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Effects of Phytochemicals In Health and Longevity

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Reviews

On The Cover: Many plants and vegetables provide beneficial nutrients and chemicals for humans. Some of these chemicals are typically detrimental in high amounts; however, lower concentrations have been seen to be health promoting. On pages 335-346 of this issue Young and colleagues discuss the beneficial effects of phytochemicals through activating cellular defensive mechanisms on improving health and lifespan. Cover image from istock.

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Review

Hormetic Effects of Phytochemicals on Health and Longevity

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Caloric restriction, intermittent fasting, and exercise activate defensive cellular responses such as autophagy, DNA repair, and the induction of antioxidant enzymes. These processes improve health and longevity by protecting cells and organs against damage, mutations, and reactive oxygen species. Consuming a diet rich in vegetables, fruits, and mushrooms can also improve health and longevity. Phytochemicals such as alkaloids, polyphenols, and terpenoids found in plants and fungi activate the same cellular processes as caloric restriction, fasting, and exercise. Many of the beneficial effects of fruits and vegetables may thus be due to activation of stress resistance pathways by phytochemicals. A better understanding of the mechanisms of action of phytochemicals may provide important insights to delay aging and prevent chronic diseases.

Highlights

Biological stress such as caloric restriction, intermittent fasting, and physical exercise extends lifespan and improves health markers in model organisms by activating stress resistance pathways.

Phytochemicals from fruits, vegetables, and mushrooms produce beneficial effects on health and longevity by modulating stress resistance pathways in a manner similar to caloric restriction, intermittent fasting, and exercise.

Phytochemicals also promote intestinal homeostasis by improving gut barrier integrity and short-chain fatty acid production and by modulating the composition of the gut microbiota.

Common sources of phytochemicals include not only fruits, vegetables, and mushrooms, but also organic foods and dietary supplements.

Biological Stress: A Double-Edged Sword?

Aging is an inevitable process that leads to organ dysfunctions, cognitive decline, and frailty. While death is inevitable, aging can be accelerated or delayed by lifestyle choices. For instance, compared with *ad libitum* feeding, reducing calories by 10–50% without incurring malnutrition extends lifespan in a variety of species, including yeasts, nematodes, fruit flies, mice, rats, and monkeys [1]. Caloric restriction (CR) not only extends lifespan but also improves organ functions and reduces the development of common chronic diseases, including type 2 diabetes, cardiovascular disease, and cancer [2]. Eating less may extend lifespan and prolong the health-span, producing major health benefits.

At the cellular level, CR rejuvenates cells and organs by activating **autophagy** (see Glossary), a process that removes damaged proteins and organelles in order to maintain energy levels and homeostasis [3]. CR also increases the levels of nicotinamide adenine dinucleotide (NAD^+), which in turn leads to activation of sirtuin-1 (SIRT1), a protein deacetylase that stimulates various cellular protective mechanisms, including autophagy and DNA repair [4]. SIRT1 activates forkhead box O (FOXO) transcription factors and induces mitochondrial biogenesis and expression of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. CR induces a switch to fat metabolism and production of ketone bodies that not only serve as a source of energy but also inhibit histone deacetylases, producing effects that complement those of SIRT1 [5].

Long-term CR represents a biological stress that is difficult to maintain due to hunger, low energy, irritability, social eating habits, and the pleasure of eating. Intermittent fasting, in which food is consumed within a short period of time during the day, has been shown to produce effects similar to CR [6]. Daily energy restriction for as little as 16 h improves health markers and prevents the development of chronic diseases such as cancer, diabetes, and cardiovascular disease in animal models [6]. Common fasting methods include eating only one meal per day or the 16:8 method, in which food is eaten within an 8-h window, resulting in fasting during the remaining 16 h of the day.

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In this context, an early feeding window in the morning as opposed to later in the day may provide further health benefits by aligning food intake with the circadian rhythm and metabolism [7]. Compared with CR, intermittent fasting may be better tolerated due to reduced hunger and higher energy levels.

In contrast to CR and intermittent fasting, cell-protective processes are inactivated in the fed state [6]. For instance, eating is associated with cell growth, energy storage, and anabolism, processes that inhibit protective mechanisms such as autophagy, FOXO expression, and SIRT1 activity. Overeating and consuming a Western diet, which is high in refined sugars, animal proteins, and energy-dense foods, are associated with weight gain, reduced longevity, and development of chronic diseases [8,9]. There is therefore a trade-off between eating and energy storage, on one hand, and cell-protective mechanisms induced by CR and fasting, on the other.

Exercise is another intervention that improves health and longevity and reduces the risk of cardiovascular disease, cognitive disorders, osteoporosis, type 2 diabetes, and cancer [10,11]. The beneficial effects of exercise are mediated by cellular and physiological responses that increase stress resistance in animals and humans in a manner similar to CR [12,13]. Energy depletion in muscles and other organs during exercise leads to activation of adenosine monophosphate-activated protein kinase (AMPK), which inhibits mammalian target of rapamycin (mTOR) and activates autophagy. Exercise activates SIRT1 and FOXO expression, leading to improved stress resistance [13]. Exercise also induces production of reactive oxygen species (ROS), which activate nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) and stimulate expression of endogenous antioxidant enzymes, thus reducing ROS levels and cellular damage [12]. Together, these cellular processes improve health and longevity when activated on a regular basis.

The beneficial effects of CR, intermittent fasting, and exercise have been attributed to **hormesis**, which posits that a biological stress that produces detrimental or toxic effects at high intensity may be beneficial at low intensity [14] (Figure 1A). When animal and human cells are exposed to biological stress, they respond by activating cellular and physiological processes that aim to maintain homeostasis, a compensation mechanism that produces long-lasting, beneficial effects [14]. The production of endogenous antioxidant enzymes induced by biological stress such as CR protects the organism against subsequent, more intense oxidative stress or other oxidative agents, such as heavy metals or pro-oxidant compounds, thus inducing cross-tolerance to other stresses [15]. Some have suggested that the hormetic response may represent a general phenomenon that occurs when cells or organisms are exposed to biological stress, including CR and exercise, but also inorganic compounds and environmental toxins [16].

Essential nutrients such as amino acids, vitamins, and minerals also produce hormetic effects at low and high doses, which can lead to deficiency and toxicity, respectively (Figure 1B). For example, chronic vitamin A deficiency leads to blindness [17], while high doses produce anemia, liver toxicity, weight loss, and bone fracture [18]. The dose or intensity of a biological stress or essential nutrient is therefore critical to determine whether they will lead to beneficial or toxic effects.

Health and Longevity: Nature's Way

Diet composition may also influence aging and longevity. Consumption of starchy carbohydrates and proteins activates the insulin and insulin-like growth factor-1 (IGF-1) pathways in cells, leading to cell growth, anabolism, and energy storage, while also inhibiting autophagy and cell-protective mechanisms [19] (Figure 2). Consistent with this observation, a low glycemic diet improves insulin sensitivity and extends lifespan in mice, even when the diet is initiated late in life [20]. Similarly, a low-protein diet improves cardiometabolic health markers and extends longevity in *ad libitum*-fed mice by reducing hepatic mTOR activation [21]. Reduced protein intake

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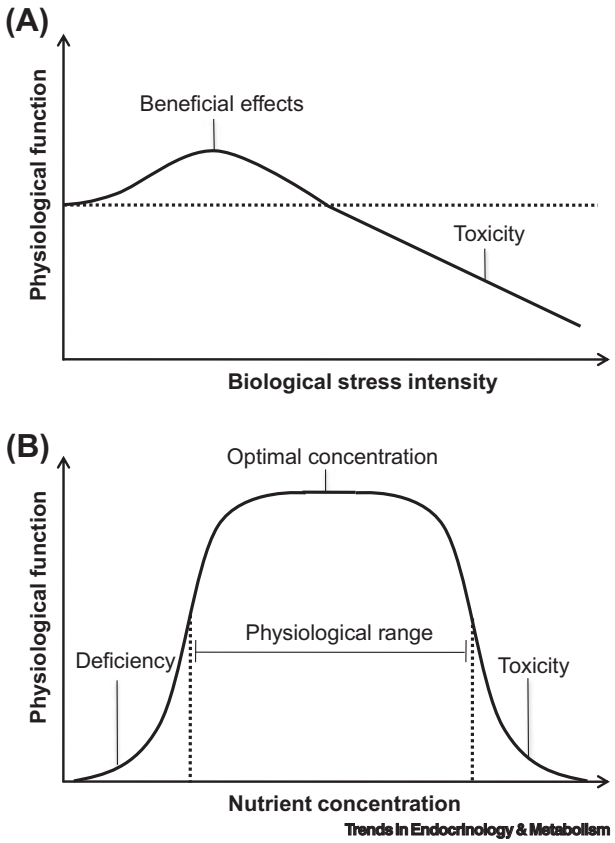

Figure 1. Hormetic Effects of Biological Stress and Essential Nutrients on Health and Longevity. (A) Biological stress such as caloric restriction, intermittent fasting, and exercise may be detrimental, toxic, or even fatal at high intensity. However, at low intensity, biological stress produces beneficial effects on physiological functions by activating resistance pathways such as autophagy, DNA repair, mitochondrial biogenesis, and expression of antioxidant enzymes. Image adapted from Calabrese *et al*. [97], with permission from Elsevier. (B) Essential nutrients such as amino acids, vitamins, and minerals maintain body functions when available within the range of physiological concentrations. However, essential nutrients may also affect physiological responses at low and high concentrations, resulting in deficiency and toxicity, respectively. Image adapted from Eaton and Gilbert [98], with permission from McGraw-Hill Education.

from meat and animal products is also associated with improved health and longevity in humans [22].

Consumption of a diet rich in fruits and vegetables, which reduces the risk of cardiovascular disease, cancer, and neurodegeneration, also improves overall health and longevity in humans [23–25]. The beneficial effects of fruits and vegetables on health and longevity may be explained in various ways. Vegetables tend to be low in simple sugars and proteins, which may delay aging by preventing activation of insulin and IGF-1 pathways. Fruits and vegetables contain dietary fiber, which is not found in other foods; dietary fiber produces a wide range of health benefits, from reducing appetite, weight gain, chronic inflammation, and insulin resistance, to modulation of the gut microbiota and the immune response [26]. Consumption of high amounts of fruits and vegetables may also reduce intake of energy-dense and processed foods. Importantly, the benefits of fruits and vegetables have been attributed to their antioxidant effects and the neutralization of ROS [27]. ROS form as byproducts of energy production in mitochondria and can damage various cellular macromolecules, contributing to organ dysfunctions and aging.

Glossary

Alkaloids: plant compounds that contain nitrogen-containing functional groups.
Autophagy: cellular process in which damaged proteins and dysfunctional organelles are degraded in intracellular vesicles that fuse with lysosomes. This process is activated by exercise or fasting and is associated with beneficial antiaging effects on cellular functions.
Gut dysbiosis: imbalances in the composition of the gut microbiota associated with negative effects on health.
Hormesis: differential response of cells and the human body to different concentrations of a bioactive compound or stress, in which a low intensity/dose of biological stress induces stress resistance mechanisms and health benefits, whereas a high intensity/dose of the same biological stress produces detrimental effects on health and longevity.
Nutraceuticals: combination of the terms 'nutrient' and 'pharmaceutical', usually used to designate a chemical compound isolated from food sources and that may produce health benefits.
Phytochemicals: small organic compounds usually produced by plants as a defense mechanism against biological stress; these compounds are not directly involved in the growth, development, or reproduction in plants and are thus classified as secondary metabolites; major classes include alkaloids, polyphenols, and terpenoids.
Polyphenols: chemical compounds that contain phenol functional groups and are produced as secondary metabolites by plants.
Polysaccharides: molecules found in plants and fungi consisting of carbohydrate monomers linked by glycosidic bonds. Polysaccharides such as starch are hydrolysable by human digestive enzymes and provide a source of energy, while other polysaccharides are not digested (e.g., resistant starch, cellulose, pectins, β-glucans); the latter category may be converted into short-chain fatty acids by the gut microbiota, providing energy and producing systemic effects on the host.
Prebiotics: compounds that produce beneficial health effects in humans by inducing the growth of specific bacterial species in the gut.
Probiotics: live microorganisms that produce beneficial health effects in

Yet, several lines of evidence indicate that fruits and vegetables may not act primarily by scavenging ROS. For instance, people who regularly consume antioxidant supplements such as vitamins A and E and beta-carotene have a slightly higher mortality risk compared with nonusers [28]. Moreover, a combination of vitamins C and E at high doses (i.e., approximately 11 and 18 times the daily recommended allowance for vitamin C and E, respectively; doses that may be obtained by supplementing with the pure vitamins, but not with common multivitamins) reduce the beneficial effects of exercise on insulin sensitivity and ROS levels in human subjects [29]. While ROS may contribute to aging by inducing cellular damage, they also play an important role as mediators of cell-signaling pathways, and blocking their action with high doses of antioxidants may not necessarily improve health and longevity.

Vegetables, fruits, and mushrooms contain a wide range of **phytochemicals** that may be responsible for the beneficial effects observed on health and longevity. Phytochemicals, which include **alkaloids**, **polyphenols**, and **terpenoids**, are organic compounds that are not directly involved in the growth, development, or reproduction of plants or fungi, and are thus classified as secondary metabolites. Many of the beneficial effects of fruits and vegetables on chronic diseases and longevity in humans have been attributed to specific phytochemicals found in these foods. For instance, high polyphenol intake is associated with reduced overall mortality in humans [30–32]. Similarly, flavonoid consumption is inversely correlated with coronary heart disease [33] and dementia [34]. Consumption of coffee, possibly the highest source of polyphenols in the human diet, is also associated with reduced mortality [35,36]. The Mediterranean diet is associated with reduced incidence of chronic diseases, an observation that has been attributed at least in part to its high polyphenol content [37].

Many plant and fungal compounds, including berberine, curcumin, fisetin, quercetin, and resveratrol, can extend lifespan and health-span in model organisms such as yeasts, nematodes, fruit flies, and rodents [19] (Table 1). These phytochemicals, many of which are available as dietary supplements (Box 1), activate the same metabolic pathways and cellular processes as CR, intermittent fasting, and exercise. For instance, some phytochemicals reduce ROS levels by activating Nrf2, which in turn induces expression of antioxidant enzymes. Epigallocatechin gallate (EGCG), a polyphenol found in green tea, produces neuroprotective effects in a rodent model of cerebral ischemia injury by activating the Nrf2 pathway [38]. Sulforaphane, an isothiocyanate compound found in broccoli and cabbage, also protects rats against hypoxia-induced brain injury by inducing the Nrf2 pathway and the expression of antioxidant enzymes [39].

Phytochemicals may also produce antiaging effects by inducing autophagy [40]. Coffee polyphenols activate autophagy in the liver, muscles, and heart of mice [41]. Resveratrol, a widely studied polyphenol found in grapes and red wine, reduces accumulation of amyloid-beta protein in the brain by activating AMPK and autophagy in a mouse model of Alzheimer's disease [42]. Curcumin, a polyphenol compound found in Indian curry, improves heart function by inducing autophagy in a mouse model of diabetic cardiomyopathy [43]. A recent study showed that the flavonoid 4,4′-dimethoxychalcone isolated from the plant *Angelica keiskei koidzumi* induces autophagy and extends lifespan in yeasts, nematodes, and fruit flies [44]. The chalcone compound also protects mice against myocardial ischemia by inducing autophagy [44]. Other dietary polyphenols that stimulate autophagy include quercetin (a polyphenol found in fruits and vegetables), genistein (a polyphenol found in soybeans and coffee), EGCG, and silibinin [a mixture of flavonolignans from milk thistle, a plant used in traditional Chinese medicine (TCM) to protect the liver] [40].

Compounds that activate AMPK represent potential candidates for the development of antiaging agents. Metformin, an antidiabetic drug that is being considered as an antiaging intervention in

humans by colonizing the gut or restoring a healthy composition of the gut microbiota.

Terpenoids: large class of fragrant hydrocarbon compounds derived from natural sources. They usually contain a multicyclic structure with oxygen-containing functional groups.

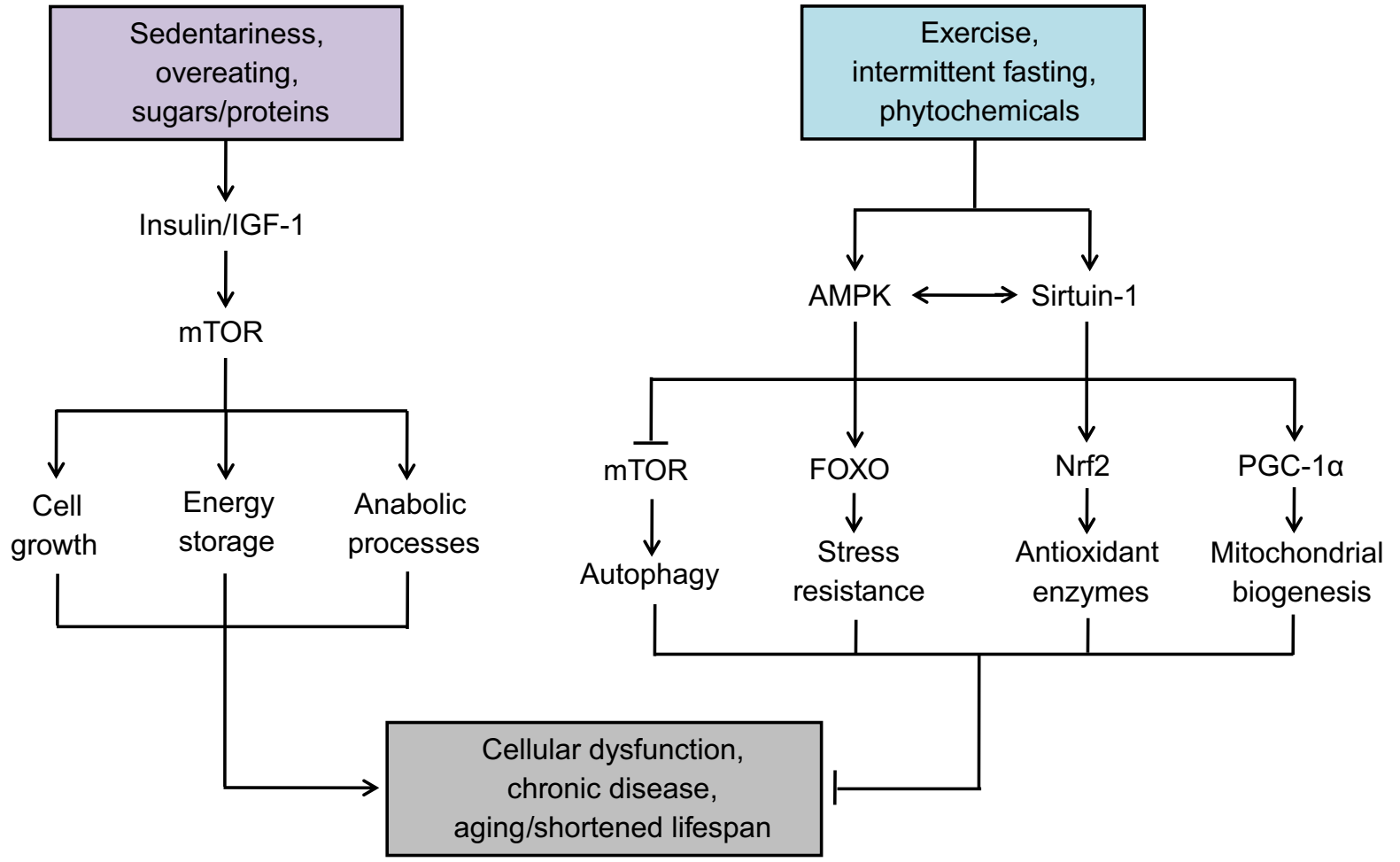

Figure 2. Molecular Pathways and Cellular Processes Involved in the Antiaging Effects of Exercise, Intermittent Fasting, and Phytochemicals in Animals and Humans. Sedentariness, overeating, and foods containing sugars and proteins induce the release of insulin and insulin-like growth factor-1 (IGF-1) into the blood, leading to activation of mammalian target of rapamycin (mTOR), cell growth, energy storage, and anabolic reactions in cells. These processes are needed for body development and maintenance, but they may induce cellular damage and premature aging if continually activated. However, exercise, intermittent fasting, and phytochemicals activate adenosine monophosphate-activated protein kinase (AMPK) and SIRT1, leading to induction of molecular pathways and cellular processes that reduce cellular damage, aging, and the development of chronic diseases. Not shown here is the fact that mTOR activation inhibits autophagy, FOXO, and Nrf2, thus inhibiting cell-protective mechanisms. Abbreviations: FOXO, forkhead box O; Nrf2, nuclear factor (erythroid-derived 2)-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α.

Table 1. Plant and Fungal Molecules That Produce Hormetic Effects on Health and Longevity in Model Organisms and Humans

Compound	Source	Mechanism	Major finding	Refs
Berberine	Chinese goldthread, dietary supplement	Autophagy↑	Lifespan↑ in flies; improvement of T2DM markers in humans	[48,99,100]
Curcumin	Turmeric spice, dietary supplement	Autophagy↑	Lifespan↑ in fruit flies (but failed to affect lifespan in mice); inflammation↓, hypertension↓ and ROS↓ in humans	[40,43,101–103]
Caffeine	Coffee	AMPK↑, mTOR↓, autophagy↑	Lifespan↑ in nematodes; CVD↓, cognitive impairment↓ and mortality↓ in humans	[35,104,105]
EGCG	Green tea, dietary supplement	SIRT1↑, FOXO↑, autophagy↑, Nrf2↑	Lifespan↑ in rats; cardiovascular disease↓, cancer↓, and neuroprotection↑ in humans	[38,40,106,107]
Emodin	Plants	Sir2.1↑, AMPK↑	Lifespan↑ in nematodes; insulin sensitivity↑ in mice	[47,108]
Fisetin	Fruits, vegetables	DAF-16/FOXO↑, ROS↓, CRP↓	Lifespan↑ in nematodes; inflammation↓ in humans	[109,110]
Glucosamine	Dietary supplement	AMPK↑, autophagy↑	Lifespan↑ in nematodes and mice; mortality↓ in humans	[78–81]
Polyphenols	Coffee	AMPK↑, mTOR↓, autophagy↑	CVD↓, cognitive impairment↓, and mortality↓ in humans	[35,41,105]
Polysaccharides	*Ganoderma lucidum* and *Hirsutella sinensis*	Prebiotic, intestinal integrity↑	Obesity↓, inflammation↓, diabetes↓ in HFD-fed mice	[90,91]
Quercetin	Vegetables, dietary supplement	AMPK↑, autophagy↑, senescence↓	Lifespan↑ in mice; hypertension↓ in humans	[40,111,112]
Resveratrol	Red wine, dietary supplement	IGF-1↓, AMPK↑, PGC-1α↑, autophagy↑	Lifespan↑ in HFD-fed mice; improved markers for Alzheimer's disease, cancer, CVD, T2DM in humans	[40,113,114]
Spermidine	Soybeans, natto, fungi	Autophagy↑	Lifespan↑ in mice; mortality↓ in humans	[82,83,115]
Sulforaphane	Broccoli, Brussels sprouts	Nrf2↑, antioxidant enzymes↑	Neuroprotection↑ in rats	[39]

Abbreviations: AMPK, adenosine-monophosphate-activated protein kinase; CRP, C-reactive protein; CVD, cardiovascular disease; EGCG, epigallocatechin gallate; FOXO, forkhead box O; HFD, high-fat diet; IGF-1, insulin-like growth factor-1; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor (erythroid-derived 2)-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; ROS, reactive oxygen species; SIRT1, sirtuin-1; Sir2.1, sirtuin-2.1; T2DM, type-2 diabetes mellitus.

healthy humans, also inhibits the electron transport chain and leads to AMPK activation [45]. Metformin may have antiaging effects in humans as diabetic individuals taking metformin appear to live longer than nondiabetic individuals [46]. Similarly, emodin, an anthraquinone derivative compound isolated from rhubarb, which has been used in TCM herbal preparations to treat fever, constipation, and pain, inhibits the electron phosphorylation chain, activates AMPK, and improves glucose tolerance in mice [47].

The alkaloid compound berberine extends lifespan and locomotor activity in fruit flies exposed to high temperature [48]. Similarly, the terpenoid compound antcin M, a steroid-like compound isolated from the mushroom *Antrodia cinnamomea*, extends lifespan in nematodes [49]. Antcin M was found to activate Nrf2 and SIRT1 in human fibroblasts, protecting the cells against glucose-induced oxidative stress [49]. Artemisinin, a sesquiterpenoid lactone possessing antimalaria activity and isolated from a plant used in TCM, was found to mimic CR by inducing mitochondrial biogenesis in mouse skeletal muscles [50].

While phytochemicals have received attention mainly for their antioxidant properties, they appear to produce antiaging effects and provide health benefits by activating stress resistance and cell-protective mechanisms in human cells.

Phytochemicals and the Hormesis Response

Many phytochemicals produce a biphasic, hormetic response on physiological functions, in which beneficial effects are observed at low doses, whereas detrimental effects are produced

Box 1. Dietary Supplements to Delay Aging?

At least half of Americans regularly consume dietary supplements and **nutraceuticals** such as multivitamins, minerals, and herbal extracts to maintain health and vitality [66]. Many dietary supplements are effective in humans, including those against immune-related disorders [67] and obesity [68]. Folic acid is recommended during pregnancy to prevent neural tube defects and reduce neonatal mortality [69], while dietary fiber supplements improve glycemic control and should be considered for patients with type 2 diabetes [70]. Other dietary supplements have produced mixed results. For instance, it remains unclear if multivitamin users have a lower incidence of cancer [71,72]. As noted by other authors [73] and consistent with the hormetic response to essential nutrients (Figure 1B), multivitamins may be effective only in people who show nutritional deficiencies. Instead of serving as substitutes for good lifestyle habits, it seems more likely that dietary supplements should be used in combination with regular exercise and a healthy lifestyle to improve health and longevity. Many clinical trials have evaluated dietary supplements only for a short period and on a small sample of subjects. Contrary to common beliefs, herbal supplements are not necessarily safe. Some herbal supplements contain carcinogens such as aristolochic acid, which has been implicated in cases of urothelial cancer [74]. We proposed earlier that manufacturers of dietary supplements need to safeguard the public and provide information about the composition, quality, efficacy, and safety of their products [75].

Dietary supplements may also delay aging and prolong lifespan [19]. A mixture of vitamins and dietary supplements extends lifespan and delays cognitive decline in transgenic mice that overexpress the growth hormone [76,77]. Glucosamine, a monosaccharide typically used to prevent cartilage loss, extends the lifespan of old mice by inducing oxidative stress and mitochondrial biogenesis [78]. An inhibitor of glycolysis, glucosamine reduces ATP production, leading to AMPK activation and induction of autophagy, as shown in nematodes [79]. Surprisingly, regular users of glucosamine supplements live longer than nonusers [80,81], suggesting possible antiaging effects in humans.

The polyamine spermidine is also considered as a dietary supplement to delay aging. It is found in human cells but also in mushrooms, aged cheese, and soybeans (notably in natto, a fermented soybean preparation from Japan). Experimental evidence indicates that spermidine extends lifespan in mice [82]. Moreover, people who have high nutritional intake of spermidine also tend to live longer [83].

at high doses (Figure 1A). For instance, a low dose of sulforaphane (1 μM) protects mesenchymal stem cells against oxidative stress and apoptosis, while a higher dose of the compound (20 μM) induces DNA damage and cytotoxic effects, leading to cell cycle arrest and apoptosis [51]. Similarly, a low dose of resveratrol (2 mg/kg) reduces indomethacin-induced stomach ulcers and inflammation in mice, whereas higher doses (5 and 10 mg/kg) increase ulcer formation and markers of inflammation [52]. The dose of phytochemicals thus determines whether these compounds produce beneficial or toxic effects.

Phytochemicals are xenobiotic compounds that are absorbed at low levels and are metabolized by detoxifying enzymes before being excreted. The concentration of sulforaphane metabolites usually found in the blood 8 h after eating 200 g of fresh broccoli is within the low micromolar range (~1 μM) [53]. After drinking a cup of coffee, ~25% of chlorogenic acid polyphenols initially found in the beverage are absorbed and can be detected in the blood or urine, mostly in the form of sulfated metabolites [54]. Following a single dose of 20 mg/kg of green tea, the polyphenols EGCG, epigallocatechin, and epicatechin reach peak concentrations of 78, 223, and 124 ng/ml in human blood 1 h and 30 min after intake [55]. A large fraction of polyphenols (90%) is removed from the circulation within 8 h, but considerable variation in metabolism is observed between individuals [55]. The low absorption and bioavailability of many phytochemicals *in vivo* has been cited as a reason against their possible beneficial effects on health. Yet, the low bioavailability of phytochemicals is consistent with the concept that these molecules may produce beneficial, hormetic effects at low doses.

Many phytochemicals may also be consumed at every meal, several times per day, thus increasing the possibility of accumulating or repeatedly producing beneficial effects on physiological functions. Some phytochemicals such as resveratrol are also highly promiscuous and have many molecular targets [56], possibly also enhancing their advantage. For phytochemicals that are found at low levels in the diet, increasing their level in the plants that produce these

compounds may also be beneficial (Box 2). Some foods enhance the bioavailability of phytochemicals in human subjects. For instance, the alkaloid compound piperine from black pepper enhances the bioavailability of curcumin from Indian curry [57], while salad dressings containing fat increases the bioavailability of carotenoids from salads [58]. From another point of view, it is important to note, however, that phytochemicals do not necessarily need to be absorbed to produce beneficial effects on the human body (Box 3).

Careful observations of a large number of hormetic responses in different studies indicate that the level of beneficial response produced by a single biological stress on animal and human cells is usually around 20–25% above that of control, which is established at 100% [59]. This observation suggests that there might be an upper limit to the beneficial stimulatory effect produced by biological stress, which may depend on the compensatory mechanisms in place to maintain homeostasis. Still, repeated stimulations with the same biological stress at low doses increase the beneficial effects observed to 60–90% above control [59]. From a mechanistic point of view, timing of stimulation and measurements thus becomes important and may play a role in assessment of the antiaging effects produced by phytochemicals.

A combination of biological stresses such as exercise, intermittent fasting, and phytochemical intake may produce additive or synergistic effects on health and longevity. In obese rats, a regimen of exercise and intake of grape polyphenols for 8 weeks produces synergistic effects on insulin resistance and endurance by promoting muscle lipid oxidation instead of glycogen use [60]. Similarly, mice fed a diet rich in fruits and vegetables show increased AMPK, SIRT1, and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) activities in muscles, and display increased strength and endurance compared with control mice fed a regular chow diet [61]. While additive and synergistic effects appear possible, observations of hormetic responses across studies suggest that the maximal level of additive or synergistic effects may still lie within the limit of 20–90% above control [59,62].

While phytochemicals produce beneficial hormetic effects that delay aging and reduce chronic diseases, a major drawback of compounds that induce autophagy is that they may induce excessive cell death and apoptosis at high doses [63]. Another possible concern is that cancer cells

Box 2. Boosting Up Levels of Phytochemicals in Vegetables

Phytochemicals are secondary metabolites produced when plants are exposed to stress, such as in conditions of low water availability, high or low temperatures, UV irradiation, and lack of nutrients. Phytochemicals are also produced in response to assault by insects and herbivores. For instance, levels of the polyphenol resveratrol increase in grape skin when the vine is infected with fungi [84]. Phytochemicals are believed to offer protection against stress and act as deterrents for insects and herbivores. A well-known example of a phytochemical deterrent is capsaicin, a pungent compound found in chili that may discourage herbivores from eating the plant by producing the burning sensation in the mouth. Obviously, this strategy has backfired when we consider people who wait in line at a restaurant to enjoy spicy foods.

For some phytochemicals, such as resveratrol, which shows relatively low concentrations in grapes and poor bioavailability in humans, interventions that increase their levels in plants may be beneficial. Notably, levels of phytochemicals are estimated to be 10–50% higher in organic vegetables compared with vegetables obtained by conventional farming [85,86]. For instance, organic wines contain more total polyphenols and resveratrol than conventional table wines [87]. Similarly, soups prepared from organically grown vegetables contain almost six times higher levels of salicylic acid than soups prepared from nonorganic ingredients [88]. Elicitors such as fungi, UV light, and cold temperatures increase the level of polyphenols in wines, while nitrogen-containing fertilizers reduce their content [84].

Activating stress resistance pathways and increasing phytochemical production may thus increase phytochemical levels in fruits and vegetables, possibly enhancing health benefits for consumers. While increasing the levels of phytochemicals in fruits and vegetables may be beneficial in some cases, very high levels of the same compounds may reduce their beneficial effects or even induce toxicity. Selecting fruits, vegetables, and mushrooms containing phytochemicals at levels that fall within the hormetic response is needed to produce health benefits.

Box 3. Dietary Fiber, Phytochemicals, and the Gut Microbiota

An unexpected association between phytochemicals and the gut microbiota was revealed in recent studies. Many plant and fungal **polysaccharides** are not digested by human digestive enzymes, resulting in poor absorption in the small intestine. These polymers are found in high amounts in plants and mushrooms, and may improve health and longevity by modulating the composition and activities of the gut microbiota [68]. The gut microbiota is involved in many physiological functions, including vitamin production, energy regulation, and toxin neutralization [89]. The observation that the gut microbiota is disturbed in obesity, diabetes, and cancer (a condition called **gut dysbiosis**) has led to the development of **prebiotics** and **probiotics** to restore a healthy gut microbiota.

We have shown that fractions containing high-molecular-weight polysaccharides (>300 kDa) isolated from *Ganoderma lucidum* and *Hirsutella sinensis* mycelium reduce body weight, inflammation, and insulin resistance in mice fed with a high-fat diet (HFD) [90,91]. Fecal transplantation indicated that the effects of the polysaccharides were mediated at least in part by the gut microbiota. Accordingly, the polysaccharide fraction increased the abundance of the gut commensal *Parabacteroides goldsteinii*, and oral intake of this bacterium produced antiobesity effects in HFD-fed mice similar to those produced by polysaccharides [91].

Our work also highlighted the concept that a HFD induces intestinal permeability and leads to endotoxemia in mice, a situation in which lipopolysaccharides found in intestinal bacteria enter the blood and cause chronic inflammation and insulin resistance [90,91]. Notably, the polysaccharides isolated from fungi enhanced expression of gap junction proteins in intestinal tissues, thus improving intestinal integrity and preventing endotoxemia. Dietary fiber may thus help to prevent the detrimental effects of a HFD, an observation that in a way shifts the focus away from the role of lipids in this context.

Polysaccharides that reach the colon may also be converted into short-chain fatty acids (SCFAs) by the gut microbiota and produce beneficial effects by serving as energy source for intestinal cells. SCFAs are also absorbed and act systemically in the host by producing anti-inflammatory effects [68,92]. These compounds have been shown to induce production of glucagon-like peptide-1 (GLP-1) by intestinal cells, leading to reduced appetite and improved insulin sensitivity [68]. SCFAs also reduce lipid accumulation in adipocytes, hepatocytes, and muscle cells, and may contribute to improving intestinal integrity.

Polyphenols found in the diet have also been shown to modulate the composition of the gut microbiota. A polyphenol-rich cranberry extract induces the growth of beneficial commensal bacteria such as *Akkermansia muciniphila*, and these prebiotic effects are associated with reduction in body weight, oxidative stress, and intestinal and hepatic inflammation as well as improved insulin sensitivity in mice fed with a diet rich in fat and sucrose [93]. Resveratrol increases expression of tight junction proteins in the intestine, and it also produces prebiotic effects by reversing HFD-induced dysbiosis in mice [94]. Other phytochemicals such as quercetin, EGCG, and ginsenosides (i.e., steroid glycosides and terpenoid saponins isolated from ginseng) modulate the gut microbiota in a similar fashion [95].

Phytochemicals may also be converted by the gut microbiota into other metabolites. For instance, the gut microbiota converts quercetin into various metabolites that are absorbed into the blood and may produce beneficial effects on the host [95]. Similarly, unabsorbed green tea polyphenols are converted by the gut microbiota to increase vitamin production (niacin) and reduce carbohydrates and bile acid metabolites in rats, observations that are consistent with the antiobesity effects of these compounds [96]. Given that this conversion is produced by specific bacteria, it is possible that the activities of phytochemicals may be influenced by antibiotic and probiotic intake and the diet, a research area with many promising applications.

Outstanding Questions

What is the optimal dose, mode of administration, and frequency of use of phytochemicals to produce optimal effects on health and longevity?

How does interindividual genetic, epigenetic, and gut microbiota variability influence the effects phytochemicals?

Can dietary supplements containing phytochemicals produce beneficial effects on health and longevity in healthy individuals or in sedentary subjects who consume a high-calorie diet?

Can modulation of stress resistance pathways be used to identify novel phytochemicals or derived compounds that produce beneficial effects on health and longevity?

show increased proliferation when stimulated with low doses of hormetic phytochemicals such as resveratrol, whereas higher doses reduce proliferation [64]. In this context, cellular processes that are protective against aging such as autophagy may provide a proliferative advantage for cancer cells [65]. Determining the possible effects of dietary phytochemicals during cancer treatment and establishing optimal dosage of anticancer agents will represent major challenges.

Concluding Remarks and Future Perspectives

It is becoming clear that aging can be modulated by biological stresses such as exercise, intermittent fasting, and phytochemicals, which induce protection against cellular damage. These cell-protective mechanisms are inactive in the fed state, which instead promotes energy storage and anabolism. Overeating and consumption of energy-rich foods promote aging and the development of chronic diseases by preventing activation of autophagy, DNA repair, and expression of antioxidant enzymes. In view of this apparent trade-off, it appears that phytochemicals could

produce some beneficial health effects in overfed and sedentary individuals. But optimal health benefits may be produced by combining phytochemical intake with exercise and intermittent fasting. Finding ways to activate antiaging pathways while regulating energy levels and anabolic processes appears to be critical to promote health and longevity.

The observation that phytochemicals in fruits, vegetables, and mushrooms activate stress resistance has many practical implications. For one, high doses of antioxidant vitamins may inhibit the hormesis response and prevent the beneficial effects of exercise, fasting, and phytochemicals. The Mediterranean diet offers an instructive example of phytochemical intake that is associated with many health benefits. Further research is needed to determine the optimal dosage and frequency of use of phytochemicals consumed in food or as dietary supplements (see Outstanding Questions). In addition, a better understanding of the interactions between phytochemical intake and other antiaging interventions such as exercise and intermittent fasting, which activate the same stress-related pathways, is needed. It appears likely that a period of rest between phytochemical intake may be beneficial by allowing anabolic processes and cellular functions to adjust, similar to what is usually recommended for exercise.

The concept of hormesis also has implications for the identification of new antiaging compounds and testing in human clinical trials. New antiaging compounds can be identified by using assays that monitor stress resistance pathways in cells and organisms. In clinical trials, various doses of each compound should be tested to delineate the hormetic zone of responses. In addition, interindividual variations in terms of drug metabolism, bioavailability, and functional response may require personalization of doses for each compound.

The existence of antiaging pathways in human cells offers the possibility to prevent and treat many chronic diseases simultaneously, instead of treating one at a time. Given that effective treatments are not available for many chronic diseases, including cardiovascular and neurodegenerative diseases, the possibility to prevent such ailments using antiaging interventions such as exercise, intermittent fasting, and phytochemicals becomes even more appealing. Moreover, antiaging interventions such as exercise and phytochemical intake are associated with improved organ function, providing the opportunity to maintain cognitive functions, exercise performance, and well-being.

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Disclaimer Statement

Y-F.K. is president of Chang Gung Biotechnology. J.D.Y. is Chairman of the Board of Chang Gung Biotechnology. The authors have filed patents related to the preparation and use of medicinal mushrooms and probiotics.

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