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REVIEW ARTICLE

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Antiaging effects of bioactive molecules isolated from plants and fungi

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Abstract

Aging is influenced by many lifestyle choices that are under human control, including nutrition and exercise. The most effective known antiaging intervention consists of calorie restriction (CR), which increases lifespan in yeasts, worms, fruit flies, mice, and nonhuman primates. CR also improves healthspan by preventing the development of various aging-related diseases such as cancer, cardiovascular disease, diabetes, and neurodegeneration. Many compounds isolated from plants and fungi prolong lifespan and prevent age-related diseases in model organisms. These plant and fungal compounds modulate the same cellular and physiological pathways as CR, including those involving insulin and insulin-like growth factor-1, mammalian target of rapamycin, and sirtuins. Modulation of these aging-related pathways results in the activation of various cellular processes such as autophagy, DNA repair, and neutralization of reactive oxygen species. Together, these cellular processes are believed to delay aging and prevent chronic diseases by improving bodily functions and stress resistance. We review here the mechanisms of action of plant and fungal molecules possessing antiaging properties and discuss the possibilities and challenges associated with the development of antiaging compounds isolated from natural products.

KEYWORDS
antiaging medicine, autophagy, dietary supplements, life extension, medicinal mushrooms

1 | INTRODUCTION

Aging is an inevitable process attributed to molecular and cellular damage that leads to a gradual loss of organ function and ultimately death. Aging and longevity are modulated by various factors that include lifestyle, nutrition, genes, and exercise. For instance, knowledge advancement and public health measures that improved sanitation, nutrition, and medical treatments in developed countries have nearly doubled human life expectancy since 1840 (Figure 1),[1,2] increasing average lifespan from approximately 45 to 82 years for women and 76 years for men. Likewise, gene polymorphism variants of insulin-like growth factor-1 (IGF-1) receptor and forkhead box O (FOXO) transcription factors are now known to be enriched in the genome of centenarians living in different regions around the globe.[3] Moreover, the predominant Western lifestyle characterized by high-calorie intake, poor nutrition, and lack of exercise has been associated with obesity, type 2 diabetes, cancer, and reduced longevity.[4] The aging process is therefore malleable and lifestyle choices have a critical effect on health and longevity.

A key observation indicating that aging could be modulated is the finding that calorie restriction (CR) extends lifespan in model organisms. Described for the first time in 1935,[5] CR—in which calorie intake is reduced by 10 to 50% while avoiding malnutrition—extends lifespan in yeasts, worms, fruit flies, mice, and nonhuman primates.[6,7] Notably, CR modulates highly conserved cellular and physiological pathways that enhance resistance to various forms of stress, such as nutrient deprivation, DNA damage, and oxidative stress.[8,9] The main cellular pathways that mediate the longevity-enhancing effects of CR involve insulin and IGF-1 signaling, mammalian target of rapamycin (mTOR), and sirtuins.[6,9] Living organisms have thus evolved to favor resistance against conditions that are unfavorable for reproduction and survival, especially in periods of starvation.[10]

While the possibility to delay aging has sometimes been viewed with skepticism, antiaging interventions such as CR have been shown to reduce the development of a wide range of aging-related chronic diseases, including cancer,

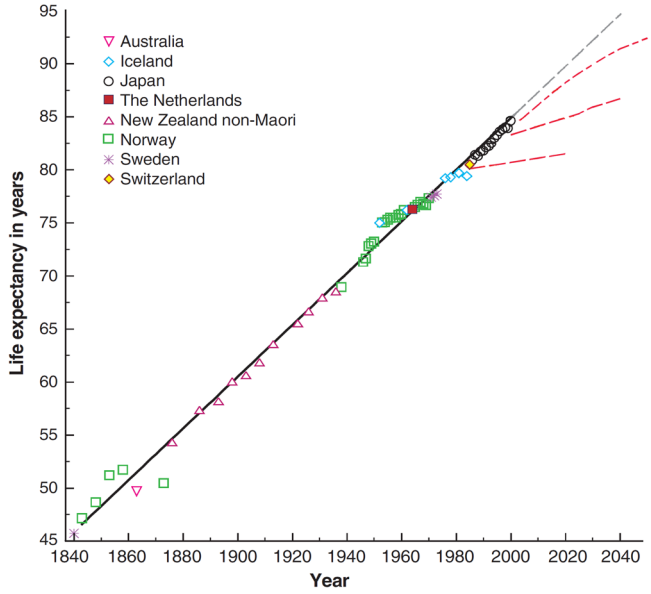

FIGURE 1 Increase of female life expectancy from 1840 to 2002. The black line represents the linear regression trend, while the dashed gray line represents projected life expectancy, assuming continuously linear increases. The dashed red lines represent life expectancy predictions for female Japanese based on analysis by the United Nations in 1986 (bottom), 1999 (middle), and 2001 (top). This image was reproduced and adapted from the work of Oeppen and Vaupel,[1] with permission from the American Association for the Advancement of Science [Color figure can be viewed at wileyonlinelibrary.com]

cardiovascular disease, diabetes, neurodegenerative diseases, and autoimmune disorders.[11] In other words, strategies that delay aging may not simply prolong the period of time spent in old and frail age but may actually maintain physiological functions and extend the period of healthy, active, and productive life (also called the "healthspan"). In humans, CR produces rejuvenating effects on muscles and the heart, and reduces metabolic markers associated with the development of cancer, cardiovascular disease, and diabetes,[12] indicating that antiaging interventions may prevent some of the most prevalent diseases in humans.

Reducing food intake or maintaining a CR diet over a long period of time represents a difficult challenge for most people due to hunger, irritability, and poor thermoregulation.[13] An alternative is to use pharmaceutical drugs that mimic the beneficial effects of CR, and increased interest has been devoted to the development of molecules that modulate the same cellular and physiological pathways as CR.[14–16] Consistent with this possibility, CR-mimetic drugs such as metformin [**1**] and rapamycin [**2**] prolong lifespan and prevent the development of chronic diseases in various model organisms (Figure 2).[17,18] These pharmaceutical drugs are being investigated as possible antiaging treatments in healthy individuals.

Central to the effects of CR on longevity is the concept of hormesis or the observation that some forms of stress that are usually toxic at a high dose may produce beneficial effects at a low dose.[19,20] An example of hormesis is the observation that short periods of exposure to hypoxia or nutrient deprivation protect the brain and the heart against more severe or prolonged hypoxia treatment or nutrient deprivation by activating cellular processes that protect against cellular stress.[21] Consistent with the hormesis concept, CR and intermittent fasting produce a mild stress that protects against the effects of aging on the body. Even though antiaging therapies have focused mainly on pharmaceutical drugs such as metformin and rapamycin, another strategy to delay aging is to induce mild stress by providing low doses of natural compounds derived from plants and fungi. Vegetables and fruits contain compounds that may induce oxidative stress resistance and the expression of detoxification enzymes in various organs, including the liver.[22] While the concept that nutrients may delay aging via hormetic effects remains to be demonstrated in humans, epidemiological studies indicate that people who regularly consume dietary supplements such as glucosamine [**3**] or have a high nutritional intake of spermidine [**4**] live longer than nonusers.[23–25]

Plants and fungi have been used for thousands of years as tonics to improve health and longevity. Archeological evidence suggests that Neanderthals who lived ~50 000 years ago used plants and fungi as medicines.[26,27] Early civilizations throughout the globe made use of plants and fungi as foods, spices, and medicines.[28] Medicinal plants continue to be used today, especially in developing countries where pharmaceutical drugs are not widely available. In Asia, medicinal plants and fungi constitute the basis of traditional Chinese medicine (TCM) and Indian Ayurveda medicine, which are often used in combination with conventional medical treatments.

Around half of pharmaceutical drugs commonly in use in medicine have been derived, directly or indirectly, from plants and fungi.[29] Well-known examples include morphine (isolated from opium poppy), the lipid-lowering statins and the immunosuppressive molecule cyclosporin A (isolated from fungi), and salicylic acid (a metabolite of acetylsalicylic acid [**5**]; initially isolated from willow bark). Plants and fungi continue to represent sources of drug leads as only a fraction of natural substances have been screened for the identification of bioactive compounds.

Dietary supplements and nutraceuticals are increasingly used to prevent or treat chronic diseases. Americans spend on average $US 40 billion on dietary supplements each year.[30] Common nutraceuticals include resveratrol [**6**], curcumin [**7**], ginseng, and medicinal mushrooms, which produce different biological effects, including antidiabetic, antiobesogenic, and immunomodulatory effects.[31–33] Notably, many nutraceuticals and phytochemicals extend lifespan and improve the healthspan of model organisms by modulating the same molecular pathways affected by CR, as described below. We review here the molecular mechanisms of these plant and fungal molecules and examine the possibility of developing novel antiaging treatments from natural sources.

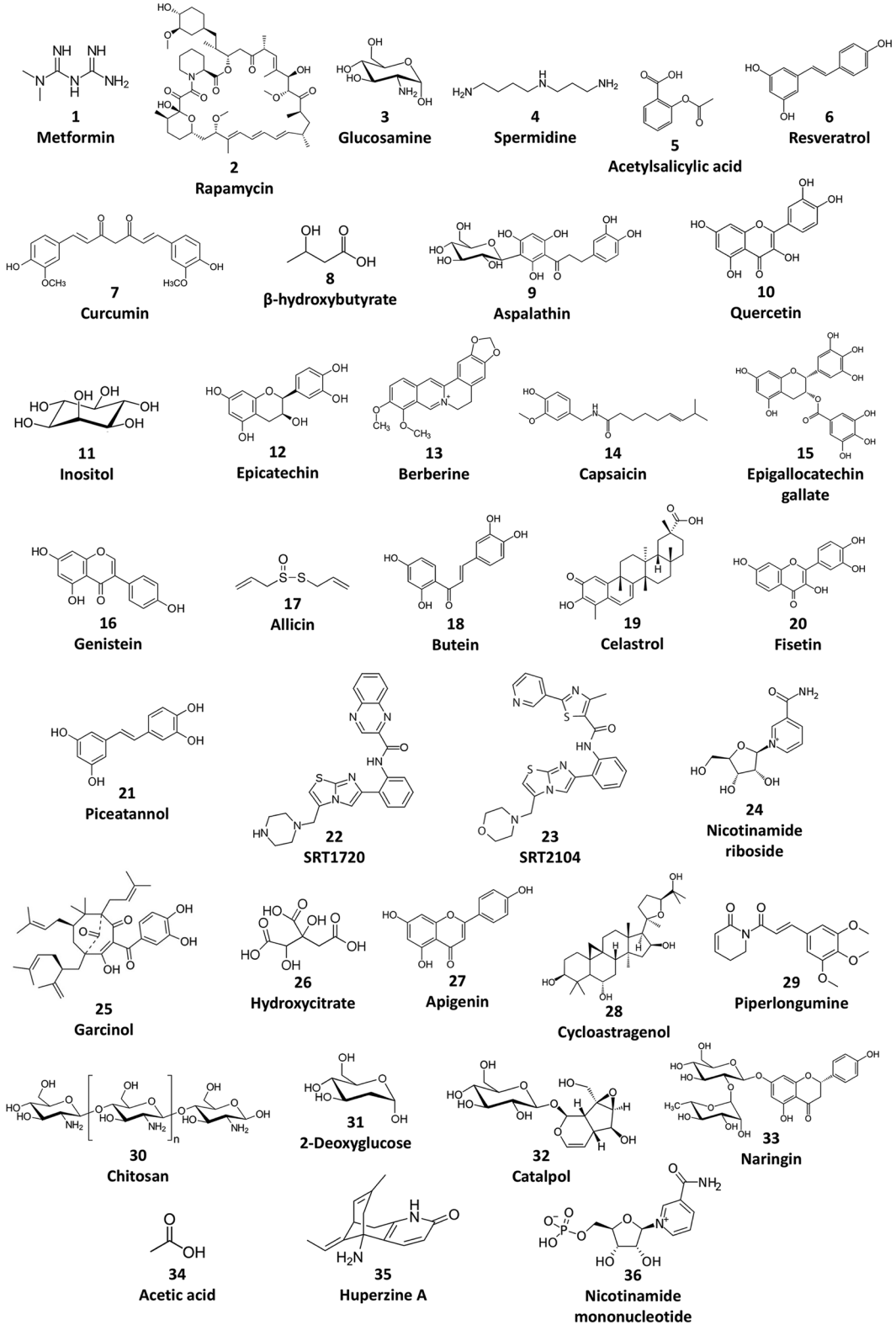

FIGURE 2 Molecules that increase lifespan and/or delay aging in model organisms

2 | MECHANISM OF LIFE EXTENSION BY MOLECULES ISOLATED FROM PLANTS AND FUNGI

2.1 | Insulin and IGF-1 signaling

A major energy-sensing pathway in the body involves insulin and IGF-1, which regulate cell growth, development, protein synthesis, and energy storage (Figure 3). When nutrients such as glucose and amino acids are abundant, insulin induces nutrient uptake by skeletal muscle and adipose tissue, and energy storage in the form of glycogen or triglycerides, thus favoring anabolism and energy storage. Conversely, when glucose levels are low, the pancreas produces glucagon, which stimulates release of stored glucose. Release of the growth hormone (GH) by the pituitary gland induces IGF-1 secretion by the liver, promoting cell growth and development of the body as well as protein synthesis and tissue repair in adults (Figure 3).

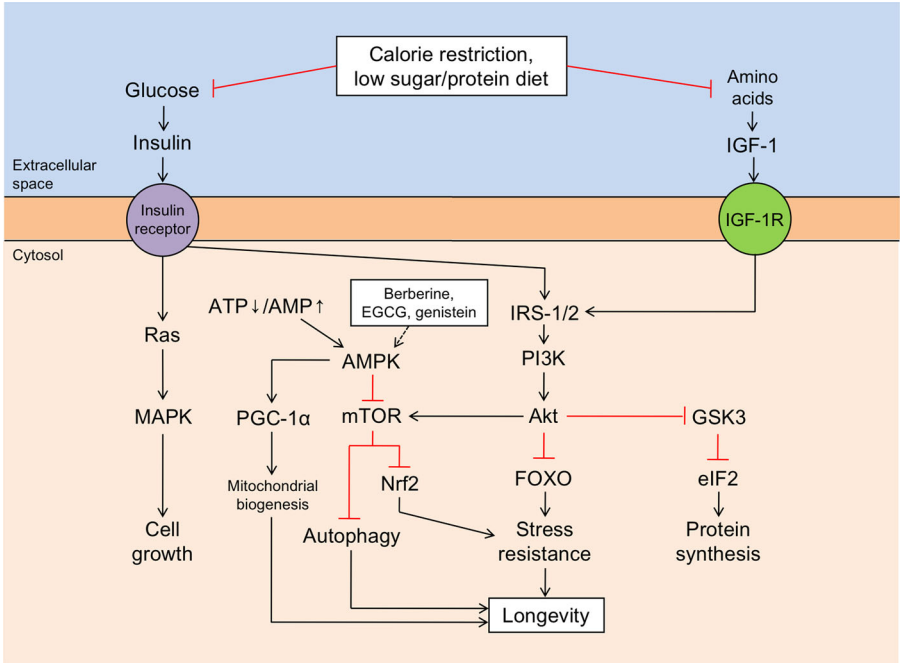

FIGURE 3 Model illustrating the cellular mechanism of the antiaging effects of plant and mushroom compounds on the insulin/IGF-1 signaling pathway. Insulin and IGF-1 are released into the bloodstream in response to increased blood glucose and amino acid levels. Insulin binds the insulin receptor on the surface of cells, leading to cell growth via activation of Ras and MAPK. AMPK is activated by a reduction of ATP and a concomitant increase of AMP. PGC-1α is activated by AMPK, which induces mitochondrial biogenesis. mTOR is inhibited by AMPK, a process that activates autophagy. Binding of insulin and IGF-1 to their respective receptors activates IRS-1/2, PI3K, and Akt, leading to inhibition of FOXO. In the absence of growth factors such as insulin and IGF-1, FOXO transcription factors activate several genes that enhance stress resistance, thus improving longevity. Amino acids derived from the digestion of dietary proteins induce IGF-1 secretion by the liver, leading to inhibition of GSK3 and activation of protein synthesis inside cells, thereby reducing autophagy and stress resistance. AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; FOXO, forkhead box O; GSK3, glycogen synthase kinase 3; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IRS-1/2, insulin receptor substrate 1/2; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PI3K, phosphoinositide 3-kinase [Color figure can be viewed at wileyonlinelibrary.com]

Although growth signals are required for normal development and tissue repair in humans, studies performed on model organisms indicate that reduction of insulin/IGF-1 signaling increases lifespan. For instance, inactivation of the insulin pathway in the worm *Caenorhabditis elegans* increases median and maximum lifespan by nearly 10 fold[34]—an intervention that produced the longest life extension effect reported thus far.[11] Female mice that harbor loss-of-function mutations in the *igf-1* gene in the liver are smaller than controls but live 16% longer.[35] Furthermore, high glucose intake throughout life increases insulin signaling and shortens lifespan in worms[36] and mice.[37]

Inactivation of the GH/IGF-1 pathway also produces the longest-known life extension in mammals (20%–70% extension of average lifespan depending on the nature of the deficiency).[6,38] Transgenic mice that overexpress the GH show signs of premature aging and reduced lifespan.[39,40] A shortened lifespan has also been observed in human individuals who have acromegaly,[18] a condition in which GH secretion is increased, mostly due to a pituitary adenoma. Similarly, centenarians showed an overepresentation in levels of heterozygous mutations that affect IGF-1 receptor function.[41] Within a species, there thus appears to be a negative correlation between body size and longevity that may be mediated mainly by the insulin/GH/IGF-1 axis.[42] Also consistent with this concept is the observation that a high-protein diet of animal source, which induces production of IGF-1 (Figure 3), is associated with reduced longevity in mice and humans.[43,44]

Recent studies have shown that reduced insulin/IGF-1 signaling extends lifespan and improves healthspan by increasing stress resistance (Figure 3). In response to a lack of nutrients, insulin and IGF-1 signaling is reduced, which activates transcription factor proteins called FOXO that in turn induce the expression of a large number of proteins such as superoxide dismutase (SOD), catalase (CAT), glutathione *S*-transferase, metallothioneins, and chaperones.[45–47] These proteins protect the cell and delay aging in various ways, including neutralization of reactive oxygen species (ROS), repair of DNA damage, maintenance of protein structure via chaperones and detoxification of heavy metals, among other functions. In humans, a *foxo3* gene variant is associated with longer lifespan,[48,49] suggesting that the activation of FOXO transcription factors produces antiaging effects in humans as well.

Reduction of insulin/IGF-1 signaling can also be accomplished by adhering to a ketogenic diet (KD), which is low in starch and simple carbohydrates and high in dietary fiber and foods containing medium-chain triglycerides such as coconut oil, avocados, and ghee. This diet is commonly used to lose weight since, in the almost complete absence of starch and simple carbohydrates and with the depletion of glycogen stores in the liver and skeletal muscles, the body predominantly burns fats which are converted into ketone bodies by the liver. In this case, the ketone bodies acetoacetate, acetone, and β-hydroxybutyrate (BHB; **8**) serve as a source of energy, replacing the usual contribution from carbohydrates. The low-carbohydrate KD increases lifespan in mice and improves healthspan by promoting motor functions, memory, physical endurance, and muscle mass.[50] The effects of KD feeding on lifespan and healthspan have been attributed at least in part to reduced insulin/IGF-1 signaling.

Various plant and fungal molecules modulate the insulin/IGF-1/FOXO pathway in worms, fruit flies, and rodents (Table 1). For instance, aspalathin [**9**], a glycoside compound isolated from rooibos tea leaves, extends the lifespan of worms by 20% to 25% under high glucose feeding.[52] The life extension effect of aspalathin is associated with reduced cellular ROS accumulation and activation of *daf-16*, the ortholog of *foxo* in worms. Notably, other studies showed that aspalathin is absorbed by mammals[118] and the compound is detected in human plasma after drinking rooibos tea.[119,120]

Quercetin [**10**], a major flavonoid polyphenol in the human diet, including in spices, vegetables, and fruits such as coriander, red onions, and cranberries, also extends lifespan in worms.[100] Quercetin increases mean and median lifespan by 18% and 21%, respectively, while maximal lifespan is not affected. Quercetin does not increase lifespan in worms lacking the *daf-2* gene, which encodes an ortholog of the human IGF-1 receptor. On the other hand, mutation of the *daf-16* gene does not prevent the life extension effect of quercetin,[100] indicating that other pathways may also be involved in the lifespan effects.

TABLE 1 Plant and fungal molecules that increase lifespan in model organisms

No.	Compounds	Source	Tested organism	Mechanism	References
1	Antcin M	*Antrodia cinnamomea*	Worm	SIRT1↑, NRF2↑	Senthil et al[51]
2	Aspalathin	Rooibos tea	Worm (ROS)	DAF-16/FOXO↑, ROS↓	Chen et al[52]
3	Berberine	Chinese goldthread	Fruit fly (heat)	Not determined	Navrotskaya et al[53]
4	Butein	Chinese lacquer tree	Yeast	SIRT1↑	Howitz et al[54]
5	Caffeine	Coffee, chocolate	Worm	DAF-16/FOXO↑, CBP-1↑	Lublin et al[55]
6	Catechin/epicatechin	Green tea, cocoa	Worm, fruit fly, mouse (HFD)	AMPK↑, ROS↓, IGF-1↓, SOD↑	Saul et al[56], Saul et al[57], Si et al[58]
7	Celastrol	*Tripterygium wilfordii*	Mouse (ALS)	TNF-α↓, iNOS↓, HSP70↑	Kiaei et al[59]
8	Chlorophyll	Vegetables	Worm	DAF-16/FOXO↑	Wang and Wink[60]
9	Coenzyme Q10	Dietary supplement	Rat (PUFA)	DNA damage↓	Quiles et al[61]
10	Creatine	Dietary supplement	Mouse	Lipofuscin↓	Bender et al[62]
11	Curcumin	Turmeric	Worm, fruit fly	Sirtuins↑, SOD↑, NF-κB↓	Lee et al[63], Liao et al[64], Shen et al[65]
12	EGCG	Tea	Worm (ROS)	HSP16.2↓, ROS↓	Abbas and Wink[66]
13	Fisetin	Fruits, vegetables	Worm, fruit fly	SIRT2↑, DAF-16↑, ROS↓	Wood et al[67], Kampkötter et al[68]
14	Genistein	Soybeans, coffee	Worm	SOD3↑, HSP16.2↑	Lee et al[69]
15	Glaucarubinone	Simaroubaceae plants	Worm	Respiration↑, TGs↓	Zarse et al[70]
16	Glucosamine	Dietary supplement	Worm, mouse	AMPK↑, mitochondria↑, glycolysis↓	Weimer et al[71]
17	Huperzine A	*Huperzia serrata*	Worm	Not determined	Liu et al[72]
18	Icariin	*Epimedium brevicornum*	Mouse	SOD↑, MDA↓	Zhang et al[73]
19	Icariside II	*E. brevicornum*	Worm	DAF-16/FOXO↑, HSP-12.3↑	Cai et al[74]
20	Inositol	Orange, cantaloupe	Fruit fly	ROS↓, FOXO↑	Hada et al[75]
21	Kaempferol	Vegetables, ginkgo	Worm	DAF-16/FOXO↑, SOD3↑, ROS↓	Kampkötter et al[68], Grünz et al[76]
22	Lipoic acid	Dietary supplement	Worm, fruit fly	ROS↓	Bauer et al[77], Brown et al[78]

(Continues)

TABLE 1 (Continued)

No.	Compounds	Source	Tested organism	Mechanism	References
23	Lutein	Vegetables, fruits	Fruit fly (ROS)	SOD↑, CAT↑, MDA↓	Zhang et al[79]
24	Melatonin	Nuts, mushrooms, beans	Mouse	Not determined	Pierpaoli et al[80], Anisimov et al[81]
25	Monascin	*Monascus purpureus*	Worm (ROS)	DAF-16/FOXO↑, SOD1↑, HSP16.2↑	Shi et al[82]
26	Myricetin	Vegetables, ginkgo, tea	Worm	DAF-16/FOXO↑, SOD3↑, ROS↓	Grünz et al[76], Büchter et al[83]
27	*N*-acetylcysteine	Dietary supplement, drug	Worm, fruit fly	rRNA↑, SOD3↑, HSP16.2↑	Brack et al[84], Shibamura et al[85], Oh et al[86]
28	NDGA	*Larrea tridentata*	Mouse	Not determined	Strong et al[87]
29	Nicotinamide riboside	Dietary supplement	Mouse	UPR↑, prohibitin↑, stem cells↑	Zhang et al[88]
30	Phloridzin	Apple	Yeast	ROS↓, SOD↑, SIRT2↑	Xiang et al[89]
31	Phycocyanin	Spirulina	Yeast	ROS↓, proteotoxicity↓	Singh et al[90]
32	Pinitol	*Sutherlandia frutescens*	Fruit fly	ROS↓, FOXO↑	Hada et al[75]
33	Polydatin	Grape juice	Worm	DAF-16/FOXO↑, SOD3↑, DAF-2↓	Wen et al[91]
34	Polyphenols	Cocoa	Rat	Not determined	Bisson et al[92]
35	Polyphenols	Green tea	Mouse	Not determined	Kitani et al[93], Kitani et al[94]
36	Polysaccharides	*Panax notoginseng*	Worm	SOD↑, CAT↑, MDA↓	Feng et al[95]
37	Polysaccharides	*Ganoderma lucidum*	Worm	DAF-16/FOXO↑	Chuang et al[96]
38	Proanthocyanidins	Fruits	Worm	AGEs↓, MDA↓, OSR-1↑	Wilson et al[97], Mekheimer et al[98]
39	Quercetin	Vegetables, ginkgo	Worm, fruit fly, mouse	DAF-16/FOXO↑, senescence↓	Kampkötter et al[68], Kampkötter et al[99], Pietsch et al[100], Spindler et al[101], Grünz et al[76], Xu et al[102]
40	Reserpine	Indian snakeroot	Worm	Stress tolerance↑	Srivastava et al[103]
41	Resveratrol	Wine, dietary supplement	Yeast, worm, fruit fly, bee, mouse (HFD)	SIRT1↑, IGF-1↓, autophagy↑, AMPK↑	Howitz et al[54], Bauer et al[77], Wood et al[67], Baur et al[104], Morselli et al[105], Rascón et al[106]
42	Rutin	Citrus fruits	Fruit fly (ROS)	FOXO↑, SOD↑, CAT↑, ROS↓	Chattopadhyay et al[107]

(Continues)

TABLE 1 (Continued)

No.	Compounds	Source	Tested organism	Mechanism	References
43	Salicylic acid	Willow bark	Worm (ROS), mouse	HAT↓, autophagy↑, ROS↓	Strong et al[87], Ayyadevara et al[108], Pietrocola et al[109]
44	Silymarin	Milk thistle seed	Worm	DAF-16/FOXO↑, SOD3↑, ROS↓	Srivastana et al[110]
45	Spermidine	Natto, mushrooms	Yeast, worm, fruit fly, mouse	HAT↓, autophagy↑, ROS↓	Eisenberg et al[111], Morselli et al[112], Eisenberg et al[113]
46	Tannic acid	Fruits, vegetables	Worm	DAF-16/FOXO↑, CBP-1↑, SEK-1↑	Saul et al[114], Saul et al[57], Lublin et al[55]
47	Taurine	Dietary supplement	Worm	Not determined	Edwards et al[115]
48	Tetrahydrocurcumin	Turmeric	Mouse	Not determined	Kitani et al[93], Kitani et al[94]
49	Theaflavin	Black tea	Fruit fly	SOD↑, CAT↑	Peng et al[116]
50	Triptolide	*T. wilfordii*	Worm	SOD3↑, HSP16.2↑, ROS↓	Kim et al[117]

Experiments were performed on wild-type strains of model organisms to show lifespan increase effects. Some studies also used transgenic strains to determine the contribution of specific genes and molecular pathways.

Abbreviations: AGE, advanced glycation end-product; ALS, amyotrophic lateral sclerosis; AMPK, adenosine monophosphate-activated protein kinase; CAT, catalase; CBP-1, calcineurin-binding protein-1; EGCG, epigallocatechin gallate; FOXO, forkhead box; HAT, histone acetyltransferase; HFD, high-fat diet; HSP, heat-shock protein; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; NDGA, nordihydroguaiaretic acid; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NRF2, nuclear factor erythroid 2 related factor 2; OSR-1, odd-skipped related protein-1; rRNA, ribosomal RNA; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SEK-1, SAPK/ERK kinase-1; SIRT1, sirtuin-1; SKN-1, protein skinhead-1; SOD, superoxide dismutase; TG, triglyceride; TNF-α, tumor necrosis factor-α; UPR, unfolded protein response.

The small carbohydrate compound inositol [**11**], which is found in fruits, beans, and nuts, has been shown to extend lifespan in fruit flies.[75] The lifespan of male and female fruit flies fed with a diet supplemented with inositol is extended by 17% and 13%, respectively. The life extension effect of inositol is attributed to activation of the *dfoxo* pathway (the ortholog of *foxo* in fruit flies), which is associated with reduced ROS levels. Inositol also improves the climbing ability of flies, suggesting that this treatment also improves the healthspan. The inositol-related compound pinitol extends lifespan in a similar fashion.[75]

In mammals, epicatechin [**12**], a flavanol compound isolated from cacao, extended the lifespan of obese diabetic mice (50% mortality was observed in untreated mice vs 8% in epicatechin-treated mice).[58] Epicatechin treatment reduced aorta and liver degeneration, and was associated with reduced systemic inflammation and improvements of muscle stress output and antioxidant levels in the liver. Notably, epicatechin treatment reduced blood IGF-1 levels, suggesting reduced activation of the IGF-1 pathway.

Another study showed that the compound resveratrol, a widely studied phenolic compound found in grapes, blueberries, and red wine, increases the lifespan of mice fed a high-calorie diet.[104] The compound enhanced insulin sensitivity and reduced blood IGF-1 levels, suggesting a reduction of insulin/IGF-1 pathway signaling. Notably, resveratrol also improved motor and balance function, and performance of the treated mice improved with time in exercise challenges. Studies showed that resveratrol reduced age-related degeneration in cognitive function, blood vessels, and bones but failed to extend lifespan in mice in the absence of a high-calorie diet or high-fat diet (HFD).[121,122]

While some natural compounds listed in Table 1 modulate IGF-1 levels in model organisms, it is unclear if these compounds act directly on GH, IGF-1, or other upstream targets. Moreover, IGF-1 is required for neurogenesis and the remodeling of neurons in the adult mammalian brain, a process termed neuroplasticity which is needed for learning and memory.[123] Accordingly, IGF-1 levels and cognitive functions decline with aging. Similarly, GH and IGF-1 have protective effects on the vasculature, which may also affect brain functions.[123] Yet, a recent study showed that targeting the IGF-1 receptor with a monoclonal antibody increased lifespan by 9% in old female mice, in addition to reducing inflammation and tumor formation.[124] It thus remains to be seen whether antiaging interventions that target IGF-1 may be viable in humans.

2.2 | mTOR and autophagy

mTOR is a kinase that regulates cell growth, metabolism, and nutrient sensing in the cell. When amino acids or glucose are scarce, as occurs during fasting, CR, and prolonged exercise, mTOR is inhibited, shutting down cell growth to maintain existing nutrient and energy levels (Figure 3).[125] Inhibition of mTOR activates autophagy, a cellular mechanism that degrades and recycles damaged molecules and organelles, thus maintaining nutrient and energy levels. Autophagy produces a rejuvenating effect on cells and tissues as it reduces the amount of damaged molecules and organelles.[126,127] mTOR is also part of the insulin/IGF-1 pathway as inhibition of mTOR reduces insulin and IGF-1 signaling,[125] thus activating FOXO and the expression of genes that increase cellular resistance to stress, as mentioned above. mTOR activity is stimulated by insulin, growth factors, serum, and oxidative stress, thus linking mTOR with other aging-related pathways.[15]

Several observations indicate that mTOR and autophagy are involved in aging. Autophagy can be activated by rapamycin, an immunosuppressive drug used to prevent organ transplant rejection in humans but which also increases lifespan in various organisms ranging from worms to mice.[125,127] Rapamycin extends lifespan by 9% to 14% in aged mice[128] and by 10% to 15% in young mice.[122] Notably, animals treated with rapamycin are healthier and show fewer signs of aging in multiple organs and tissues.

Autophagy decreases with age, a process that may lead to cellular and organ dysfunction and the development of various chronic and degenerative diseases.[127] Mice in which autophagy is inactivated in the brain by conditional knockout of the autophagy-related gene *atg7* show increased neuronal degeneration and a shorter lifespan.[129] Autophagy degrades protein aggregates associated with neurodegenerative diseases, including amyloid-β and tau

(involved in development of Alzheimer's disease), mutant huntingtin (associated with the development of Huntington's disease), and parkin (a protein mutated in some cases of autosomal recessive Parkinson's disease).[130] The decrease in autophagy may thus contribute to the development of neurodegenerative diseases.

mTOR inhibition is mediated by adenosine monophosphate-activated protein kinase (AMPK), an enzyme that acts as an energy sensor within cells (Figure 3). AMPK is activated by adenosine monophosphate (AMP) and inhibited by adenosine triphosphate (ATP), therefore coupling AMPK activity with energy levels.[131] Activation of AMPK enhances formation of ATP by promoting lipid oxidation while also inhibiting ATP-consuming pathways involved in the biosynthesis of new molecules such as gluconeogenesis in the liver. In addition to inhibiting mTOR and inducing autophagy, AMPK activates peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), inducing expression of genes involved in lipid oxidation and mitochondria biogenesis.[132]

AMPK activity is also regulated by nutrients and hormonal status.[131] CR and prolonged exercise activate AMPK, resulting in catabolism and conversion of lipids into energy. AMPK is also activated by adiponectin, a protein hormone that regulates glucose and fatty acid breakdown. Adiponectin levels increase during CR, leading to enhanced insulin sensitivity, mTOR inhibition, and autophagy. Finally, AMPK activity regulates the energy status of the whole body by regulating food intake via its activity on specific neurons of the hypothalamus.[131]

The dietary supplement glucosamine, a monosaccharide derived from crustaceans and fungi, extends the lifespan of worms and aging mice by increasing AMPK activity[71] (Table 1). Glucosamine induces AMPK activity by inhibiting glycolysis, which induces mitochondrial biogenesis in the liver, thereby shifting metabolism toward amino acids as a source of energy. While glucosamine has been mainly used as a dietary supplement to prevent cartilage loss in osteoarthritic patients, people who consume glucosamine live longer than nonusers.[23,24] Regular intake of glucosamine is also associated with reduced risk of colorectal and lung cancer.[133–135]

The antidiabetic drug metformin (a biguanide compound that was obtained by chemical modification of guanidine, originally isolated from French lilac) activates AMPK (although indirectly), leading to mTOR inhibition and autophagy. Metformin increases lifespan of worms and mice in an AMPK-dependent manner.[136,137] In mice, a diet containing a low dose of metformin increases lifespan by 5%, whereas toxicity is observed at a high dose. Metformin also increases healthspan and physical fitness of mice, which performed better than untreated controls in exercise challenges.[137] Another study showed that metformin treatment increases mean lifespan of mice by 38% and maximum lifespan by 10%.[138] Epidemiological evidence suggests that diabetic patients who take metformin live longer than untreated diabetic patients and healthy, nondiabetic individuals.[139] Metformin is also associated with a reduced incidence of cancer[140] and cardiovascular disease.[141]

Autophagy is required for the life extension effects of resveratrol and CR in worms, fruit flies, and mice.[105,127] Resveratrol and CR do not extend the lifespan of worms in the absence of beclin-1, a protein involved in autophagy. In mice fed a high-calorie diet, resveratrol extends lifespan by increasing AMPK activity, which leads to increased PGC-1α activity and mitochondrial biogenesis.[104] Similarly, epicatechin from cacao activates AMPK in the liver and skeletal muscles[58] (Table 1). Other natural compounds that activate AMPK include berberine (**13**; an alkaloid from *Berberis* plants), capsaicin (**14**; a pungent compound found in chili), epigallocatechin gallate (**15**; EGCG; a polyphenol found in green and black tea), genistein (**16**; an isoflavone compound found in various foods including soybeans and coffee), ginsenosides (steroid glycosides isolated from ginseng), and curcumin (from turmeric, the plant used to make curry).[142–145]

Coffee, one of the most widely consumed beverages in the world, induces autophagy in the liver, heart, and muscles in mice.[146] It was proposed that coffee polyphenols may be responsible for inducing autophagy as both noncaffeinated and caffeinated coffee induced autophagy.[146] Yet, caffeine also inhibits mTOR signaling on its own,[147] possibly contributing to the autophagy-inducing effect of coffee. Notably, regular consumption of coffee is associated with reduced all-cause mortality,[148,149] an observation that may be due at least in part to the induction of autophagy. On the other hand, the autophagy-activating effects of coffee may be reduced or neutralized by the relatively large quantity of proteins usually consumed in a typical western breakfast.

Other foods that inhibit the mTOR pathway and induce autophagy include garlic[150] and medicinal mushrooms such as *Ganoderma lucidum* and *Hirsutella sinensis*.[151,152] Natural compounds that inhibit mTOR and may induce autophagy include allicin (**17**; an organosulfur compound isolated from garlic), butein (**18**; a chalcone found in plants), celastrol (**19**; a triterpenoid compound isolated from the plant *Trypterygium wildfordii*, a plant used in TCM to treat arthritis and fever), fisetin (**20**; a flavonoid found in vegetables and fruits), and quercetin.[153–156] Given that mTOR inhibition represents one of the most effective mechanisms to increase lifespan, these compounds and their derivatives represent ideal candidates for the development of antiaging nutraceuticals.

2.3 | Sirtuins and acetyltransferases

Sirtuins are a group of histone deacylase enzymes that modulate cellular functions by removing acyl groups on histones and other proteins.[157] Sirtuin activity requires the cofactor nicotinamide adenine dinucleotide (NAD^+) as an acyl group acceptor and the enzyme is inhibited by the reduced form of the compound (NADH; Figure 4). Given that NAD^+ and NADH are involved in nutrient oxidation to produce energy, sirtuin activity varies according to the energy status of the cell. Accordingly, sirtuins' deacylase activity increases during fasting and exercise while it is reduced during periods of overnutrition and anabolism.[158]

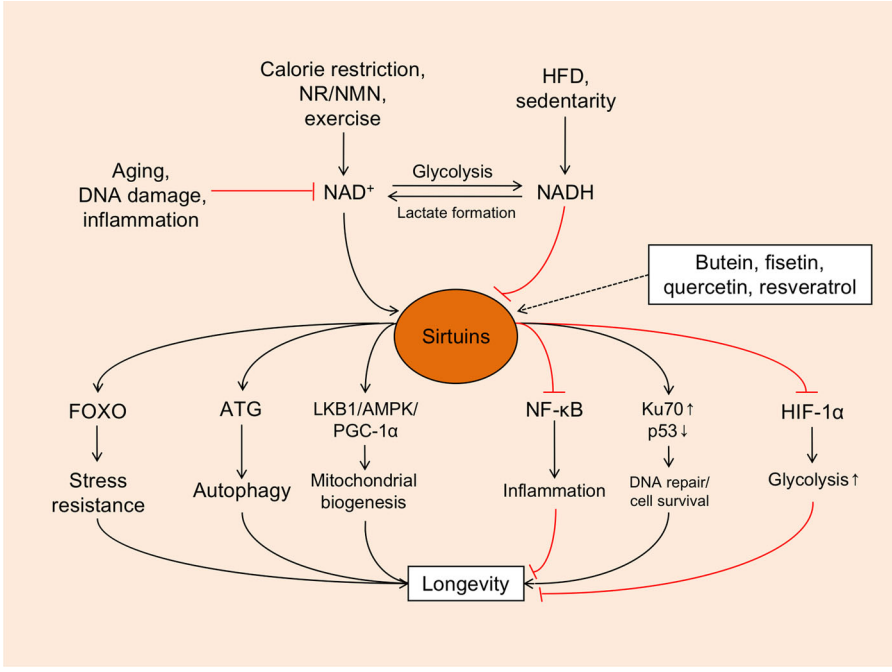

FIGURE 4 Model depicting the regulation of sirtuin activities by plant and mushroom compounds and their effects on longevity. Sirtuins use NAD^+ as a cofactor to deacetylate various proteins involved in stress resistance, autophagy, mitochondrial biogenesis, inflammation, DNA repair, and cell survival. Some plant compounds including butein, fisetin, quercetin, and resveratrol may indirectly activate sirtuins and produce beneficial effects on longevity. Sirtuin activity can also be induced by calorie restriction, NR, NMN, and exercise, which increase NAD^+ levels. On the other hand, aging, DNA damage, and inflammation may reduce sirtuin activity by consuming NAD^+. A HFD and sedentarity may increase NADH levels and inhibit sirtuins. AMPK, adenosine monophosphate-activated protein kinase; FOXO, forkhead box O; HFD, high-fat diet; HIF-1α, hypoxia-inducible factor-1α; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside [Color figure can be viewed at wileyonlinelibrary.com]

Sirtuins are involved in aging in yeasts, worms, fruit flies, and mice. Overexpression of *sirt2* extends lifespan in worms and fruit flies.[159,160] In mice, overexpression of *sirt6* throughout the body extends the lifespan of male mice by 15%.[161] *Sirt1* overexpression in the brain also extends the lifespan of mice.[162] Moreover, *sirt1* activation reduces various age-related diseases, including diabetes, cardiovascular disease, inflammation, and neurodegeneration in model organisms.[163] Conversely, *sirt6*-deficient mice show premature aging associated with genomic instability and DNA repair defects at the cellular level.[164] Activation of sirtuin activity, therefore, represents a target for prolonging lifespan and delaying aging.

Sirtuins modulate lifespan and aging by regulating various cellular pathways (Figure 4). For instance, sirtuin-1 deacetylates and activates PGC-1α, thereby inducing fatty acid oxidation and mitochondrial biogenesis.[165] SIRT1 also deacetylates FOXO proteins, leading to their activation and transcription of proteins that improve stress resistance.[166] Other target proteins of SIRT1 include hypoxia-inducible factor-1α (HIF-1α), which may promote cell longevity by inhibiting glycolysis, as well as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), leading to its inactivation and reduced inflammation.[157,167] Sirtuins also deacetylate the DNA repair protein Ku70 in response to DNA damage, thus promoting DNA repair and cell survival.[168] Similarly, SIRT2 deacetylates the tumor suppressor p53 in response to oncogenic overexpression, preventing senescence and inducing cell survival.[169] Sirtuins also deacetylate LKB1, a key regulator of AMPK, thus reducing senescence.[170]

Several plant-derived polyphenol compounds including butein, fisetin, piceatannol (**21**; a resveratrol derivative), quercetin and resveratrol activate SIRT1 (Figure 4).[54] But other studies showed that resveratrol may also activate SIRT1 indirectly by acting on an upstream target such as AMPK.[163] Nonetheless, resveratrol extends lifespan in yeasts, worms, and fruit flies, and these effects were associated with increased SIRT1 or SIRT2 activities.[54,67,105] Resveratrol also improves the healthspan in various animal disease models.[171] Sirtuin-activating compounds (STACs) have been developed and these have been described to be 1000 times more active than resveratrol at activating SIRT1.[172] One of these molecules, called SRT1720 [**22**], extends mean and maximum lifespan in HFD-fed mice and is associated with improved insulin sensitivity, locomotor activity, and inflammatory profile.[173] SRT2104 [**23**] also prolonged the mean and maximum lifespan of male mice and produced other beneficial health effects, including enhanced motor coordination and maintenance of bone and muscle mass.[174] While many STACs are more bioavailable than resveratrol and have produced beneficial effects on aging-related diseases in preliminary clinical trials,[175] it still remains unclear whether they may be used to improve health and longevity in humans.

Another means to increase sirtuin activity is to supplement with molecules that increase NAD^+ levels (Figure 4). Supplementation with NAD^+ does not appear feasible since mice experience hyperglycemia, possibly due to increased glycogenolysis.[176] The NAD^+ precursor nicotinamide riboside (NR; **24**), which is available as a dietary supplement, increases lifespan in mice, an effect associated with improved mitochondrial and stem cell functions[88] (Table 1). On the other hand, given the multiple activities of NAD^+ in cellular metabolism, it is likely that other effects contribute to the antiaging properties of this compound.

Other studies have shown that some sirtuins may also have proaging properties. For instance, a study showed that *sirt2* deficiency in nondividing yeasts increased the longevity-enhancing effects of CR and further enhanced the lifespan of long-lived Sch9 yeasts.[177] Furthermore, mice lacking *sirT1* (the mammalian ortholog of yeast *sirt2*) showed reduced signs of oxidative stress in the brain, but these animals had a reduced lifespan under a normal or CR diet.[178] It thus appear that sirtuin activity may play both antiaging and proaging roles, depending on cell types, species and experimental conditions.

Besides sirtuins, other enzymes that affect protein acetylation include acetyltransferases that acetylate various cellular proteins and also modulate aging pathways. Levels of acetyl coenzyme A (acetyl CoA), derived from carbohydrates and lipids via glycolysis and β-oxidation and used as a source of energy via oxidation in the citric acid cycle, decrease during fasting or CR, and this process regulates protein acetylation and autophagy. In the presence of abundant nutrients and acetyl CoA, the acetyltransferase EP300 inhibits autophagy by adding acetyl groups onto various autophagy core proteins (ATG5, ATG7, ATG12, and LC3).[179] Several plant compounds such as curcumin, EGCG, and garcinol (**25**; a compound isolated from *Garcinia indica*) inhibit EP300 in cultured cells.[180–182]

Another molecule that inhibits acetyltransferase enzymes is spermidine (Table 1), an endogenous cellular compound also found in high amounts in foods such as natto (a Japanese fermented soybean preparation), mushrooms, soybeans, and aged cheese.[183] Studies have shown that spermidine inhibits the acetyltransferase EP300, and this inhibition is sufficient to induce autophagy and produce antiaging effects in mice.[183] Spermidine fed life-long or late in life enhances the lifespan of mice and produces cardioprotection effects in an ATG5-dependent manner, indicating that autophagy is involved. In addition, spermidine improves blood pressure in an animal model of hypertension-induced congestive heart failure in rats. Furthermore, epidemiological evidence indicates that spermidine consumption is associated with reduced all-cause mortality in humans.[25]

The anti-inflammatory drug acetylsalicylic acid (aspirin) and its metabolite salicylic acid were also shown to induce autophagy by inhibiting EP300 in worms and mice[109] (Table 1). Both compounds increased lifespan in worms,[108] and acetylsalicylic acid increased mean lifespan in genetically heterogeneous male mice but no effect was observed in female mice.[87] Long-term consumption of low dose acetylsalicylic acid is associated with reduced cancer and all-cause mortality in humans.[184,185] While this observation has been attributed to the anti-inflammatory and antithrombotic activities of the compound, recent work suggests that the autophagy-inducing effect of this compound may also contribute to improving survival. Acetylsalicylic acid is thus being considered as a CR mimetic,[186] although it is not devoid of negative side effects (eg, bleeding, gastrointestinal ulcers, and nausea). Moreover, a recent study showed that acetylsalicylic acid did not prolong disability-free survival over a 5-year period in healthy elderly subjects,[187] implying that the effects of acetylsalicylic acid on aging are not as straightforward as previously assumed.

Given that acetyl CoA is needed for protein acetylation, depletion of acetyl CoA pools in the cell may also affect autophagy. Accordingly, hydroxycitrate [**26**], a compound isolated from *Garcinia cambogia* fruits which have been used as a dietary supplement for weight loss,[188] depletes acetyl CoA levels and induces autophagy in vivo.[189] Hydroxycitrate affects acetyl CoA levels by inhibiting citrate lyase, a key enzyme in the citric acid cycle. Oral intake of hydroxycitrate in mice for 2 days induces autophagy throughout the body.[189] This compound is thus likely to produce antiaging effects by mimicking CR.

DNA damage, which increases with aging, leads to activation of poly(ADP-ribose) polymerase, marking DNA for repair and consuming NAD^+.[157] HFD-induced inflammation may also reduce NAD^+ levels by inhibiting nicotinamide phosphoribosyltransferase, an enzyme involved in the conversion of nicotinamide into NMN.[157] Levels of the NADase enzyme CD38 also increase in aging, which may further contribute to reducing NAD^+ levels and sirtuin activity in aging tissues.[190,191] Quercetin and apigenin (**27**; a flavone compound found in many plants) inhibit CD38[192] and represent good candidates to produce antiaging effects by inducing sirtuin activity.

2.4 | ROS and antioxidants

Aging is associated with a progressive accumulation of molecular and cellular damage, eventually leading to organ malfunction and a decline in physiological function. With time, accumulation of mutations in DNA, aggregated proteins, and oxidation of lipids are believed to overwhelm the reparative capacity of the body and eventually lead to organ failure and disease. In the 1950s, it was proposed that ROS produced as a by-product of cellular respiration in mitochondria may be the cause of aging.[193] Consistent with this concept, ROS accumulate with age as mitochondrial function declines and high levels of ROS may lead to protein damage, organelle dysfunction, DNA damage, and aging.[194] Antioxidants may directly neutralize ROS, thus preventing cell damage and improving cellular functions. Various phytochemicals produce antioxidant activities and increase lifespan in worms, fruit flies, and rodents (Table 1).

On the other hand, antioxidants do not increase lifespan in all circumstances. For instance, overexpression of antioxidant enzymes increased lifespan in invertebrates such as fruit flies[195] but failed to increase lifespan in mice.[196,197] In humans, while some large epidemiological studies found a positive correlation between antioxidant

vitamin intake and reduced mortality,[198,199] systematic reviews of clinical trials indicate that antioxidant supplements such as vitamins A and E and β-carotene were associated with a slightly increased mortality risk.[200,201]

The inconsistent observations regarding the effects of ROS and antioxidants on aging may be due to species-related variation in oxidative stress resistance or to the signaling and functional roles of ROS in different species. In mammals, production of ROS in immune cells such as macrophages and neutrophils is beneficial to kill pathogens. In addition, ROS may also act as a secondary messenger to activate various cellular processes, especially those involved in the protection of cellular damage and the repair process; and at low levels, ROS also plays a beneficial role in response to physiological stimuli such as insulin by reversibly oxidizing and inhibiting protein phosphatases.[202] For instance, glucosamine supplementation increases lifespan by stimulating the formation of ROS which induces mitochondrial biogenesis in worms and aging mice.[71] Moreover, exercise induces ROS production and the expression of antioxidant enzymes such as SOD and CAT to protect cells and tissues from oxidation. Surprisingly, consumption of antioxidants may prevent the exercise-induced increase in ROS and reduce the beneficial effects of exercise on insulin sensitivity and neutralization of ROS.[203]

ROS may participate in the aging process, and neutralization of free radicals by antioxidants may delay aging and prolong lifespan under some circumstances. Yet, reduction of ROS formation may also interfere with cellular pathways involved in stress resistance and damage repair and, at low levels, ROS may play a beneficial role in normal cellular function; thus the need for careful consideration of the interventions used. It is also worth noting that natural antioxidant compounds may increase lifespan via other ROS-independent mechanisms (Table 1).

2.5 | Telomerase activation

The ends of chromosomes are susceptible to erosion with time and cell divisions due to oxidation, recognition by DNA repair enzymes as broken DNA, or shortening due to incomplete replication by DNA polymerases during cell division. Telomerase protects telomeres by adding sequence-specific DNA at chromosomal ends. While telomerase is active in most cells during fetal development as well as in stem cells and continuously-replicating cells after birth, most somatic cells have low or no telomerase activity and are unable to prevent telomere erosion.[204] Telomere shortening is believed to contribute to the replicative limit of cells, which leads to senescence.

Consistent with this possibility, telomere length has been shown to reflect the replication potential of cultured cells.[205] Moreover, reintroduction of the telomerase gene renders many human primary cell lines immortal.[206] Mice that lack telomerase have short telomeres and show premature tissue degeneration associated with reduced stem cells in the bone marrow and skin.[207,208] Telomere length is predictive of mortality from age-associated pathologies in humans, including heart disease and infections.[209]

The potential to reactivate telomerase in somatic cells has shown promise to prevent senescence and increase lifespan. A natural plant compound called cycloastragenol [**28**] isolated from the roots of *Astragalus membranaceus* (a plant used as a tonic in TCM) has been reported to activate telomerase in cultured human $CD4^+$ and $CD8^+$ T lymphocytes.[210–212] Cycloastragenol delayed telomere shortening, increased replicative capacity, and improved immune function in cultured $CD8^+$ T lymphocytes isolated from human immunodeficiency virus-positive individuals.[213] In female mice, cycloastragenol, also called TA-65, increased telomere length in some tissues, most notably in the liver, and improved some healthspan indicators including glucose tolerance, osteoporosis, and skin aging but no lifespan increase was observed.[214] Notably, TA-65 treatment did not increase cancer incidence in this study.

A randomized controlled clinical trial of 117 healthy volunteers aged 53 to 87 years who took the dietary supplement for one year showed that cycloastragenol increased telomere length, while the telomeres of people in the control group became shorter during this period.[215] A clinical trial showed that TA-65 used in combination with a vitamin supplement improved bone density, blood pressure, and metabolic markers in healthy individuals over a 5-year period but the contribution of TA-65 alone was not determined.[216] Another small double-blind, placebo-controlled trial done on 38 individuals showed that TA-65 improved macular function in patients with age-related macular degeneration.[217]

Perhaps encouraging in this area are the findings that lifestyle changes involving smoking cessation, exercise and a proper diet increase telomere length and may delay signs of aging and age-associated diseases in humans,[218] although it is unclear whether these changes can be attributed to elongated telomeres. In view of the preliminary data described in this field, it remains to be seen if telomerase reactivation by phytochemicals may delay aging at the organismal level. Moreover, a possible side effect of telomerase activation is the increased risk of cancer, which may preclude the use of this intervention in healthy humans.

2.6 | Senolytics

Senescence is an irreversible state in which cells stop replicating and usually become resistant to apoptosis.[219] A variety of cellular stress can induce senescence, including DNA damage (telomere erosion), oncogenic expression (Ras), nutrients (high glucose), metabolites (ROS and ceramides), hormones (GH and IGF-1), molecular damage (protein aggregation, the unfolded protein response), and inflammation (interleukin-1β and interleukin-6). Senescent cells often attract immune cells and induce inflammation by secreting proinflammatory cytokines and danger-associated molecular patterns. Senescent cells accumulate in various tissues during aging and contribute to organ dysfunction and the development of chronic disease. As such, injection of senescent cells into the joint is sufficient to induce the development of an osteoarthritis-like condition in mice.[220] Consistent with these results, elimination of senescent cells using a drug-inducible transgenic "suicide" gene improved healthspan in genetically-modified mice.[221] Based on these observations, the elimination of senescent cells has emerged as a promising strategy to delay aging and reduce age-related diseases.

Senolytics are a new class of compounds that kill senescent cells by rendering them susceptible to apoptosis. The tyrosine kinase dasatinib and the flavonoid quercetin induce apoptosis of senescent cells without affecting normal cells.[222] The flavone compound fisetin also has senolytic properties in cells cultured in vitro.[223] Other compounds such as curcumin and resveratrol did not possess senolytic properties in the assay used.[224] The plant compound piperlongumine [**29**], a compound isolated from various plants of the *Piper* genus, showed proapoptotic properties in senescent cells.[225] Piperlongumine derivatives obtained by chemical modification also induced apoptosis in senescent cells.

In mice, many senolytic compounds eliminate senescent cells and produce beneficial effects in the host. The mixture of desatinib and quercetin took orally for a few days reduced the number of senescent cells in old mice.[222] A single course of the senolytic cocktail improved cardiovascular function in old mice. Moreover, a single dose of the mixture enhanced physical endurance in mice in which one leg had been irradiated to induce accumulation of senescent cells. Notably, the desatinib and quercetin cocktail increased mouse lifespan compared with controls.[102] Desatinib and quercetin also reduced senescent cell accumulation in the lungs, inflammation, fibrosis, and respiratory dysfunctions in a model of bleomycin-induced pulmonary fibrosis.[226]

The field of senolytics is relatively new and more studies will be needed to determine the possibility of using such treatments to delay aging. One interesting advantage in this study is the fact that many of cellular pathways involved in senescence are known. These advances may facilitate the development of active compounds to target senescent cells.

2.7 | Other potential antiaging mechanisms

Inhibition of fat absorption represents a possible mechanism that may produce CR-mimetic effects on longevity and health.[15] Natural compounds that have been considered in this category include dietary fiber, which reduces lipid levels in the body by blocking their absorption by the intestine.[31] Similarly, chitosan [**30**], a polysaccharide produced by deacetylation of chitin from cell walls of fungi or crustaceans, may reduce body weight, total cholesterol, and blood pressure.[227] On the other hand, no long-term studies have been performed to determine whether these compounds prolong lifespan in animals.

Other ways to mimic the effects of CR include suppression of appetite or inhibition of the intestinal enzymes responsible for carbohydrate and lipid digestion.[15] Several molecules isolated from plants and fungi have been shown to suppress appetite.[31] For instance, celastrol suppresses appetite and food intake in HFD-fed mice by increasing leptin sensitivity.[228] Similarly, various plant-derived molecules that inhibit intestinal enzymes responsible for carbohydrate and lipid digestion may have a beneficial effect on health.[31,229]

Natural compounds that inhibit glycolysis may also exhibit antiaging effects. One of the first CR mimetics studied was 2-deoxyglucose [**31**], a glycolysis inhibitor that reduced body temperature and fasting serum insulin levels in rats.[230] On the other hand, this compound was later found to induce cardiotoxicity and increase mortality in the treated animals.[231] Glucosamine also inhibits glycolysis and extends lifespan in worms and mice (Table 1). This compound mimics a low-carbohydrate diet and represents a promising candidate for reducing aging.

Excess glucose may combine covalently with proteins, DNA and lipids, to form advanced glycation end-products (AGEs) which impair physiological function and contribute to organ dysfunction and aging.[232] AGEs are also found in food that are heated or cooked and are readily found in human blood.[233] In animal models, the level of AGEs in the diet correlates with blood AGE levels, and they stimulate inflammation and oxidative stress, leading to the development of diabetes, cardiovascular disease, chronic kidney disease, and neurodegeneration.[234] Some phytochemicals such as proanthocyanidins found in fruits (Table 1) and catalpol [**32**] found in plants of the *Rehmannia* genus (Table 2) reduce the levels of AGEs in worms and mice, respectively.

Dampening inflammation may be beneficial for prolonging lifespan and improving the healthspan.[303] While inflammation is required for immune responses against infection or for wound healing, tissue damage that increases with aging may induce chronic inflammation. Low levels of chronic inflammation are also associated with the development of other chronic diseases, from heart disease, cancer, and stroke, to Alzheimer's disease and type 2 diabetes. Many plant and fungal compounds that increase lifespan and improve healthspan reduce signs of inflammation in model organisms (Tables 1 and 2). The immunosuppressive drug rapamycin also produced robust lifespan-enhancing effects in rodents (mainly through its inhibitory effects on mTOR).[122,128] Chronic inflammation is associated with overactivation of mTOR, indicating that mTOR inhibition may also produce antiaging effects by reducing inflammation.[125]

The gut microbiota plays a role in many physiological functions[304] and may also influence longevity.[305] A search for bacteria that are beneficial in worms has shown that specific bacterial mutants lacking a single gene can extend lifespan in worms.[306] Some of these mutants protect the host against age-related tumor formation or amyloid-β deposition, or modulate the unfolded protein response. Some probiotics extend the lifespan in mice by producing polyamine compounds that induce anti-inflammatory effects and improve colonic mucosal function.[307] Similarly, a mixture of prebiotics (inulin-type fructans) and probiotics (*Lactobacillus reuteri*) reduced hepatic cell proliferation and muscle wasting and improved survival in leukemic mice.[308] Compounds that increase longevity and healthspan such as rapamycin and metformin also influence the composition of the gut microbiota. Metformin increased the abundance of beneficial bacteria (ie, *Akkermansia muciniphila*, *Clostridium cocleatum*) and affected bacterial metabolism associated with beneficial effects on the host,[309] whereas rapamycin induced changes in the gut microbiota that are observed in obesity and diabetes, including reducing levels of Marinilabiliaceae and *Turicibacter* spp.[310]

The gut microbiota may also mediate the lifespan-enhancing effects of phytochemicals. For instance, the gut microbiota of the large intestine ferments dietary fiber and polysaccharides to produce short-chain fatty acids (SCFAs), which may have beneficial effects on the host. Butyrate is a SCFA that is converted into the ketone body BHB which enhances the mean lifespan of worms by ~20%.[311] BHB levels in the blood also increase during fasting, intense exercise, or KD feeding. BHB acts as a source of energy independent of glucose (thus reducing insulin and IGF-1 signaling) but it also inhibits histone deacetylases, thus activating PGC-1α and the FOXO pathway and possibly delaying aging by increasing stress resistance.[312,313] Based on these observations, some authors proposed that the life extension effects of CR and KD may be mediated at least in part by BHB.[312,313] In addition, BHB inhibits the NLRP3 inflammasome, thereby further reducing inflammation.[314]

TABLE 2 Plant and fungal molecules that improve the healthspan in mammals

No.	Compounds	Source	Condition	Effect	Mechanism	References
1	Acteoside	*Cistanche* spp.	Rat (Alz)	Cognitive function↑	Amyloid-β↓	Shiao et al[235]
2	Allicin	Garlic	Mouse (Alz)	Cognitive function↑, memory↑	SOD↑, GSH-Px↑, ROS↓, Nrf2↑	Li et al[236], Li et al[237]
3	Andrographolide	*Andrographis paniculata*	Rat (STZ)	Glycemia↓, cognitive function↑	GLUT4↑, ROS↓	Yu et al[238], Thakur et al[239]
4	Antcin C	*Antrodia cinnamomea*	Mouse (AAPH)	Liver damage↓	ALT↓, AST↓, Nrf2↑	Gokila Vani et al[240]
5	Astaxanthin	Phaffia, dietary supplement	Rat (gal)	HYP damage↓	SOD↑, GSH-Px↑, ROS↓	Wu et al[241]
6	Astragaloside	*Astragalus membranaceus*	Mouse	Motor function↑, memory↑	Not determined	Lei et al[242]
7	Berberine	Chinese goldthread	Mouse, rat (HFD)	Insulin sensitivity↑, obesity↓	AMPK↑	Lee et al[143], Yin et al[243]
8	Caffeic acid/CAPE	Propolis	Rat (Alz)	Liver damage↓, cognitive function↑	CAT↑, ROS↓	Esrefoglu et al[244], Deshmukh et al[245]
9	Carnosine	Dietary supplement	Rat (gal)	Liver injury↓, brain damage↓	SOD↑, GSH-Px↑, ROS↓	Kalaz et al[246], Aydin et al[247]
10	Catalpol	*Rehmannia glutinosa*	Mouse (gal)	Cholinergic function↑	IL-1β↓, TNF-α↓, AGEs↓	Zhang et al[248]
11	Celastrol	*Tripterygium wilfordii*	Mouse (ALS)	Motor function↑, ALS↓	TNF-α↓, iNOS↓, HSP70↑	Kiaei et al[59]
12	Chlorogenic acid	Coffee, tea	Mouse (gal)	Liver, kidney damage↓	SOD↑, CAT↑, TNF-α↓	Feng et al[249]
13	Creatine	Dietary supplement	Mouse	Memory↑, exploration↑	Lipofuscin↓	Bender et al[62]
14	Curcumin	Turmeric	Mouse (Alz), rat (gal, STZ)	Memory↑, HYP volume↑, Alz↓	ROS↓, AMPK↑, amyloid-β↓	Lim et al[250], Na et al[251], Banji et al[252], Fleenor et al[253]
15	Cycloastragenol	*A. membranaceus*	Mouse	Glucose tolerance↑, osteoporosis↓	Telomerase↑	Bernardes de Jesus et al[214]
16	Epicatechin	Cocoa	Mouse (HFD)	Blood vessel and liver damage↓	AMPK↑, ROS↓, IGF-1↓, SOD↑	Si et al[58]

(Continues)

TABLE 2 (Continued)

No.	Compounds	Source	Condition	Effect	Mechanism	References
17	EGCG	Green tea	Mouse (gal)	Cognitive function↑, motor function↑	SOD↑, GSH-Px↑, MDA↓	He et al[254]
18	Gallic acid	Rose flower	Mouse (gal)	Liver, kidney, brain oxidation↓	MDA↓, GSH-Px↑, ROS↓	Li et al[255]
19	Gastrodin	*Gastrodia elata*	Mouse (Parkinson), rat (dementia)	Cognitive function↑, motor function↑	MDA↓, GSH-Px↑, ROS↓	Chen et al[256], Wang et al[257], Li et al[258]
20	Genistein	Soybeans, coffee	Mouse (diabetic)	Vascular inflammation↓	MCP-1↓, KC↓, IL-10↑	Babu et al[259], Jia et al[260]
21	Gingerol	Ginger	Rat (gentamicin)	Nephrotoxicity↓	TNF-α↓, SOD↑, ROS↓	Rodrigues et al[261]
22	Ginsenoside Rg1	Ginseng	Rat, mouse (gal)	Cognitive function↑	Telomerase↑, IL-1β↓, ROS↓	Zhu et al[262], Li et al[263]
23	Huperzine A	*Huperzia serrata*	Mouse, rat (hypoperfusion)	Cognitive function↑, neurogenesis↑	TNF-α↓	Wang et al[264], Ma et al[265]
24	Icariin	*Herba epimedii*	Mouse	Cardiac inflammation↓	SIRT6↑, NF-kB↓	Chen et al[266]
25	IDHP	Danshen	Rat (isoprenaline)	Cardiac fibrosis↓	ROS↓	Yin et al[267]
26	Lipoic acid	Dietary supplement	Mouse (Alz, gal)	Memory↑, learning↑	ROS↓, SOD↑, MDA↓	Cui et al[268], Farr et al[269]
27	Lutein	Green vegetables	Mouse (AMD, UVB)	AMD↓, skin aging↓	ROS↓, SOD↑, MCP-1↓	Astner et al[270], Kamoshita et al[271]
28	Luteolin	Vegetables, tea	Mouse (TNF-α)	Vascular inflammation↓	MCP-1↓, KC↓, NF-kB↓	Jia et al[272]
29	Monascin	*Monascus purpureus*	Mouse (HFD)	NAFLD↓	AMPK↑, PGC-1α↑	Hsu et al[273]
30	Nicotinamide	Dietary supplement	Mouse (Alz, HFD)	Cognitive function↑, NAFLD↓	Autophagy↑, β-amyloid↓, infl.↓	Liu et al[274], Mitchell et al[276]
31	NMN	Dietary supplement	Mouse, rat (Alz)	Blood flow↑, endurance↑	NAD^+↑, Sirt-1↑	Wang et al[275], Das et al[277]
32	Nicotinamide riboside	Dietary supplement	Mouse (Alz)	Memory↑, learning↑	Tau↓, infl.↓, DNA repair↑	Hou et al[278]

(Continues)

TABLE 2 (Continued)

No.	Compounds	Source	Condition	Effect	Mechanism	References
33	NDGA	*Larrea tridentata*	Mouse (ALS)	Motor function↑, ALS↓	Tau↓, gliosis↓	West et al[279]
34	Oligonol	Fruits	Rat (STZ)	Insulin sensitivity↑	ROS↓	Park et al[280]
35	Quercetin	Vegetables, ginkgo	Mouse	Brain function↑, endurance↑	AMPK↑, PGC-1α↑, Sirt-1↑	David et al[281], Lu et al[282]
36	Polyphenols	Cocoa	Rat	Cognitive function↑	Not determined	Bisson et al[92]
37	Polysaccharides	*Ganoderma lucidum*	Mouse (HFD)	Obesity↓, diabetes↓, NAFLD↓	Infl.↓, prebiotic	Chang et al[283]
38	Polysaccharides	*Hirsutella sinensis*	Mouse (HFD)	Obesity↓, diabetes↓, NAFLD↓	Infl.↓, prebiotic	Wu et al[284]
39	Polysaccharides	Shiitake mushroom	Mouse	Immune function↑	Cytokines↑, prebiotic	Xu et al[285]
40	Proanthocyanidins	Cranberries	Mouse (gal)	Hepatic, brain reactive compounds↓	GSH-Px↑	Jiao et al[286]
41	Orientin	*Trollius chinensis*	Mouse (gal)	Brain weight↑	ROS↓, SOD↑, CAT↑, GSH-Px↑	An et al[287]
42	Resveratrol	Wine, dietary supplement	Mouse (HFD, stroke), rat (Parkinson, heart disease)	Aortic elasticity↑, endurance↑, Alz↓, heart failure↓, Parkinson disease↓, fertility↑, obesity↓, insulin sensitivity↑, motor function↑	IGF-1↓, ROS↓, AMPK↑, PGC-1α↑	Lagouge et al[288], Baur et al[104], Pearson et al[121], Karuppagounder et al[289], Yang et al[290], Khan et al[291], Sakata et al[292], Um et al[293], Liu et al[294]
43	Shogaol	Ginger	Mouse (LPS)	Neuroprotection↑	IL-1β↓, TNF-α↓, NF-kB↓	Ha et al[295]
44	Spermidine	Natto, mushrooms	Mouse, rat (gal)	Cardioprotection↑, muscle atrophy↓	Autophagy↑, AMPK↑, FOXO↑	Eisenberg et al[113], Fan et al[296]
45	Tetrahydrocurcumin	Turmeric	Mouse (iron)	Vascular dysfunction↓, renal injury↓	ROS↓, GSH-Px↑	Okada et al[297], Sangartit et al[298]
46	Theaflavin	Black tea	Rat (HFD)	FA oxidation↑, lipogenesis↓	AMPK↑	Lin et al[299]
47	Tiliroside	Fruits	Mouse (obese)	Insulin sensitivity↑, FA oxidation↑	Adiponectin↑, AMPK↑	Goto et al[300]
48	Triterpenoids	*A. cinnamomea*	Mouse (STZ)	Diabetes↓, wound healing↓	Infl.↓, CCL1↓, adiponectin↑	Wu and Chen[301]

(Continues)

TABLE 2 (Continued)

No.	Compounds	Source	Condition	Effect	Mechanism	References
49	Urolithin A	Berries	Mouse	Endurance↑	Autophagy↑, muscle function↑	Ryu et al[302]
50	Vitexin	*T. chinensis*	Mouse (gal)	Brain weight↑	ROS↓, SOD↑, CAT↑, GSH-Px↑	An et al[287]

Abbreviations: AAPH, 2,2′-azobis(2-amidinopropane) dihydrochloride; AGE, advanced glycation end-product; ALS, amyotrophic lateral sclerosis; ALT, alanine aminotransferase; Alz, Alzheimer's disease; AMD, age-related macular degeneration; AMPK, adenosine monophosphate-activated protein kinase; AST, aspartate transaminase; CAT, catalase; CCl1, chemokine (C-C) ligand 1; EGCG, epigallocatechin gallate; FA, fatty acid; FOX, forkhead box O; gal, galactose; GLUT4, glucose transporter type 4; GSH-Px, glutathione peroxidase; HFD, high-fat diet; HSP, heat-shock protein; HYP, hippocampus; IDHP, isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxylpropanoate; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; infl., inflammation; iNOS, inducible nitric oxide synthase; KC, keratinocyte chemoattractant; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2, NF-E2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; ROS, reactive oxygen species; SOD, superoxide dismutase; STZ, streptozotocin; TNF-α, tumor necrosis factor-α; UVB, ultraviolet B.

Stem cells are also involved in the aging process as the inability to replenish tissues with stem cells may lead to cellular dysfunction and tissue degeneration. Plant extracts can stimulate stem cell growth and represent potential candidates for antiaging formulations.[315] Plant-derived compounds in this category include resveratrol, genistein, quercetin, and naringin [**33**]. Notably, the NAD^+ precursor NR increases lifespan in mice at least in part by rejuvenating muscle stem cells and preventing senescence in neural and melanocyte stem cells.[88] The possibility of controlling stem cell fate using plant-derived molecules has also been examined.[316] Furthermore, hematopoietic stem cells from old mice show increased mTOR activity, and rapamycin restored hematopoiesis and hematopoietic stem cell self-renewal in old mice,[317] indicating that compounds that inhibit mTOR may delay aging by improving stem cell function.

3 | ADDITIVE AND SYNERGISTIC EFFECTS OF PLANT AND FUNGAL MOLECULES ON LIFESPAN

One could envision delaying aging by developing a cocktail of molecules isolated from plants and fungi that affect different aging-related pathways, with the hope of producing additive or synergistic effects. This strategy is reminiscent of the "herbal shotgun" approach used with most plant extracts, in which various compounds affect a multitude of cellular and physiological targets; in contrast with the "magic bullet" approach, in which a pharmaceutical drug targets a single pathway.[31,318] The polypharmacy approach is also used in medicine when several drugs are combined to treat a specific ailment or condition.

At doses in which neither resveratrol nor spermidine alone increased autophagy, the two compounds used in combination induced autophagy in a synergistic manner in yeasts and worms.[112] Similarly, a mixture of acetic acid [**34**] and polysaccharides derived from *G. lucidum* extended the lifespan of worms by 30% to 40%, an effect that was more intense than the sum of the effects produced by the two compounds alone.[96] These studies suggest that combining several compounds may produce synergistic effects on aging-related pathways.

A mixture of compounds containing vitamins B, C, D, and E, α-lipoic acid, coenzyme Q10, and extracts derived from cod liver oil, flax seed oil, garlic, ginger, *Ginkgo biloba*, ginseng, and green tea prolonged the lifespan of normal mice and GH-overexpressing transgenic mice by 11% and 28%, respectively.[319] Designed to reduce ROS formation and inflammation, promote mitochondrial integrity, and increase insulin sensitivity,[320] the mixture reduced brain cell loss and cognitive decline in aged mice that overexpress GH.[320,321] While it is unclear whether additive or synergistic effects were produced in this case, this study demonstrates the feasibility of the strategy to increase lifespan and healthspan. On the other hand, the nutraceutical mixture did not extend the lifespan of the long-lived F1 strain of mice,[322] suggesting involvement of the genetic background of the animals tested.

Another mixture of plant extracts and dietary supplements containing pterostilbene (a chemical related to resveratrol), theanine (an amino acid isolated from tea leaves), *A. membranaceus* root, *Pterocarpus marsupium* bark, and pine bark extended lifespan in fruit flies maintained under stress conditions.[323] The treated fruit flies showed increased resistance to partial starvation and heat, suggesting that at least some antiaging pathways may have been activated. The dietary supplement was designed to modulate aging pathways related to antioxidant potential, inflammation, metabolism, and vascular endothelial growth factor (VEGF). These studies suggest that a mixture of molecules may modulate the activities of multiple pathways in vivo, possibly producing additive or synergistic effects.

4 | EFFECTS OF PLANT AND FUNGAL COMPOUNDS ON HEALTHSPAN

Many studies examined the possibility that plant and fungal compounds may reduce signs of aging by comparing physiological functions in young and old animals (Table 2). Another strategy has examined the effects of plant and fungal compounds on animals treated with galactose, which has been used to enhance aging. Natural compounds

have also been tested for their ability to delay age-related disease in animal models, including Alzheimer's disease, amyotrophic lateral sclerosis, liver and kidney damage, chronic inflammation, obesity, and diabetes (Table 2).

Several plant and fungal compounds delay brain aging in animal models. For instance, astragalosides derived from *A. membranaceus* delay motor decline and improve memory in galactose-induced aged mice.[242] Similarly, EGCG reduces oxidative stress in the hippocampus and improves cognitive functions and locomotive activity in galactose-treated mice.[254] Huperzine A [**35**], a sesquiterpene compound isolated from the firmoss *H. serrata*, increases neurogenesis and reduces cognitive decline when fed orally to rodents.[264,265]

Our group showed that high-molecular-weight polysaccharides isolated from the medicinal fungus *G. lucidum* reduce obesity, insulin resistance, and inflammation in HFD-fed mice.[283] These effects were associated with reduced intestinal permeability and modulation of the composition of the gut microbiota, indicating that the polysaccharides act as prebiotics. High-molecular-weight polysaccharides isolated from the medicinal mushroom *H. sinensis*, the anamorph of *Ophiocordyceps sinensis*, also reduces obesity and insulin resistance in HFD-fed mice.[284]

While projects to study the effects of resveratrol on the lifespan of healthy mammals have yielded disappointing results, the compound has been shown to reduce symptoms of aging in animal models. For instance, resveratrol reduces inflammation, endothelial cell apoptosis, and cataract formation, while improving aortic elasticity, motor coordination, and bone density in mice.[121] Resveratrol also induces gene expression patterns similar to those observed in CR and intermittent fasting in multiple organs and tissues. Other studies indicate that resveratrol prevents the development of type 2 diabetes, stroke, heart failure, Alzheimer's disease, and Parkinson's disease in animal models, in addition to increasing physical endurance (Table 2). Notably, resveratrol and red wine containing equivalent amounts of resveratrol delay vascular aging and improve aerobic performance and exercise capacity in rats, without extending lifespan.[324]

In humans, resveratrol produced CR-mimetic effects in obese individuals but not in healthy individuals.[325] The changes observed in obese individuals included a reduction in resting metabolic rate as well as activation of AMPK, increased PGC-1α and SIRT1 protein levels, and improved mitochondrial respiration in muscles. Use of resveratrol as an adjuvant to drug treatment in diabetic patients reduced systolic blood pressure, hemoglobin A1c, and creatinine but failed to affect diastolic blood pressure or other metabolic markers such as fasting glucose, insulin sensitivity, or blood lipids.[326] A small trial conducted on the sirtuin-1 activator SRT2104 suggested that the compound may improve measures of arterial stiffness in healthy smokers and diabetic patients.[327] Clinical trials are being performed to assess the effects of drugs targeting sirtuin activities in humans.[328]

The NAD^+ precursor nicotinamide mononucleotide (NMN; **36**) reduced diabetes in aging mice.[329] Another study show that NMN increases physical endurance in old mice by activating SIRT1 in endothelial cells.[277] The effects of NMN are associated with increased muscle angiogenesis. Supplementation with nicotinamide also improves glucose homeostasis, hepatic steatosis and inflammation in HFD-fed mice.[276] Similarly, NR increases NAD^+ levels in the body and reduces noise-induced hearing loss[330] and HFD-induced obesity.[331] Preliminary clinical studies indicate that NR supplementation increases blood NAD^+ levels and is well tolerated in humans,[332,333] paving the way for further clinical trials.

5 | REMAINING CHALLENGES

While phytochemicals have been reported to improve lifespan and delay aging in model organisms (Tables 1 and 2), some natural substances failed to affect lifespan. For instance, curcumin and the cholesterol-lowering drug simvastatin (isolated from the fungus *Aspergillus terreus*) did not increase lifespan in genetically heterogenous mice.[122,334] Lipoic acid improved memory and learning by reducing brain oxidation levels in senescence-prone mice but the treatment also reduced lifespan.[269] EGCG increased lifespan of worms under oxidative stress[66] but failed in normal conditions,[78] suggesting that the beneficial effects of some compounds may be observed only under stress conditions. Fish oil did not enhance lifespan in senescence-prone mice[335] and genetically heterogenous mice.[336]

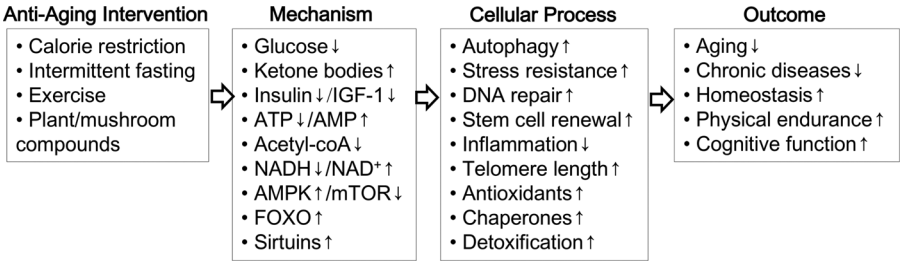

FIGURE 5 Proposed molecular and cellular mechanisms involved in the antiaging effects of plant and mushroom compounds. Antiaging interventions including calorie restriction, intermittent fasting, exercise, and calorie restriction mimetics derived from plants and fungi modulate different molecular effectors in cells and tissues of the body. These effects include modulation of energy levels (eg, glucose, ketone bodies, ATP/AMP, acetyl CoA, and NAD^+/NADH) and activation of transcription factors (eg, FOXO), and enzymes (eg, AMPK, mTOR, and sirtuins). In turn, cellular processes are activated, including autophagy, stress resistance, and DNA repair, which together delay the aging process, reduce the development of chronic disease and improve homeostasis, physical endurance, and cognitive function. AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; FOXO, forkhead box O; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide

However, it remains unclear whether this observation may be due to the use of oxidized fish oils.[337] While fish oil shows benefits for some aging-related disease conditions, it does not appear to improve lifespan.[338]

It remains to be seen whether the life extension effects of phytochemicals may be applied to healthy humans. Many questions also remain regarding the optimal dosage, absorption, bioavailability, and efficacy of these compounds. Given that long-lived organisms such as humans may possess better protection mechanisms against aging than worms, fruit flies, and mice, it is likely that the antiaging effects in humans may be more modest than in model organisms. On the other hand, even modest improvements in lifespan and healthspan in response to natural CR mimetics may be highly beneficial. But given that antiaging pathways are activated during CR and exercise, and even though drugs such as rapamycin produce antiaging effects in the absence of CR, the act of overeating may partially or entirely reverse the effects produced by natural CR mimetics or nutraceuticals. For this reason, optimal life extension and antiaging effects may be produced by combining natural CR-mimetic compounds with some forms of CR, intermittent fasting, KD feeding and/or regular exercise (Figure 5).

While most of the plant and fungal compounds described here do not produce serious side effects, a few produced unwanted toxic effects in some cases. For instance, melatonin (an endogenous hormone found in the human body as well as in vegetables and fruits) increased lifespan in mice but it also reduced fertility and increased tumor formation.[339] Similarly, the lignan compound nordihydroguaiaretic acid (found in creosote bushes) improved lifespan in mice but these results were associated with increased tumor formation and peritoneal hemorrhage.[340] Cellular processes involved in aging including telomere shortening and senescence also protect us from cancer,[341] indicating that the safety of compounds that modulate these pathways should be carefully examined. Molecules that inhibit mTOR such as rapamycin may produce adverse effects on immune functions, insulin sensitivity, and the gut microbiota. Some of the adverse side effects of these compounds could be diminished by varying the dosage or frequency of use, or by chemically modifying the compounds to improve their pharmacological properties.

Many of the dietary supplements discussed here are not usually subjected to regulation for potency, safety, and efficacy. The use of natural substances is rarely accompanied by any guarantee of purity and efficacy, and usually no description of optimal dosage or possible side effects are provided. Producers of dietary supplements should perform testing to determine the mechanism of action and confirm the safety, optimal dosage, and efficacy of natural health products.[33] This testing is probably the first step that needs to be taken before any of the antiaging properties of natural health products can be considered seriously by a broader community of health care practitioners.

6 | CONCLUSION

Many plants and fungi consumed as foods, drinks, and spices contain antiaging molecules that prolong lifespan in model organisms. These foods and drinks contain active compounds that modulate the same cellular and physiological pathways affected by CR and exercise. Molecules that increase lifespan and healthspan mimic the effects of CR, fasting, and KD, often by reducing insulin/IGF-1 signaling and activating autophagy and other cellular processes that increase resistance to stress (Figure 5). These plant and fungal molecules increase longevity but also improve health and quality of life by reducing the development of chronic diseases, including cancer, cardiovascular disease, diabetes, and neurodegeneration. Various strategies exist for use of the antiaging compounds described here, including dietary supplementation, increasing intake of foods containing high amounts of the compounds, and/or consuming prebiotics and probiotics that enhance blood levels of the compounds. The observation that some nutraceuticals and natural compounds are associated with longer lifespan in humans suggests that this strategy is feasible for delaying aging and improving healthspan. Plant and fungal compounds that possess antiaging properties in model organisms may also lead to the identification and characterization of new bioactive compounds for the development of improved CR mimetics to delay human aging.

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CONFLICTS OF INTEREST

YFK is president of Chang Gung Biotechnology Corporation; JDY is chairman of the board of Chang Gung Biotechnology Corporation; and the authors own patents related to the preparation and use of natural health products, prebiotics, and probiotics to treat human disease.

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