaysheh S, Korzeniewski K, Patnaik P, Marumganti A, et al. An antiinflammatory and reactive oxygen species suppressive effects of an extract of polygonum cuspidatum containing resveratrol. J Clin Endocr Metab. 2010; 95:E1–8. [PubMed: 20534755]
37. Brasnyo P, Molnar GA, Mohas M, Marko L, Laczy B, Cseh J, et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Brit J Nutr. 2011; 106:383–9. [PubMed: 21385509]
38. Wong RHX, Howe PRC, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr Metab Cardiovas. 2011; 21:851–6.
39. Kennedy DO, Wightman EL, Reay JL, Lietz G, Okello EJ, Wilde A, et al. Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebocontrolled, crossover investigation. Am J Clin Nutr. 2010; 91:1590–7. [PubMed: 20357044]
40. clinicaltrials.gov. Resveratrol and health in clinic trials. 2013. http://clinicaltrials.gov/ct2/results?term=resveratrol&Search=Search
41. Kim H, Keeney PG. (−)-Epicatechin content in fermented and unfermented cocoa beans. J Food Sci. 1984; 49:1090–2.
42. Arts ICW, van de Putte B, Hollman PCH. Catechin contents of foods commonly consumed in The Netherlands. 1. Fruits, vegetables, staple foods, and processed foods. J Agricult Food Chem. 2000; 48:1746–51.
43. Arts ICW, van de Putte B, Hollman PCH. Catechin contents of foods commonly consumed in The Netherlands. 2. Tea, wine, fruit juices, and chocolate milk. J Agricult Food Chem. 2000; 48:1752–7.
44. Bayard V, Chamorro F, Motta J, Hollenberg Nk. Does flavanol intake influence mortality from nitrix oxide-dependent processes? Ischemic heart disease, stroke, diabetes mellitus, and cancer in Panama. Int J Med Sci. 2007; 4:53–8. [PubMed: 17299579]
45. Hollenberg NK, Martinez G, McCullough M, Meinking T, Passan D, Preston M, et al. Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. Hypertension. 1997; 29:171–6. [PubMed: 9039098]
46. Hollenberg NK, Naomi F. Is it the dark in dark chocolate? Circulation. 2007; 116:2360–2. [PubMed: 18025400]
47. Kirschbaum J. Effect on human longevity of added dietary chocolate. Nutrition. 1998; 14:869. [PubMed: 9834932]
48. Ding EL, Hutfless SM, Ding X, Girotra S. Chocolate and prevention of cardiovascular disease: a systematic review. Nutr Metab (Lond). 2006; 3:2. http://dx.doi.org/10.1186/1743-7075-3-2. [PubMed: 16390538]
49. Heiss C, Dejam A, Kleinbongard P, Schewe T, Sies H, Kelm M. Vascular effects of cocoa rich in flavan-3-ols. Jama. 2003; 290:1030–1. [PubMed: 12941674]
50. Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, et al. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. J Am Coll Cardi. 2008; 51:2141–9.
51. Bisson JF, Nejdi A, Rozan P, Hidalgo S, Lalonde R, Messaoudi M. Effects of long-term administration of a cocoa polyphenolic extract (Acticoa powder) on cognitive performances in aged rats. Brit J Nutr. 2008; 100:94–101. [PubMed: 18179729]
52. Schroeter H, Heiss C, Balzer J, Kleinbongard P, Keen CL, Hollenberg NK, et al. (−)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. Proc Natl Acad Sci U S A. 2006; 103:1024–9. [PubMed: 16418281]
53. Holt RR, Actis-Goretta L, Momma TY, Keen CL. Dietary flavanols and platelet reactivity. J Cardiovasc Pharmacol. 2006; 47(Suppl 2):S187–96. discussion S206-9. [PubMed: 16794457]
54. Si H, Fu Z, Babu PV, Zhen W, Leroith T, Meaney MP, et al. Dietary epicatechin promotes survival of obese diabetic mice and Drosophila melanogaster. J Nutr. 141:1095–100. [PubMed: 21525262]
55. Sunagawa T, Shimizu T, Kanda T, Tagashira M, Sami M, Shirasawa T. Procyanidins from apples (Malus pumila mill) extend the lifespan of caenorhabditis elegans. Planta Med. 2011; 77:122–7. [PubMed: 20717869]

56. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr. 2005; 81:243S–55S. [PubMed: 15640487]
57. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. 2005; 81:230S–42S. [PubMed: 15640486]
58. Pietsch K, Saul N, Menzel R, Sturzenbaum SR, Steinberg CE. Quercetin mediated lifespan extension in Caenorhabditis elegans is modulated by age-1, daf-2, sek-1 and unc-43. Biogerontology. 2009; 10:565–78. [PubMed: 19043800]
59. Saul N, Pietsch K, Menzel R, Steinberg CE. Quercetin-mediated longevity in Caenorhabditis elegans: is DAF-16 involved? Mech Ageing Dev. 2008; 129:611–3. [PubMed: 18692520]
60. Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, Gonos ES. Anti-ageing and rejuvenating effects of quercetin. Exp Gerontol. 2010; 45:763–71. [PubMed: 20619334]
61. Arts MJTJ, Dallinga JS, Voss HP, Haenen GRMM, Bast A. A new approach to assess the total antioxidant capacity using the TEAC assay. Food Chem. 2004; 88:567–70.
62. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008; 585:325–37. [PubMed: 18417116]
63. Vanacker SABE, Tromp MNJL, Haenen GRMM, Vandervijgh WJF, Bast A. Flavonoids as scavengers of nitric-oxide radical. Biochem Bioph Res Co. 1995; 214:755–9.
64. Bureau G, Longpre F, Martinoli MG. Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. J Neurosci Res. 2008; 86:403–10. [PubMed: 17929310]
65. Manjeet KR, Ghosh B. Quercetin inhibits LPS-induced nitric oxide and tumor necrosis factor-alpha production in murine macrophages. Int J Immunopharmacol. 1999; 21:435–43. [PubMed: 10454017]
66. Itokawa H, Shi Q, Akiyama T, Morris-Natschke SL, Lee KH. Recent advances in the investigation of curcuminoids. Chin Med. 2008; 3:11. [PubMed: 18798984]
67. Ammon HP, Wahl MA. Pharmacology of curcuma longa. Planta Med. 1991; 57:1–7. [PubMed: 2062949]
68. Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett. 1995; 94:79–83. [PubMed: 7621448]
69. Singh AK, Jiang Y, Benlhabib E, Gupta S. Herbal mixtures consisting of puerarin and either polyenylphosphatidylcholine or curcumin provide comprehensive protection against alcohol-related disorders in P rats receiving free choice water and 15% ethanol in pure water. J Med Food. 2007; 10:526–42. [PubMed: 17887948]
70. Shen LR, Xiao F, Yuan P, Chen Y, Gao QK, Parnell LD, et al. Curcumin-supplemented diets increase superoxide dismutase activity and mean lifespan in Drosophila. Age (Dordr). 2013; 35:1133–42. [PubMed: 22653297]
71. Soh JW, Marowsky N, Nichols TJ, Rahman AM, Miah T, Sarao P, et al. Curcumin is an early-acting stage-specific inducer of extended functional longevity in Drosophila. Exp Gerontol. 2013; 48:229–39. [PubMed: 23063786]
72. Lee KS, Lee BS, Semnani S, Avanesian A, Um CY, Jeon HJ, et al. Curcumin extends life span, improves health span, and modulates the expression of age-associated aging genes in Drosophila melanogaster. Rejuvenation Res. 2010; 13:561–70. [PubMed: 20645870]
73. Liao VH, Yu CW, Chu YJ, Li WH, Hsieh YC, Wang TT. Curcumin-mediated lifespan extension in Caenorhabditis elegans. Mech Ageing Dev. 2011; 132:480–7. [PubMed: 21855561]
74. Kitani K, Osawa T, Yokozawa T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. Biogerontology. 2007; 8:567–73. [PubMed: 17516143]
75. Banji D, Banji OJ, Dasaroju S, Annamalai AR. Piperine and curcumin exhibit synergism in attenuating d-galactose induced senescence in rats. Eur J Pharmacol. 2013; 703:91–9. [PubMed: 23200897]
76. Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. JPEN J Parenter Enteral Nutr. 2006; 30:45–51. [PubMed: 16387899]

77. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life Sci. 2006; 78:2081–7. [PubMed: 16413584]

78. Barzegar A, Moosavi-Movahedi AA. Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin. Plos One. 2011; 6:e26012–9. [PubMed: 22016801]

79. Basu A, Lucas EA. Mechanisms and effects of green tea on cardiovascular health. Nutr Rev. 2007; 65:361–75. [PubMed: 17867370]

80. Davalli, P.; Rizzi, F.; Caporali, A.; Pellacani, D.; Davoli, S.; Bettuzzi, S., et al. Anticancer activity of green tea polyphenols in prostate gland. Oxid Med Cell Longev. 2012. http://dx.doi.org/10.1155/2012/984219

81. Thielecke F, Boschmann M. The potential role of green tea catechins in the prevention of the metabolic syndrome - a review. Phytochemistry. 2009; 70:11–24. [PubMed: 19147161]

82. Sae-tan S, Grove KA, Lambert JD. Weight control and prevention of metabolic syndrome by green tea. Pharmacol Res. 2011; 64:146–54. [PubMed: 21193040]

83. Li Q, Li Y. Review on the neuroprotective effects of green tea polyphenols for the treatment of neurodegenerative diseases. Wei Sheng Yan Jiu. 2010; 39:123–6. [PubMed: 20364607]

84. Li YM, Chan HYE, Yao XQ, Huang Y, Chen ZY. Green tea catechins and broccoli reduce fat-induced mortality in Drosophila melanogaster. J Nutr Biochem. 2008; 19:376–83. [PubMed: 17707629]

85. Abbas S, Wink M. Epigallocatechin gallate from green tea (Camellia sinensis) increases lifespan and stress resistance in Caenorhabditis elegans. Planta Med. 2009; 75:216–21. [PubMed: 19085685]

86. Zhang LZ, Jie GL, Zhang JJ, Zhao BL. Significant longevity-extending effects of EGCG on Caenorhabditis elegans under stress. Free Radical Biol Med. 2009; 46:414–21. [PubMed: 19061950]

87. Aires DJ, Rockwell G, Wang T, Frontera J, Wick J, Wang WF, et al. Potentiation of dietary restriction-induced lifespan extension by polyphenols. BBA-Mol Basis Dis. 1822; 2012:522–6.

88. Sadakata S, Fukao A, Hisamichi S. Mortality among female practitioners of Chanoyu. Tohoku J Exp Med. 1992; 166:3.

89. Moriguchi T, Saito H, Nishiyama N. Anti-ageing effect of aged garlic extract in the inbred brain atrophy mouse model. Clin Exp Pharmacol Physiol. 1997; 24:235–42. [PubMed: 9131291]

90. Xiang L, Sun KY, Lu J, Weng YF, Taoka A, Sakagami Y, Qi JH. Anti-aging effects of phloridzin, an apple polyphenol, on yeast via the SOD and Sir2 genes. Biosci Biotech Bioch. 2011; 75:854–8.

91. Kampkotter A, Nkwonkam CG, Zurawski RF, Timpel C, Chovolou Y, Watjen W, et al. Effects of the flavonoids kaempferol and fisetin on thermotolerance, oxidative stress and FoxO transcription factor DAF-16 in the model organism Caenorhabditis elegans. Arch Toxicol. 2007; 81:849–58. [PubMed: 17551714]

92. Zarse K, Bossecker A, Muller-Kuhrt L, Siems K, Hernandez MA, Berendsohn WG, et al. The phytochemical glaucarubinone promotes mitochondrial metabolism, reduces body fat, and extends lifespan of Caenorhabditis elegans. Horm Metab Res. 2011; 43:241–3. [PubMed: 21264793]

93. Wilson MA, Shukitt-Hale B, Kalt W, Ingram DK, Joseph JA, Wolkow CA. Blueberry polyphenols increase lifespan and thermotolerance in Caenorhabditis elegans. Aging Cell. 2006; 5:59–68. [PubMed: 16441844]

94. Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. Physiol Rev. 1979; 59:527–605. [PubMed: 37532]

95. Harman D. The biologic clock: the mitochondria? J Am Geriatr Soc. 1972; 20:145–7. [PubMed: 5016631]

96. Linnane AW, Marzuki S, Ozawa T, Tanaka M. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. Lancet. 1989; 1:642–5. [PubMed: 2564461]

97. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell. 2005; 120:483–95. [PubMed: 15734681]

98. Chang TS, Cho CS, Park S, Yu S, Kang SW, Rhee SG. Peroxiredoxin III, a mitochondrion-specific peroxidase, regulates apoptotic signaling by mitochondria. J Biol Chem. 2004; 279:41975–84. [PubMed: 15280382]

99. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci U S A. 1994; 91:10771–8. [PubMed: 7971961]
100. Sohal RS, Sohal BH. Hydrogen peroxide release by mitochondria increases during aging. Mech Ageing Dev. 1991; 57:187–202. [PubMed: 1904965]
101. Asensi M, Sastre J, Pallardo FV, Lloret A, Lehner M, Garcia-de-la Asuncion J, et al. Ratio of reduced to oxidized glutathione as indicator of oxidative stress status and DNA damage. Methods Enzymol. 1999; 299:267–76. [PubMed: 9916205]
102. Nenadis N, Wang LF, Tsimidou M, Zhang HY. Estimation of scavenging activity of phenolic compounds using the ABTS(*+) assay. J Agric Food Chem. 2004; 52:4669–74. [PubMed: 15264898]
103. Lu M, Cai YJ, Fang JG, Zhou YL, Liu ZL, Wu LM. Efficiency and structure-activity relationship of the antioxidant action of resveratrol and its analogs. Pharmazie. 2002; 57:474–8. [PubMed: 12168529]
104. Yokozawa T, Chen CP, Dong E, Tanaka T, Nonaka GI, Nishioka I. Study on the inhibitory effect of tannins and flavonoids against the 1,1-diphenyl-2 picrylhydrazyl radical. Biochem Pharmacol. 1998; 56:213–22. [PubMed: 9698075]
105. Cao G, Sofic E, Prior RL. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. Free Radic Biol Med. 1997; 22:749–60. [PubMed: 9119242]
106. Wolfe KL, Liu RH. Structure-activity relationships of flavonoids in the cellular antioxidant activity assay. J Agric Food Chem. 2008; 56:8404–11. [PubMed: 18702468]
107. Modak B, Contreras ML, Gonzalez-Nilo F, Torres R. Structure-antioxidant activity relationships of flavonoids isolated from the resinous exudate of Heliotropium sinuatum. Bioorg Med Chem Lett. 2005; 15:309–12. [PubMed: 15603945]
108. Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci U S A. 2004; 101:3381–6. [PubMed: 14985508]
109. Shih PH, Yen GC. Differential expressions of antioxidant status in aging rats: the role of transcriptional factor Nrf2 and MAPK signaling pathway. Biogerontology. 2007; 8:71–80. [PubMed: 16850181]
110. Asha Devi S, Prathima S, Subramanyam MV. Dietary vitamin E and physical exercise: II. Antioxidant status and lipofuscin-like substances in aging rat heart. Exp Gerontol. 2003; 38:291–7. [PubMed: 12581793]
111. Unlu ES, Koc A. Effects of deleting mitochondrial antioxidant genes on life span. Ann N Y Acad Sci. 2007; 1100:505–9. [PubMed: 17460215]
112. Phillips JP, Campbell SD, Michaud D, Charbonneau M, Hilliker AJ. Null mutation of copper/zinc superoxide dismutase in Drosophila confers hypersensitivity to paraquat and reduced longevity. Proc Natl Acad Sci U S A. 1989; 86:2761–5. [PubMed: 2539600]
113. Elchuri S, Oberley TD, Qi W, Eisenstein RS, Jackson Roberts L, Van Remmen H, et al. CuZnSOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life. Oncogene. 2005; 24:367–80. [PubMed: 15531919]
114. Lebovitz RM, Zhang H, Vogel H, Cartwright J Jr, Dionne L, Lu N, et al. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proc Natl Acad Sci U S A. 1996; 93:9782–7. [PubMed: 8790408]
115. Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond MH, et al. Extension of murine life span by overexpression of catalase targeted to mitochondria. Science. 2005; 308:1909–11. [PubMed: 15879174]
116. Singh S, Das Roy L, Giri S. Curcumin protects metronidazole and X-ray induced cytotoxicity and oxidative stress in male germ cells in mice. Prague Med Rep. 2013; 114:92–102.
117. Kesherwani V, Atif F, Yousuf S, Agrawal SK. Resveratrol protects spinal cord dorsal column from hypoxic injury by activating Nrf-2. Neuroscience. 2013; 241:80–8. [PubMed: 23523995]
118. Roy S, Sannigrahi S, Vaddepalli RP, Ghosh B, Pusp P. A novel combination of methotrexate and epigallocatechin attenuates the overexpression of pro-inflammatory cartilage cytokines and modulates antioxidant status in adjuvant arthritic rats. Inflammation. 2012; 35:1435–47. [PubMed: 22453361]

119. Uygur, R.; Yagmurca, M.; Alkoc, OA.; Genc, A.; Songur, A.; Ucok, K., et al. Effects of quercetin and fish n-3 fatty acids on testicular injury induced by ethanol in rats. Andrologia. 2013. http://dx.doi.org/10.1111/and.12085
120. Itoh K, Tong KI, Yamamoto M. Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. Free Radic Biol Med. 2004; 36:1208–13. [PubMed: 15110385]
121. Kobayashi M, Yamamoto M. Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. Antioxid Redox Signal. 2005; 7:385–94. [PubMed: 15706085]
122. Khor TO, Huang MT, Prawan A, Liu Y, Hao X, Yu S, et al. Increased susceptibility of Nrf2 knockout mice to colitis-associated colorectal cancer. Cancer Prev Res (Phila). 2008; 1:187–91. [PubMed: 19138955]
123. Son TG, Camandola S, Mattson MP. Hormetic dietary phytochemicals. Neuromolecular Med. 2008; 10:236–46. [PubMed: 18543123]
124. Ma Q, He X. Molecular basis of electrophilic and oxidative defense: promises and perils of Nrf2. Pharmacol Rev. 2012; 64:1055–81. [PubMed: 22966037]
125. Vauzour D, Buonfiglio M, Corona G, Chirafisi J, Vafeiadou K, Angeloni C, et al. Sulforaphane protects cortical neurons against 5-S-cysteinyl-dopamine-induced toxicity through the activation of ERK1/2, Nrf-2 and the upregulation of detoxification enzymes. Mol Nutr Food Res. 2010; 54:532–42. [PubMed: 20166144]
126. Yu R, Lei W, Mandlekar S, Weber MJ, Der CJ, Wu J, et al. Role of a mitogen-activated protein kinase pathway in the induction of phase II detoxifying enzymes by chemicals. J Biol Chem. 1999; 274:27545–52. [PubMed: 10488090]
127. Wu CC, Hsu MC, Hsieh CW, Lin JB, Lai PH, Wung BS. Upregulation of heme oxygenase-1 by Epigallocatechin-3-gallate via the phosphatidylinositol 3-kinase/Akt and ERK pathways. Life Sci. 2006; 78:2889–97. [PubMed: 16378625]
128. Wruck CJ, Claussen M, Fuhrmann G, Romer L, Schulz A, Pufe T, et al. Luteolin protects rat PC12 and C6 cells against MPP+ induced toxicity via an ERK dependent Keap1-Nrf2-ARE pathway. J Neural Transm Suppl. 2007; 72:57–67. [PubMed: 17982879]
129. Rushworth SA, Ogborne RM, Charalambos CA, O'Connell MA. Role of protein kinase C delta in curcumin-induced antioxidant response element-mediated gene expression in human monocytes. Biochem Biophys Res Commun. 2006; 341:1007–16. [PubMed: 16460683]
130. Jeong WS, Keum YS, Chen C, Jain MR, Shen G, Kim JH, et al. Differential expression and stability of endogenous nuclear factor E2-related factor 2 (Nrf2) by natural chemopreventive compounds in HepG2 human hepatoma cells. J Biochem Mol Biol. 2005; 38:167–76. [PubMed: 15826493]
131. Apfeld J, O'Connor G, McDonagh T, DiStefano PS, Curtis R. The AMP-activated protein kinase AAK-2 links energy levels and insulin-like signals to lifespan in C. elegans. Genes Dev. 2004; 18:3004–9. [PubMed: 15574588]
132. Kumar A, Singh CK, Lavoie HA, Dipette DJ, Singh US. Resveratrol restores Nrf2 level and prevents ethanol-induced toxic effects in the cerebellum of a rodent model of fetal alcohol spectrum disorders. Mol Pharmacol. 2011; 80:446–57. [PubMed: 21697273]
133. Shah ZA, Li RC, Ahmad AS, Kensler TW, Yamamoto M, Biswal S, et al. The flavanol (−)-epicatechin prevents stroke damage through the Nrf2/HO1 pathway. J Cereb Blood Flow Metab. 2010; 30:1951–61. [PubMed: 20442725]
134. Granado-Serrano AB, Martin MA, Haegeman G, Goya L, Bravo L, Ramos S. Epicatechin induces NF-kappaB, activator protein-1 (AP-1) and nuclear transcription factor erythroid 2p45-related factor-2 (Nrf2) via phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) and extracellular regulated kinase (ERK) signalling in HepG2 cells. Br J Nutr. 2010; 103:168–79. [PubMed: 20030899]
135. Si H, Liu D. Genistein, a soy phytoestrogen, upregulates the expression of human endothelial nitric oxide synthase and lowers blood pressure in spontaneously hypertensive rats. J Nutr. 2008; 138:297–304. [PubMed: 18203895]
136. Steinberg GR, Kemp BE. AMPK in health and disease. Physiol Rev. 2009; 89:1025–78. [PubMed: 19584320]

137. Bergeron R, Previs SF, Cline GW, Perret P, Russell RR 3rd, Young LH, et al. Effect of 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside infusion on in vivo glucose and lipid metabolism in lean and obese Zucker rats. Diabetes. 2001; 50:1076–82. [PubMed: 11334411]
138. Jorgensen SB, Wojtaszewski JF, Viollet B, Andreelli F, Birk JB, Hellsten Y, et al. Effects of alpha-AMPK knockout on exercise-induced gene activation in mouse skeletal muscle. FASEB J. 2005; 19:1146–8. [PubMed: 15878932]
139. Carling D, Sanders MJ, Woods A. The regulation of AMP-activated protein kinase by upstream kinases. Int J Obes (Lond). 2008; 32(Suppl 4):S55–9. [PubMed: 18719600]
140. Witczak CA, Sharoff CG, Goodyear LJ. AMP-activated protein kinase in skeletal muscle: from structure and localization to its role as a master regulator of cellular metabolism. Cell Mol Life Sci. 2008; 65:3737–55. [PubMed: 18810325]
141. Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci U S A. 2007; 104:12017–22. [PubMed: 17609368]
142. Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC, et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell. 1999; 98:115–24. [PubMed: 10412986]
143. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell. 1998; 92:829–39. [PubMed: 9529258]
144. Greer EL, Banko MR, Brunet A. AMP-activated protein kinase and FoxO transcription factors in dietary restriction-induced longevity. Ann N Y Acad Sci. 2009; 1170:688–92. [PubMed: 19686213]
145. Ruderman NB, Xu XJ, Nelson L, Cacicedo JM, Saha AK, Lan F, et al. AMPK and SIRT1: a long-standing partnership? Am J Physiol Endocrinol Metab. 2010; 298:E751–60. [PubMed: 20103737]
146. Fisslthaler B, Fleming I. Activation and signaling by the AMP-activated protein kinase in endothelial cells. Cir Res. 2009; 105:114–27.
147. Nagata D, Hirata Y. The role of AMP-activated protein kinase in the cardiovascular system. Hypertens Res. 2010; 33:22–8. [PubMed: 19911004]
148. Qiang W, Weiqiang K, Qing Z, Pengju Z, Yi L. Aging impairs insulin-stimulated glucose uptake in rat skeletal muscle via suppressing AMPKalpha. Exp Mol Med. 2007; 39:535–43. [PubMed: 17934342]
149. Reznick RM, Zong H, Li J, Morino K, Moore IK, Yu HJ, et al. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. Cell Metab. 2007; 5:151–6. [PubMed: 17276357]
150. Dong Y, Zhang M, Liang B, Xie Z, Zhao Z, Asfa S, et al. Reduction of AMP-activated protein kinase alpha2 increases endoplasmic reticulum stress and atherosclerosis in vivo. Circulation. 2010; 121:792–803. [PubMed: 20124121]
151. You M, Matsumoto M, Pacold CM, Cho WK, Crabb DW. The role of AMP-activated protein kinase in the action of ethanol in the liver. Gastroenterology. 2004; 127:1798–808. [PubMed: 15578517]
152. Ajmo JM, Liang X, Rogers CQ, Pennock B, You M. Resveratrol alleviates alcoholic fatty liver in mice. Am J Physiol Gastrointest Liver Physiol. 2008; 295:G833–42. [PubMed: 18755807]
153. Porquet D, Casadesus G, Bayod S, Vicente A, Canudas AM, Vilaplana J, et al. Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8. Age (Dordr). 2013; 35:1851–65. [PubMed: 23129026]
154. Kim MY, Lim JH, Youn HH, Hong YA, Yang KS, Park HS, et al. Resveratrol prevents renal lipotoxicity and inhibits mesangial cell glucotoxicity in a manner dependent on the AMPK-SIRT1-PGC1alpha axis in db/db mice. Diabetologia. 2013; 56:204–17. [PubMed: 23090186]
155. Um JH, Park SJ, Kang H, Yang S, Foretz M, McBurney MW, et al. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. Diabetes. 2010; 59:554–63. [PubMed: 19934007]

156. Nieman DC, Williams AS, Shanely RA, Jin F, McAnulty SR, Triplett NT, et al. Quercetin's influence on exercise performance and muscle mitochondrial biogenesis. Med Sci Sports Exerc. 2010; 42:338–45. [PubMed: 19927026]

157. Davis JM, Murphy EA, Carmichael MD, Davis B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol. 2009; 296:R1071–7. [PubMed: 19211721]

158. Ye, Q.; Ye, L.; Xu, X.; Huang, B.; Zhang, X.; Zhu, Y.; Chen, X. Epigallocatechin-3-gallate suppresses 1-methyl-4-phenyl-pyridine-induced oxidative stress in PC12 cells via the SIRT1/PGC-1alpha signaling pathway. BMC Complement Altern Med. 2012. http://dx.doi.org/10.1186/1472-6882-12-82

159. Kim T, Davis J, Zhang AJ, He X, Mathews ST. Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. Biochem Biophys Res Commun. 2009; 388:377–82. [PubMed: 19665995]

160. Soetikno V, Sari FR, Sukumaran V, Lakshmanan AP, Harima M, Suzuki K, et al. Curcumin decreases renal triglyceride accumulation through AMPK-SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats. J Nutr Biochem. 2013; 24:796–802. [PubMed: 22898567]

161. Gasser SM, Cockell MM. The molecular biology of the SIR proteins. Gene. 2001; 279:1–16. [PubMed: 11722841]

162. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science. 2000; 289:2126–8. [PubMed: 11000115]

163. Rogina B, Helfand SL. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. Proc Natl Acad Sci U S A. 2004; 101:15998–6003. [PubMed: 15520384]

164. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, et al. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science. 2004; 305:390–2. [PubMed: 15205477]

165. Jeong J, Juhn K, Lee H, Kim SH, Min BH, Lee KM, et al. SIRT1 promotes DNA repair activity and deacetylation of Ku70. Exp Mol Med. 2007; 39:8–13. [PubMed: 17334224]

166. Langley E, Pearson M, Faretta M, Bauer UM, Frye RA, Minucci S, et al. Human SIR2 deacetylates p53 and antagonizes PML/p53-induced cellular senescence. EMBO J. 2002; 21:2383–96. [PubMed: 12006491]

167. Zu Y, Liu L, Lee MY, Xu C, Liang Y, Man RY, et al. SIRT1 promotes proliferation and prevents senescence through targeting LKB1 in primary porcine aortic endothelial cells. Circ Res. 2010; 106:1384–93. [PubMed: 20203304]

168. Zhang J. The direct involvement of SirT1 in insulin-induced insulin receptor substrate-2 tyrosine phosphorylation. J Biol Chem. 2007; 282:34356–64. [PubMed: 17901049]

169. Bordone L, Motta MC, Picard F, Robinson A, Jhala US, Apfeld J, et al. Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic beta cells. PLoS Biol. 2006; 4:e31. http://dx.doi.org/10.1371/journal.pbio.0040031. [PubMed: 16366736]

170. Daitoku H, Hatta M, Matsuzaki H, Aratani S, Ohshima T, Miyagishi M, et al. Silent information regulator 2 potentiates Foxo1-mediated transcription through its deacetylase activity. Proc Natl Acad Sci U S A. 2004; 101:10042–7. [PubMed: 15220471]

171. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science. 2004; 303:2011–5. [PubMed: 14976264]

172. Price NL, Gomes AP, Ling AJ, Duarte FV, Martin-Montalvo A, North BJ, et al. SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. Cell Metab. 2012; 15:675–90. [PubMed: 22560220]

173. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell. 2006; 127:1109–22. [PubMed: 17112576]

174. Beher D, Wu J, Cumine S, Kim KW, Lu SC, Atangan L, et al. Resveratrol is not a direct activator of SIRT1 enzyme activity. Chem Biol Drug Des. 2009; 74:619–24. [PubMed: 19843076]

175. Pacholec M, Bleasdale JE, Chrunyk B, Cunningham D, Flynn D, Garofalo RS, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. J Biol Chem. 2010; 285:8340–51. [PubMed: 20061378]

176. Park SJ, Ahmad F, Philp A, Baar K, Williams T, Luo H, et al. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. Cell. 2012; 148:421–33. [PubMed: 22304913]

177. de Boer VC, de Goffau MC, Arts IC, Hollman PC, Keijer J. SIRT1 stimulation by polyphenols is affected by their stability and metabolism. Mech Ageing Dev. 2006; 127:618–27. [PubMed: 16603228]

178. Choi KC, Jung MG, Lee YH, Yoon JC, Kwon SH, Kang HB, et al. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. Cancer Res. 2009; 69:583–92. [PubMed: 19147572]

179. Feng Y, Wu J, Chen L, Luo C, Shen X, Chen K, et al. A fluorometric assay of SIRT1 deacetylation activity through quantification of nicotinamide adenine dinucleotide. Anal Biochem. 2009; 395:205–10. [PubMed: 19682970]

180. Berryman DE, Christiansen JS, Johannsson G, Thorner MO, Kopchick JJ. Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models. Growth Horm IGF Res. 2008; 18:455–71. [PubMed: 18710818]

181. Bartke A, Peluso MR, Moretz N, Wright C, Bonkowski M, Winters TA, et al. Effects of soy-derived diets on plasma and liver lipids, glucose tolerance, and longevity in normal, long-lived and short-lived mice. Horm Metab Res. 2004; 36:550–8. [PubMed: 15326565]

182. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. Diabetes. 2012; 61:1315–22. [PubMed: 22618766]

183. Holzenberger M. The GH/IGF-I axis and longevity. Eur J Endocrinol. 2004; 151 (Suppl 1):S23–7. [PubMed: 15339240]

184. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res. 2003; 13:113–70. [PubMed: 12914749]

185. Janssen JA, Lamberts SW. Is the measurement of free IGF-I more indicative than that of total IGF-I in the evaluation of the biological activity of the GH/IGF-I axis? J Endocrinol Invest. 1999; 22:313–5. [PubMed: 10342368]

186. Ning J, Clemmons DR. AMP-activated protein kinase inhibits IGF-I signaling and protein synthesis in vascular smooth muscle cells via stimulation of insulin receptor substrate 1 S794 and tuberous sclerosis 2 S1345 phosphorylation. Mol Endocrinol. 2010; 24:1218–29. [PubMed: 20363874]

187. Youreva V, Kapakos G, Srivastava AK. Insulin-like growth-factor-1-induced PKB signaling and Egr-1 expression is inhibited by curcumin in A-10 vascular smooth muscle cells. Can J Physiol Pharmacol. 2013; 91:241–7. [PubMed: 23537438]

188. Vanamala, J.; Reddivari, L.; Radhakrishnan, S.; Tarver, C. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. BMC Cancer. 2010. http://dx.doi.org/10.1186/1471-2407-10-238

189. Shimizu M, Shirakami Y, Sakai H, Tatebe H, Nakagawa T, Hara Y, et al. EGCG inhibits activation of the insulin-like growth factor (IGF)/IGF-1 receptor axis in human hepatocellular carcinoma cells. Cancer Lett. 2008; 262:10–8. [PubMed: 18164805]

190. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, et al. The origins of age-related proinflammatory state. Blood. 2005; 105:2294–9. [PubMed: 15572589]

191. Brod SA. Unregulated inflammation shortens human functional longevity. Inflamm Res. 2000; 49:561–70. [PubMed: 11131295]

192. Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA)–a precursor steroid or an active hormone in human physiology. J Sex Med. 2011; 8:2960–82. [quiz 83]. [PubMed: 22032408]

193. Franceschi C, Bonafe M, Valensin S. Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine. 2000; 18:1717–20. [PubMed: 10689155]

194. Sansoni P, Vescovini R, Fagnoni F, Biasini C, Zanni F, Zanlari L, et al. The immune system in extreme longevity. Exp Gerontol. 2008; 43:61–5. [PubMed: 17870272]

195. Chung HY, Sung B, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. Antioxid Redox Signal. 2006; 8:572–81. [PubMed: 16677101]

196. Zou Y, Jung KJ, Kim JW, Yu BP, Chung HY. Alteration of soluble adhesion molecules during aging and their modulation by calorie restriction. FASEB J. 2004; 18:320–2. [PubMed: 14688195]

197. Bisht K, Wagner KH, Bulmer AC. Curcumin, resveratrol and flavonoids as anti-inflammatory, cyto- and DNA-protective dietary compounds. Toxicology. 2010; 278:88–100. [PubMed: 19903510]

198. Babu PVA, Si HW, Liu DM. Epigallocatechin gallate reduces vascular inflammation in db/db mice possibly through an NF-kappa B-mediated mechanism. Mol Nutr Food Res. 2012; 56:1424–32. [PubMed: 22753231]

199. Indra MR, Karyono S, Ratnawati R, Malik SG. Quercetin suppresses inflammation by reducing ERK1/2 phosphorylation and NF kappa B activation in Leptin-induced Human Umbilical Vein Endothelial Cells (HUVECs). BMC Res Notes. 2013; 6:275. http://dx.doi.org/10.1186/1756-0500-6-275. [PubMed: 23856194]

200. Cuervo AM. Autophagy and aging: keeping that old broom working. Trends Genet. 2008; 24:604–12. [PubMed: 18992957]

201. Hansen M, Chandra A, Mitic LL, Onken B, Driscoll M, Kenyon C. A role for autophagy in the extension of lifespan by dietary restriction in C elegans. PLoS Genet. 2008; 4:e24. http://dx.doi.org/10.1371/journal.pgen.0040024. [PubMed: 18282106]

202. Del Roso A, Vittorini S, Cavallini G, Donati A, Gori Z, Masini M, et al. Ageing-related changes in the in vivo function of rat liver macroautophagy and proteolysis. Exp Gerontol. 2003; 38:519–27. [PubMed: 12742529]

203. Ghosh HS, McBurney M, Robbins PD. SIRT1 negatively regulates the mammalian target of rapamycin. Plos One. 2010; 5:e9199. http://dx.doi.org/10.1371/journal.pone.0009199. [PubMed: 20169165]

204. Roy SK, Chen QH, Fu JS, Shankar S, Srivastava RK. Resveratrol Inhibits Growth of Orthotopic Pancreatic Tumors through Activation of FOXO Transcription Factors. Plos One. 2011; 6:e25166. http://dx.doi.org/10.1371/journal.pone.0025166. [PubMed: 21980390]

205. Devika PT, Prince PS. Preventive effect of (−)epigallocatechin-gallate (EGCG) on lysosomal enzymes in heart and subcellular fractions in isoproterenol-induced myocardial infarcted Wistar rats. Chem Biol Interact. 2008; 172:245–52. [PubMed: 18294627]

206. Arlorio M, Bottini C, Travaglia F, Locatelli M, Bordiga M, Coisson JD, et al. Protective Activity of Theobroma cacao L. Phenolic Extract on AML12 and MLP29 Liver Cells by Preventing Apoptosis and Inducing Autophagy. J Agricult Food Chem. 2009; 57:10612–8.

207. Klappan AK, Hones S, Mylonas I, Bruning A. Proteasome inhibition by quercetin triggers macroautophagy and blocks mTOR activity. Histochem Cell Biol. 2012; 137:25–36. [PubMed: 21993664]

208. Alavez S, Vantipalli MC, Zucker DJS, Klang IM, Lithgow GJ. Amyloid-binding compounds maintain protein homeostasis during ageing and extend lifespan. Nature. 2011; 472:226–9. [PubMed: 21451522]

209. Wu JC, Lai CS, Badmaev V, Nagabhushanam K, Ho CT, Pan MH. Tetrahydrocurcumin, a major metabolite of curcumin, induced autophagic cell death through coordinative modulation of PI3K/Akt-mTOR and MAPK signaling pathways in human leukemia HL-60 cells. Molecular Nutr Food Res. 2011; 55:1646–54.

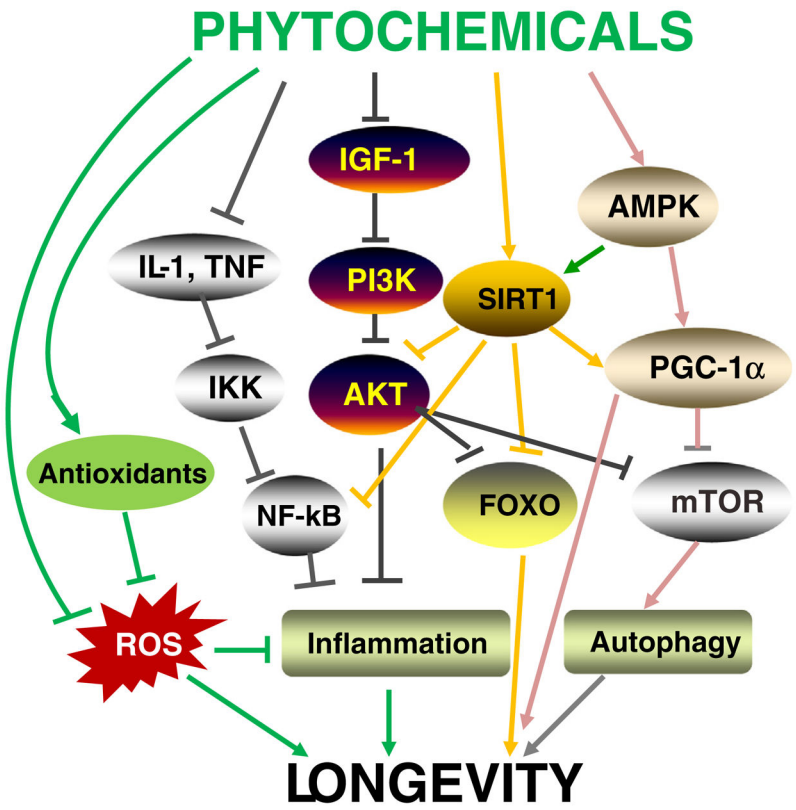

Fig. 1.

Hypothetical cellular and molecular mechanisms of the antiaging effects of phytochemicals. Phytochemicals extend lifespan through reducing oxidative stress, suppressing low-grade chronic inflammation and inducing autophagy. As shown, there are cross talk and interaction at both cellular and molecular levels between these events.

Table 1

Classification of phytochemicals and their food sources

Category			Chemical	Food/Plant resources
Phenolic compounds	Natural monophenols		Rosemarinol	Rosemary
	Flavonoids (polyphenols)	Flavonols	Quercetin	Onions, tea, wine, apples
			Kaempferol	Tea, strawberries, gooseberries
			Fisetin	Tea, grape, onions
			Myricetin	Grapes, red wine, berries
		Flavanones	Naringenin	Citrus fruits
		Flavones	Apigenin	Chamomile, celery, parsley
			Luteolin	Beets, artichokes, celery
		Flavan-3-ols	Catechin	white tea, green tea, black tea
			(−)-Epicatechin	Tea, cocoa, grape
			EGCG	green tea
			Theaflavin	Black tea
		Anthocyanins/Anthocyanidins	Pelargonidin	Bilberry, raspberry, strawberry
			Delphinidin	Bilberry, blueberry, eggplant
		Isoflavones	Genistein	Soy, red clover, peanuts
		Chalconoids	Butein	Rhus verniciflua, dalbergia odorifera
			Phlorizin	Pear, apple, cherry
	Phenolic acids		Ellagic acid	Walnuts, strawberries, cranberries
			Curcumin	Turmeric, mustard
	Hydroxycinnamic acids		Caffeic acid	Burdock, hawthorn, artichoke
	Lignans		Matairesinol	Flax seed, sesame seed, rye bran
	Tyrosol esters		Tyrosol	olive oil
	Stilbenoids		Resveratrol	Grape, wine, nuts
	Alkylresorcinols			Wheat, rye and barley
Terpenes	Carotenoids	Carotenes	Carotene	Carrots, pumpkins, maize,
		Xanthophylls	Lutein	Spinach, turnip greens, lettuce
	Monoterpene	Limonene		Oils of citrus, cherries, spearmint
	Saponins			Soybeans, beans, other legumes
	Lipids	Phytosterols	Sitosterol	Avocados, almonds, wheat germ
	Triterpenoid	Glaucarubinone		Simaroubaceae plants
Betalains	Betacyanins	Betanin		Beets, chard
	Betaxanthins	Indicaxanthin		Beets, sicilian prickly pear
Organosulfides	Polysulfides	Allyl methyl trisulfide		Garlic, onions, leeks
Indoles, glucosinolates/sulfur compounds	Indole-3-carbinol			Cabbage, kale, brussels sprouts
	Sulforaphane			Broccoli, cauliflower, brussels sprouts
	Allicin			Garlic

Category		Chemical	Food/Plant resources
Protein inhibitors	Protease inhibitors		Soy, legumes
Other organic acids	Oxalic acid		Orange, spinach, rhubarb
	Anacardic acid		Cashews, mangoes