 DOI 10.1002/mnfr.201100509 *Mol. Nutr. Food Res.* 2012, *56*, 88–115

REVIEW

# Molecular mechanisms for anti-aging by natural dietary compounds

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Aging is defined as a normal decline in survival with advancing age; however, the recent researches have showed that physiological functions of the body change during the aging process. Majority of the changes are often subject to a higher risk of developing diseases, such as cardiovascular disease, type II diabetes, Alzheimer's disease, Parkinson's disease, as well as the dysregulated immune and inflammatory disorders. Aging process is controlled by a complicated and precise signaling network that involved in energy homeostasis, cellular metabolism and stress resistance. Over the past few decades, research in natural dietary compounds by various organism and animal models provides a new strategy for anti-aging. Natural dietary compounds act through a variety mechanisms to extend lifespan and prevent age-related diseases. This review summarizes the current understanding on signaling pathways of aging and knowledge and underlying mechanism of natural dietary compounds that provide potential application on anti-aging and improve heath in human.

Received: July 26, 2011
Revised: August 20, 2011
Accepted: September 2, 2011

**Keywords:**
Anti-aging / Lifespan / Molecular mechanisms / Natural dietary / Signal transduction

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**Abbreviations: 4E-BP1,** 4E-binding protein 1; **ACC1,** acetyl-CoA carboxylase 1; **AceCS1,** acetyl-CoA synthase 1; **AGEs,** advanced glycation end-products; **AgRP,** Agouti-related peptide; **AMPK,** AMP-activated protein kinase; **APP,** amyloid precursor protein; **ATG; atg,** autophagy-related gene; **Bec-1,** Beclin-1; **BITC,** benzyl isothiocyanate; ***clk-1,*** *CLocK (biological timing) abnormality*; **DAF,** daf, Dauer formation; **DHA,** docosahexaenoic acid; **DNMT,** DNA methyltransferase; **EGCG,** epigallocatechin gallate; ***eIF4G,*** *eukaryotictranslation initiation factor 4 gamma*; **EPA,** eicosapentaenoic acid; **ERK,** extracellular signal-regulated kinase; **ETC,** electron transport chain; **eNOS,** endothelial nitric oxide synthase; **FasL,** Fas ligand; **FAS,** fatty acid synthase; **FOXO,** Forkhead Box O; **G6Pase,** glucose-6-phosphatase; **GADD45α,** growth arrest and DNA-damage inducible gene 45α; **GAP,** GTPase activating protein; **GDH,** glutamate dehydrogenase; **GLUT4,** glucose transporter type 4; **GPx,** glutathione peroxidase; **H3K9,** histone H3 lysine 9; **H4K12,** histone H4 lysine 12; **HIF,** hypoxia-inducible factor; **HMGCR,** 3-hydroxy-3-methylglutaryl-CoA reductase; **HSF,** heat shock factor; **HUVEC,** human umbilical vein endothelial cells; **ICAM1,** intercellular adhesion molecule-1; **IGF,** insulin-like growth factor; **IL-6,** Interleukin-6; **IRS,** insulin receptor substrate; **ISP,** iron sulfur protein; **JNK,** Jun *N*-terminal kinase; **LC3,** light chain 3; **LKB1,** liver kinase B1; **MG,** methylglyoxal; **mtDNA,** mitochondrial DNA; **NADPH,** nicotinamide adenine dinucleotide phosphate; **NF-κB,** nuclear factor-κB; **NGF,** neural growth factor; **NPY,** neuropeptide Y; **Nrf2,** nuclear factor E2-related factor 2; **ox-LDL,** oxidative low-density-lipoprotein; **PEITC,** phenethyl isothiocyanate; **PEPCK,** phosphoenolpyruvate carboxykinase; **PGC,** peroxisome proliferator-activated receptor gamma coactivator; **PI3K,** phosphatidylinositol 3-kinase; **PIKK,** phosphatidylinositol kinase-related kinase; **POT,** protection of telomeres; **RANKL,** receptor activator of NF-κB ligand; **Rheb,** Ras homolog enriched in brain; **ROS,** reactive oxygen species; **S6K,** S6 kinase; **SAM,** senescence-accelerated mouse; **SIRT,** sirtuin proteins; **SOD,** superoxide dismutase; **SREBP,** sterol-regulatory element-binding protein; **TF-1,** theaflavin; **TF-2a,** theaflavin-3-gallate; **TF-2b,** theaflavin 3′-gallate; **TF-3,** theaflavin-3,3′-digallate; **TERC,** telomerase RNA component; **TERT,** telomerase reverse transcriptase; **TNF-α,** tumor necrosis factor-α; **TOR,** target of rapamycin; **TRF,** telomeric repeat binding factor; **TSC,** tuberous sclerosis complex; **VCAM-1,** vascular cell adhesion molecule-1; **VSMC,** vascular smooth muscle cell

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## 1 Introduction

Aging is a normal biological process that follows a natural birth, growth, maturity to death in all species. For most species, progressive accumulation of damaged and defective cellular components, loss of cell or organ physiological function and failure of physical activity is occurred during aging process. However, the lifespan, rates of aging and decline are different among species because of genetic background and environmental effect. Over the past century, due to the improvement of the quality on diet and nutrition, and the advancement in biology, chemistry and medicine, we have extended the average lifespan in humans. The average life expectancy in the 18th century was 35 years and increased to about 67 years in the early 21st century. Even though the average lifespan have been extended, most elderly people still suffer from degenerative diseases caused by aging. Epidemiological reports have predicted that cancers due to aging will become a leading cause of disease and death in most developed countries [1]. Nevertheless, researchers found that Japanese females in Okinawa have the longest average lifespan with better health and lowest rates of cancer and cardiovascular diseases than other elderly people in the world [2]. This promotes us to focus on re-thinking aging and understanding biological mechanism/process of aging.

Many theories of aging have been proposed and some of the most widely accepted including DNA/genetic theory, free radical theory, neuroendocrine theory, membrane theory, Hayflick limit theory, telomerase theory and mitochondrial decline theory [3, 4]. However, yet no single theory is able to account for all views of aging. In the last two decades, scientists attempted to investigate the mystery of longevity and aging. With the first discovery of mutation in an individual gene may play a direct role in regulation longevity that also opens new perspectives for healthy aging [5]. Aging research has advanced rapidly by using many genetic and organism model, including yeast (*Saccharomyces cerevisiae*), nematode (*Caenorhabditis elegans*), flies (*Drosophila*) and rodents, and have been successfully identified certain genes with a profound influence on extending lifespan [6]. These longevity genes control aging and lifespan through multiple mechanisms that involve in a complex array of cellular functions [7]. Nowadays, a number of genes with genetic mutation or loss of function are found to affect lifespan. Inspiring, those longevity genes identified from different organism model are also found in human homolog [7, 8]. It is now clear that these genes directly and/or indirectly regulate aging and longevity through acting on cellular stress response, energy and metabolism control, growth modulation, gene dysregulation, genetic stability and nutrition sensing. In addition to genetic change, numerous signaling molecules and enzymes also play important roles in modulation of various important facets of cellular responses that can extend lifespan or retard aging such as insulin/insulin-like growth factor (IGF), target of rapamycin (TOR) and sirtuin (SIRT).

## 2 Signal transduction in aging

Although classical genetic mutation is critical for aging, evidence emerges that aging is controlled by genetic mechanisms involving complicated signal transduction pathways (Fig. 1). The coordinated action of these signaling networks systematically modulates cellular/organism homeostasis and function that response to stress, damage, nutrition and temperature. Imbalance of these signaling pathways has been noted in various organs and tissues during age-related pathology.

### 2.1 Mitochondria, reactive oxygen species (ROS) and oxidative stress

Multitudinous studies have linked oxidative stress to aging. In 1956, Harman advocated excessive ROS or increased oxidative stress leading to progressive and irreversible macromolecular oxidative damage in aging process which known as free radical theory of aging [9]. In general, ROS is generated from mitochondria, peroxisomes, cytosolic enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase as a result of intracellular metabolism. Among these, mitochondria electron transport chain (ETC) has been considered as the main source of ROS. Otherwise, increased ROS normally reduced by antioxidant defense includes enzymatic system such as catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and non-enzymatic system (glutathione, vitamins) to maintain physiological function. Several studies have evidenced the correlation among ROS, mitochondria and lifespan. Mutation of *CLocK (biological timing) abnormality (clk-1)* gene that encodes protein required in the biosynthesis of coenzyme Q resulted in increased 40% lifespan extension in *C. elegans* [10]. Mice with *clk-1* gene deletion also displayed an increased lifespan than wild-type mice [11]. Overexpression of *clk-1* gene shows a life-shortening phenotype in *C. elegans* [12]. Moreover, mutation of *iron sulfur protein (ISP)-1* of complex III shows an extended lifespan in *C. elegans* [13]. Deleted *shc66* gene in mice that encodes an Src homology 2 domain containing (SHC) transforming protein 1 within mitochondrial intermembrane space also caused an increased lifespan [14]. By contrast, *C. elegans* with mutant *ctl-1* gene that encodes cytosolic catalase displays a decreased lifespan about 25% [15]. Overexpression of *catalase* in mitochondria leads to reduction of oxidative stress and extension of lifespan [16]. Although some detailed mechanisms are still unclear, the mutation of those genes involved in mitochondria ETC is believed to extend lifespan through lowering metabolism and decreasing cellular damage caused by ROS and oxidative stress.

Numerous researches have documented the role of mitochondrial dysfunction in aging process. Oxidative stress derived from imbalance of ROS and anti-oxidant caused by

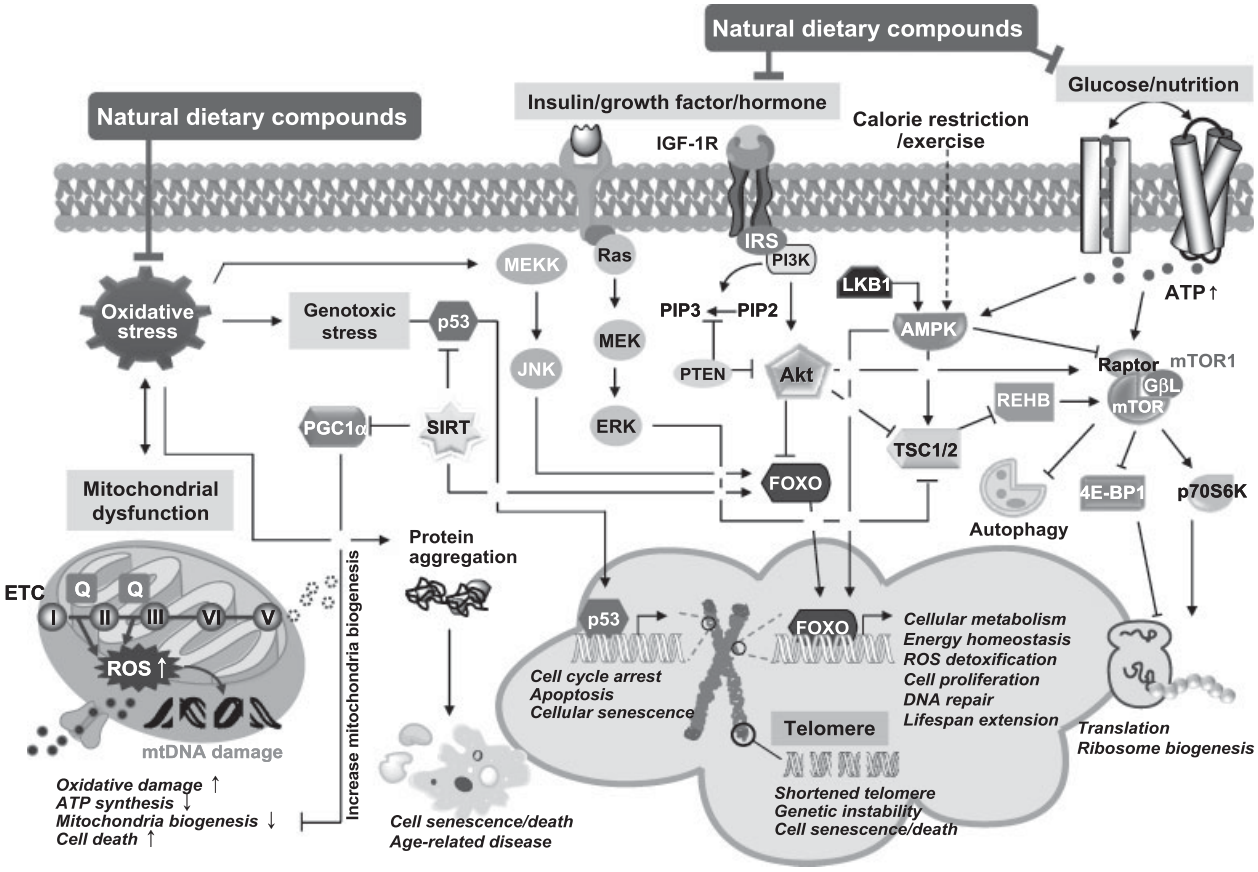



**Figure 1.** Current understanding of aging signaling pathways. Oxidative stress, mitochondrial dysfunction, genome instability, insulin/IGF signaling, nutrition sensing are integrated into complex aging signaling network that associated with alteration of cellular and organismal homeostasis, mitochondrial function, senescence, metabolism and stress resistance. In mammals, mitochondrial dysfunction caused by oxidative stress leading to increased ROS production from ETC or lipid peroxidation, damage to mtDNA results in mitochondria decline and cell death. Oxidative stress also induces cellular genotoxicity through p53-dependent growth arrest and apoptosis. Insulin/IGF-triggered aging signaling through activation of IRS and Ras which in turn up-regulation of several intercellular signaling molecules such as PI3K/Akt and MAPK kinases, subsequently phosphorylate/inactivate FOXO transcription factors, thus inhibit FOXO-dependent transcription. Nutrition stimulates activation of mTOR that further phosphorylation of p70S6 K and 4E-BP1 leading to promote translation. mTOR activation also suppresses autophagy in response to nutrient signaling. Under calorie restriction or starvation, activated AMPK blockes mTOR-dependent signaling through phosphorylation of raptor of mTOR1 complex or TSC1/2 that results in suppression of mTOR-medicated translation. AMPK also up-regulates FOXO activation and promotes its transcriptional activity. SIRT deacetylases regulate various molecules such as p53, PGC-1$\alpha$ and FOXO that involved in modulation of apoptosis/cell survival, nutrition signaling and gene transcription.

exogenous and endogenous sources with toxic effect for biological molecules including DNA, RNA and protein. Accumulated mitochondrial DNA (mtDNA) damage was found in age-dependent manner in various tissues, such as skeletal muscle, cardiac muscle and brain [17]. ROS causes the damage of ETC components, mtDNA and the loss of mitochondrial membrane function, results in further over-production of ROS and mitochondrial dysfunction, subsequently decreases mitochondria biosynthesis, ATP synthesis and ultimately cell death. In addition to mtDNA, increased oxidant-damaged nuclear DNA also occurs in aging cells and organisms [18]. ROS causes nuclear DNA damage that trigger DNA-damage response through p53-dependent pathways and leads to cell cycle arrest, apoptosis and cellular senescence. In mid-1960s, Hayflick showed that cellular senescence is a phenomenon that characteristic of isolated cells have a limited capacity to divide in culture by various irreversible damages, and is thought to involve in age-related pathology [19]. Despite p53 has been known as tumor suppressor, many studies indicated that it is also a key regulator of senescence in aging signaling by inducing downstream genes that participate in cell cycle arrest such as *p21* and *p16*, results in senescence growth arrest [20]. Another ROS caused toxic effect is irreversible protein oxidation and aggregation. The accumulation of oxidative intracellular protein and protein aggregates is known to result in loss of cellular function and associated with senescence and aging pathology in many organisms [21, 22].

ROS attacks on either backbone or specific amino acid side chains lead to oxidation of protein, results in formation of protein–protein cross-linkages and carbonyl derivatives or protein fragmentation. Since these oxidative proteins are conformationally unstable and readily aggregate to become insoluble complexes, eventually accumulate in cell and accelerates cellular senescence and death [22].

### 2.2 Insulin/IGF/hormone

The molecular connection between insulin/IGF-1 signaling and aging/longevity has been well documented in *C. elegans* and *Drosophila*, and many of its components are highly conserved in mammals [23, 24]. Mutation of *dauer formation* (*daf*)*-2* and *age-1* genes, which encode an insulin/IGF receptor and a catalytic subunit of phosphoinositide 3-kinase (PI3K), respectively, both lead to significant lifespan extension in *C. elegans* [25]. Soon after findings in *daf-2* and *age-1* gene mutation, the downstream signal cascade in regulation of aging by insulin/IGF has been elucidated [24]. Insulin/IGF and hormones (growth factor) initiate activation of both the PI3K/Akt and Ras/MEK/extracellular signal-regulated kinase (ERK) signalings that lead to phosphorylation and inactivation of Forkhead Box O (FOXO) transcription factors (DAF-16, orthologous to mammalian FOXO1, FOXO3a and FOXO4) that affect organismal longevity. FOXO family transcription factors are important for cellular response and maintenance of tissue homeostasis by transcription of genes involved in regulation of glucose metabolism (glucose-6-phosphatase; G6Pase, phosphoenolpyruvate carboxykinase; PEPCK), energy homeostasis (Agouti-related peptide; AgRP, neuropeptide Y; NPY), ROS detoxification (catalase, MnSOD), cell cycle arrest (p21, p27), apoptosis (Bim, Fas ligand; FasL), autophagy (light chain-3; LC-3, autophagy-related gene; Atg), DNA repair (growth arrest and DNA-damage inducible gene 45α; GADD45α) [26]. In insulin/IGF-trigger signaling, Akt-dependent phosphorylation of FOXO promotes their exclusion from nucleus to cytoplasm by binding to 14-3-3 protein that decreases the ability of FOXO binds to DNA, thus blocks downstream gene transcription [27]. Many genetic studies have confirmed the role of insulin/IGF-1 signaling and FOXO in longevity and age-dependent pathology. Mutation of *daf-2* gene in *C. elegans* demonstrates that FOXO (daf-16) is necessary for increase lifespan [26]. Overexpression of *FOXO* in *Drosophila* fat body also extends lifespan and decreases the stress-induced heart failure as well as age-related changes [28, 29]. In mice with mutated either *FOXO1* or *FOXO3*, displays diabetic phenotype or decreased glucose uptake [30].

Insulin/IGF/FOXO signaling also acts as stress and nutrition sensor through functional overlap between Jun *N*-terminal kinase (JNK) and AMP-activated protein kinase (AMPK) pathways that modulates cell metabolism and longevity [24]. Oxidative stress-activated JNK signaling also involved in FOXO regulation in several organisms, but with an opposing effect with PI3K/Akt signaling by phosphorylation of different sites [26]. In stress response, JNK either directly phosphorylates on FOXO proteins that promotes their translocation from the cytoplasm to the nucleus or phosphorylates on 14-3-3 protein that leads to its disassociation of FOXO proteins [31]. The study also indicates that activation of JNK extends lifespan and resistances to stress in *C. elegans* which is dependent on Daf-16 transcription factors [32]. Furthermore, the energy-sensing AMPK directly phosphorylates on FOXOs and leads to its nuclear translocation that modulates the transcriptional activity of FOXOs [33]. Regulation functions of FOXOs are also through different post-translational modifications such as deacetylation by SIRTs.

### 2.3 Nutrient sensing

Numerous studies have demonstrated that nutrient sensing signaling controls lifespan in many species. High-caloric diet has been known to decrease lifespan and accelerate age-associated pathology in various experimental models [6, 34]. Dietary or caloric restriction without malnutrition is widely known for the retardation of aging phenotypes and diseases as well as increase lifespan in many organisms such as yeast, worms, mice and monkeys [6]. A study in rhesus monkeys shows great impact on caloric restriction. Reduction of 30% daily caloric intake in rhesus monkeys demonstrates an 80% survived compared with 50% of control animals [35]. In addition, rhesus monkeys subjected to caloric restriction show decreased of age-associated pathologies including increased insulin sensitivity, reduced adiposity and oxidative damage and improved cardiovascular profiles, providing a significant effect of caloric restriction on reduction of aging and extension of lifespan [35, 36]. Dissection of the mechanism of nutrient sensing and caloric restriction, several signaling pathways are linked to coordinate modulation of each other that control cellular responses and organismal lifespan, including insulin/IGF, TOR, AMPK, SIRTs.

AMPK is a central energy switch that activates in response to alterations of nutrition and intracellular energy states in conditions of either lowered ATP or evaluated AMP within cell during nutrition deprivation, exercise or hypoxia [37]. Binding of evaluated AMP to Bateman domains of AMPK γ regulator subunit induces a conformational change and subsequently leads to activation of α catalytic subunit, whereas binding of ATP to AMPK shows an antagonistic effect [35, 36]. Studies have shown that the overexpression of *AMPK* in *C. elegans* increases lifespan [38]. Also, AMPK is necessary for increased lifespan in *C. elegans* during caloric restriction. The serine-threonine kinase liver kinase 1 (LKB1) is another upstream activator of AMPK through phosphorylation of AMPKα activation loop, a catalytic subunit of AMPK. The study indicates that the LKB1-AMPK signaling pathway serves as a metabolic checkpoint and has

crucial roles in glucose and lipid metabolism such as glucose uptake, glycolysis, gluconeogenesis, fatty acid oxidation, lipolysis and cholesterol and protein synthesis [35–37]. AMPK increases glucose uptake and metabolism by inducing translocation of glucose transporter type (GLUT) 4 to the plasma membrane through multiple kinase cascades that contribute to the regulation of insulin sensitivity. Phosphorylation of metabolic enzyme acetyl-CoA carboxylase 1 (ACC1) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) by AMPK promotes fatty acid oxidation and reduces cholesterol synthesis. In response to lower ATP levels, activation of AMPK may medicate the switch of fatty acid synthesis to oxidation. Moreover, AMPK also involves in the modulation of FOXO activity that connects the signaling between insulin/IGF and nutrient sensing [35–37]. Activated AMPK increases lifespan of *C. elegans* through FOXO-dependent manner in caloric restriction [39]. AMPK directly phosphorylates FOXOs caused by energy depletion and promotes a range of gene expression involved in resistance to stress and extend lifespan [37]. Furthermore, caloric restriction can prevent age-dependent mitochondrial dysfunction. Activation of AMPK increases the activities of citrate synthase and succinate dehydrogenase that may regulate mitochondrial biogenesis in response to energy depletion [40]. AMPK also phosphorylates peroxisome proliferator-activated receptor gamma coactivator (PGC) 1α, a key regulator of mitochondrial biogenesis and metabolism, which increases gene expression involved in mitochondrial biogenesis and fatty acid oxidation [40].

TOR pathway is another important nutrition sensor and growth factors that control cell growth, metabolism and lifespan across species includes eukaryotes [41]. TOR is highly conserved serine/threonine protein kinase belonging to the phosphatidylinositol kinase-related kinase (PIKK) family that first identified in yeast. In mammals, TOR proteins are found at the core of two distinct signaling complexes, mTORC1 and mTORC2. mTORC1 is nutrients/rapamycin-sensitive and central element in TOR signaling network that is composed of serine/threonine kinase mTOR, rapator (regulatory associated protein of mTOR), GβL (also known as mLST8) and deptor (only in mammals). By contrast, mTORC2 is nutrient-independent as well as insensitive to rapamycin. Studies in diverse model organism reflect extension lifespan in loss of function of TOR such as *C. elegans*, *Drosophila* and mice [41, 42]. mTORC1 acts as a key regulator in aging through acting as signaling core and medication of different signaling molecules. In response to a wide range of upstream inputs, activated PI3K/Akt phosphorylates tuberous sclerosis complex (TSC) 2 and ultimately lead to hyperactivation of mTORC1. Once activation, mTORC1 phosphorylates and inhibits eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) or activates ribosomal S6 kinase (S6 K, also known as p70S6 K) which in turn stimulates translation of cell cycle molecules such as cyclin D1 and myc, and ultimately leads to cell growth and proliferation [41, 42]. mTORC1 has been considered as another sensor of nutrient, regulates a variety of metabolic pathways at the transcriptional, translational, and post-translational levels in various tissue. Many reports show that mTORC1 activates the sterol-regulatory element-binding protein (SREBP) 1 transcription factor that drives sterol and lipid biosynthesis by promoting its post-translational processing via S6K1 in many mammalian cell types [43]. mTORC1 also activates hypoxia-inducible factor (HIF) in a 4E-BP-dependent manner that controls genes involved in cellular metabolism such as glycolytic enzymes and multiple members of the glucose transporter family [41]. AMPK is found to inhibit activation of mTOR in energy depletion through phosphorylation on two proteins, raptor and TSC2. Direct phosphorylation of two conserved serines in raptor by AMPK induced 14-3-3 bind to raptor and resulted in the suppression of mTORC1 kinase activity [42]. The inhibition of mTORC1 caused by the AMPK-mediated phosphorylation of raptor is required for cell-cycle arrest, thus slow cell growth in response to energy depletion [44]. AMPK phosphorylates on TSC2 at Ser1345 stimulates its Ras homolog enriched in brain (Rheb)-GTPase activating protein (GAP) activity that subsequently leads to the suppression of mTORC1 [45].

The mechanisms of mTOR on aging are contribute by the modulation of protein synthesis, ribosome biogenesis, metabolism and autophagy. Recent studies have exhibited the importance of mTOR signaling and translation in lifespan. Knockdown of *eukaryotic translation initiation factor 4 gamma* (*eIF4G*) and *p70S6 K* in *C. elegans* results in extension lifespan [46]. In *S6K1* gene deletion mice, against obesity and enhancing insulin sensitivity were occurred in high-fat diet administration [47]. However, knockout of *4E-BP1* and *4E-BP2*, function to repress translation by binding to eIF4E, displays obesity phenotype such as reduced lipolysis, increased fatty acid synthesis and insulin resistance [48]. Otherwise, autophagy is also required for lifespan extension that is evidenced by mutation of *beclin-1 (bec-1)*, *atg-18* and *unc-51* gene in *C. elegans* resulting in accelerated tissue aging and shortened lifespan [46]. In the presence of nutrients and growth factors, mTORC1 inhibits the initiation of autophagy through diverse mechanism while caloric restriction or inactivation of mTORC1 promotes autophagy that contributes to increase lifespan [46].

### 2.4 SIRTs

SIRTs are highly conserved protein deacetylases that identified early in yeast known as silent information regulator (Sir) 2. A number of studies suggest Sir2 to increase lifespan in many organismal models such as yeast, *C. elegans* and *Drosophila* [49]. There are seven SIRT proteins (SIRT1-7) in mammals that are either NAD-dependent deacetylases or protein ADP-ribosyltransferases and display diversity of functions [49]. Among them, SIRT1 is most extensively

studied for aging and longevity and implicated as a key mediator in caloric restriction. Studies have shown that *SIRT1* gene knockout mice display metabolic disorder and insulin resistance while overexpression of *SIRT1* improves metabolism with increased glucose tolerance resemble in caloric restriction [50]. Activation of SIRT1 by resveratrol contributes to the extended lifespan in high-fat diet mice [51].

Growing evidences exhibit that SIRT1 plays a major role in energy metabolism that regulate by cellular nutrient status, and then, trigger stress response and signaling to transcriptional level [51, 52]. Under fasting or caloric restriction, SIRT1 senses and responses to metabolic status such as increased intracellular levels of NAD, then activates and deacetylates many proteins involved in stress resistance, mitochondrial function, metabolism and aging. SIRT1 deacetylases and activates FOXO that increases FOXO-dependent transcriptional control of stress response genes [51]. SIRT1 regulates localization and transcriptional activity PGC-1α through deacetylation that promotes mitochondria biogenesis [51]. Deacetylation of p53 by SIRT1 reduces its transcriptional activity that suppresses stress-induced apoptosis and senescence [52]. Loss of function of SIRT1 in mouse fibroblast results in replicative senescence caused by genotoxic stress [51, 52]. Recent study demonstrated that AMPK regulates SIRT1 activity through increasing cellular NAD levels, leads to deacetylation of downstream targets such as PCG-1α and FOXOs that control energy metabolism [53]. Moreover, SIRT1 also deacetylates protein Ku70, p65 subunit of transcription factor nuclear factor-κB (NF-κB), peroxisome proliferator-activated receptor (PPAR) γand acetyl-CoA synthase 1 (AceCS1) that contributes to enhance DNA repair capacity, reduce ageing-inflammatory/immune responses, promote lipid metabolism [54–56]. In addition to SIRT1, other SIRT members are implicated in modulation of DNA repair, cell survival, metabolism control and mitochondrial function. For example, SIRT3 has been reported to regulate mitochondrial fatty acid oxidation and increases FOXO3-dependent gene expression that plays an important role in energy metabolism [57, 58]. SIRT4 is an ADP-ribosylates glutamate dehydrogenase (GDH) that controls insulin secretion in response to calorie restriction [59]. Although SIRT6-deficient mouse displays aging-phenotype and rapidly dies after birth, however, it is found to prevent telomere dysfunction and deacetylation of histone H3 lysine 9 (H3K9) at NF-κB target gene promoters that attenuate NF-κB signaling and might contribute to prevent aging [60].

### 2.5 Telomere

Shortening telomere length has been linked to cellular senescence and aging [61]. Telomeres are specialized repeated sequences (TTAGGG) located at the ends of liner chromosomes with primary function to protect DNA damage and maintain genome stability during replication. The end-replication problem is major cause of shortening telomere in DNA replication that owing to incapability of DNA polymerase to fully replicate the end of DNA strand. Telomere length is monitor by a specific proteins complex shelterin that consists of telomeric repeat binding factor (TRF) 1 and 2 as well as protection of telomeres (POT) that bind to chromosome end. Extension of telomeres requires of telomerase which is a ribonucleoprotein complex consisting of a catalytic subunit of component telomerase reverse transcriptase (TERT) for the synthesis of new telomeric DNA repeats, and telomerase RNA component (TERC) that function as a template [61]. Telomerase is highly expressed in cells with high mitotic activity such as progenitor, hematopoietic and immune cells by adding telomeric repeat to telomere thus maintain telomere length. However, telomerase activity do not express in most somatic cells that unable to maintain telomere length [62]. Hence, loss of 30–150 bp telomeres in each mitosis and cell division that leads to decrease ability for shelterin complex binding to telomeric DNA repeats, and ultimately, loss the protective function for genomic DNA [62]. This impairment results in chromosome instability and activation of p53-dependent pathway that cause cellular senescence and apoptosis. Accelerated aging phenotype is occurred both in *TERC* and *TERT* gene knockout mice [61, 63]. Moreover, it has been believed that telomeres are highly sensitive to oxidative damage because to its guanine-rich telomeric DNA that results in the acceleration of telomeres shortening [62].

Recent studies indicate that telomerase function is regulated by epigenetic mechanism such as histone methylation and deacetylation as well as CpG methylation. Deficient *DNA methyltransferase* (*DNMT)1*, or both *DNMT3a* and *DNMT3b* in mouse embryonic stem cells exhibit dramatically extended telomeres [64]. Increased telomeres length is found in histone methyltransferase-deficient MEFs. Elimination of acetylated histone H4 lysine 12 (H4K12) at telomeric heterochromatin caused reduction of telomere replication and recombination [65]. SIRT1 has been found to regulate telomere length and reduce telomere shortening associated through interaction with telomeric repeats during aging [66].

## 3 Aging-related diseases

Aging is known as a largest risk factor for development and progression of numerous diseases that cause most mortality in elderly people. Age-related changes impair cellular functions predispose to pathogenesis, finally lead to loss function of organs and tissues that display ageing phenotypes. A number of aging-phenotypes have been listed across species including sarcopenia, decreased fitness, reduced memory and learning, decreased mitochondrial function, genome instability and many age-related diseases.

### 3.1 Neurodegeneration

Increasing age is thought to be a major risk factor for aging-associated progressive neurodegenerative disorder such as Alzheimer's disease, Parkinson's disease amyotrophic lateral sclerosis and other nervous system pathologies. Accumulation of oxidatively damaged proteins and protein aggregates is a characteristic feature in brain during aging that contribute to neurological decline [67]. In Alzheimer's disease (AD), increased β amyloid (Aβ) formation resulted from cleavage product of amyloid precursor protein (APP) and aggregation which are neurotoxic to neuronal cells through induction of oxidative damage and neuroinflammation. Parkinson's disease is another neurodegenerative disorder in central nervous system that caused by accumulation of α-synuclein protein of Lewy bodies and loss of dopaminergic neurons [68]. Study demonstrates age-dependent accumulated Aβ is found in *C. elegans* whereas activation of DAF-16, is homologous to human FOXO1, and heat shock factor (HSF)-1 involved in insulin/IGF signaling reduce formation of toxic aggregates [69]. Similar effects are observed in transgenic mouse model of AD, showing reduced neuronal loss and inflammation by blockage of insulin/IGF signaling [69]. Epidemiological researches demonstrated that dietary with low calorie may reduce risk of both Alzheimer's disease and Parkinson's disease. Calorie restriction also decreases neuropathology both in APP transgeneic mice and Squirrel monkeys through reduced accumulated Aβin temporal cortex and correlated to SIRT1 protein expression [70]. Overexpression of *SIRT1* reduces Aβ and plaques in the brain of the transgeneic mice model of Alzheimer's disease [71].

Although oxidative stress and neuroinflammation are considered as etiology of neurodegenerative disorders, studies have indicated telomere and autophagy contribute to pathogenesis of Alzheimer's disease and Parkinson's disease. Shorter telomere length is found in lymphocytes that may impair immune function in patients with Alzheimer's disease [61]. Shorter mean telomere length is also found in Japanese male patients with Parkinson's disease [62]. Furthermore, knockdown *ATG5* in mouse neuronal cells increases protein aggregations. *ATG*-deficient *7* mice exhibit decreased motor function, accumulated protein inclusion bodies and neurodegeneration that contribute to reduced autophagy [72]. Blocking mTOR signaling by rapamycin reduces Aβ levels and improves cognitive function that may caused by increased autophagy in Alzheimer's disease mouse model [73].

### 3.2 Atherosclerosis and cardiovascular disease

Atherosclerosis and cardiovascular disease are systemic diseases that most affected during aging process. A number of risk factor implicated in pathogenesis of cardiovascular disease includes chronic inflammation, hypertension, dyslipidaemia, hypercholesterolemia, glucose tolerance and metabolic symptoms that all attribute to aging. Vascular endothelium is important for regulation of vascular homeostasis and blood pressure; however, endothelial dysfunction is known as an early symptom in atherosclerotic diseases caused by oxidative stress, inflammatory condition and high level of cholesterol and oxidative low-density-lipoprotein (ox-LDL) leading to formation of atherosclerotic plaques [74]. Increased oxidative stress is considered a major mechanism involved in the pathogenesis of endothelial dysfunction that impaired endothelium-dependent vasodilation. It has been shown that detectable excessive ROS is found in pre-atherosclerotic blood vessels. In addition, autophagy might possess protective effect for plaque cells against oxidative stress through facilitating the removal of damaged organelles during atherosclerosis [75]. Vascular endothelial cell proliferation, migration and damage caused by advanced glycation end-products (AGEs) is found in atherosclerosis whereas increased microtubule-associated protein 1 light chain 3-II (LC3-II) results in autophagy in human umbilical vein endothelial cells (HUVECs) that protects against AGEs-injury [76]. Activation of IGF-1R signaling and downstream Akt/FOXO3a is observed in aged rats that contributes to influence aortic vascular smooth muscle cell (VSMC) function and atherosclerosis [77]. Deficient *SIRT1* and *SIRT-7* results in cardiac defects in mice that contributes to hyperacetylated p53 [49]. In human umbilical vein endothelial cells, downregulated SIRT1 induces premature senescence while activation of SIRT1 prevents oxidative stress-induced premature senescence [78]. Deacetylation of endothelial nitric oxide synthase (eNOS) by SIRT1 is found in mice with caloric restriction that leads to improvement of endothelium-dependent vasodilation [78]. Several studies have indicated the connection between telomere length in peripheral blood mononuclear cells and cardiovascular disease. Shortened telomere lengths in patients with cardiovascular disease may contribute to age-dependent loss of function in vascular cells [61]. Telomere shortening caused cell senescence is a possible mechanism to the development of atherosclerosis. Moreover, telomere length shortening is associated with increased oxidative stress and hypertension [61]. *TERT* gene knockout mice are found to sensitive oxidative stress and susceptible to the development of stroke [62].

### 3.3 Diabetes

Advanced age is associated with insulin resistance and increased risk of diabetes. Aging-related loss of muscle mass, decreased β-cell proliferation and dysregulation of insulin signaling result in insulin resistance and glucose intolerance that promote development of diabetes and decrease lifespan [24]. Studies have demonstrated that insulin receptor substrate (IRS) 2 signaling, a downstream adaptor protein of IGF-1R, is important for regulation of

β-cell function [24]. Increased IRS-2 expression has been found to promote β-cell growth and survival whereas in the absence of IRS-2 results in spontaneous apoptosis of β-cells thus lead to loss of β-cells and diabetes [79]. Moreover, accumulated advanced AGEs are central marker in diabetes [80]. Increased methylglyoxal (MG) generated by nonenzymatic reactions of carbohydrates and oxidized lipids reacts to amino and sulfhydryl group of proteins to form AGEs that impair protein function is found under hyperglycemic conditions in diabetes. In *C. elegans*, overexpression of *glyoxalase-1* gene, involved in MG metabolism, reduces AGE formation and increases lifespan [81]. In *glyoxalase-1* transgenic rats, overexpression of glyoxalase-1 against streptozotocin-induced diabetes is evidenced by decreased plasma AGEs and oxidative stress [82]. Otherwise, glucose intolerance, increased β-cell death and decreased proliferation are found in *Atg7* gene knockout mice. Because Atg7 is necessary for the formation of autophagosomes, thus indicating regulation of autophagy may play a role in diabetes [83]. Telomere shortening is also a risk factor of diabetes. Patients with type II diabetes displayed shorter telomere length in leukocyte and correlated to increased oxidative stress which is known to cause telomere shortening [84]. In *TERT*-deficient mice, reduced islet size (loss of pancreatic β-cells) leads to impairment of insulin secretion and glucose intolerance [85].

### 3.4 Osteoporosis and osteoarthritis

Both osteoporosis and osteoarthritis are classical age-related disorders. Osteoporosis is characterized by loss of bone mass, decreased bone density, increased bone fragility and resulting in fractures. Although it has been known that the oestrogen deficiency is a most important factor of osteoporosis pathogenesis, emerging clinical and molecular evidences suggest that aging-associated immunosenescence and inflammation might have pivotal role in osteoporosis [86]. Immune system in mammals becomes less effective with advancing age. Aged-related dysregulated inflammation from recruitment of immune cells produces excessive proinflammatory cytokines which trigger activation and differentiation of osteoclast, and decrease osteoblastogenesis that impairs bone remodeling. In addition, increased ROS from aging process also influence the generation and survival of osteoclasts. FOXO1 is found to regulate osteoclast proliferation and resistance to oxidative stress through interferes with p53 in osteoblast *FoxO1* deletion mice [87]. Collagen cross-links resulted from accumulation of AGEs during aging is also considered as another pathological mechanism of osteoporosis [88]. Bone loss and osteoporosis phenotype are observed in telomere-deficient mice [89]. Osteoarthritis is a cartilage degenerative disorder that characterize by joint inflammation. Studies exhibit that replicative limitation and oxidative stress result in the senescence-associated phenotype of chondrocytes and increase production of cytokines. Ex vivo studies show that decreased activity of mitochondrial electron transport chain activity, mutation of mtDNA and high levels of proinflammatory mediators may impair chondrocyte biosynthesis and increased chondrocyte apoptosis [90]. Shortening telomere in chondrocytes also contributes to osteoarthritis that occurred in older adults [61]. Recent evidences demonstrated that Beclin1 and LC3 protein expression are reduced in osteoarthritis chondrocytes indicating autophagy may protect chondrocytes death that acts as a homeostatic mechanism in normal cartilage [91].

### 3.5 Metabolic syndrome

Epidemiological research exhibits the correlation of the prevalence of metabolic syndrome to elderly population, including obesity, hypertension, hyperinsulinemia, fatty liver disease, diabetes and chronic kidney disease [92]. In the case of obesity, dramatic advances support that aging is frequent associated with obesity with a chronic low-grade inflammation. Release of cytokines from preadipocytes influences the function of fat tissue and recruitment of immune and inflammatory cells that promotes inflammatory state. It has been found that tumor necrosis factor (TNF)-α and interleukin (IL)-6 are highly secreted in preadipocytes from older rats and affect adipogenesis [93]. Increased TNF-α, an adipokine, resulted from obesity interferes with insulin/IGF signaling and decrease in glucose uptake and expression of GLUT4 that lead to insulin resistance. In aged rats, obesity is associated with increased insulin resistance [94]. In adipose tissue of specific insulin receptor gene knockout mice, reduced fat mass and metabolic abnormalities are found that protect against age-induced obesity and increase lifespan [95]. Decline in preadipocyte replication is occurred with aging that impair adipocyte function in adipose tissue. Adipocytes senescence is associated with decreased adiponectin production, increased lipid accumulation, adipose inflammation and insulin resistance. A direct connection of obesity and age is evidenced by high calorie diet accelerates age-related phenotypes and decreases lifespan in various organism model [34]. By contract, calorie restriction extends lifespan in organisms ranging from yeast to mammals.

## 4 Natural dietary compounds: Promising candidate for anti-aging

Despite aging as a multifactorial process, numerous identified longevity/aging genes and verified signaling cascades in different species have provided novel strategy for anti-aging and prolonging lifespan. In anti-aging research, caloric restriction is most widely accepted for health improvement and lifespan extension. However, much attention has been focused on natural phytochemicals in our

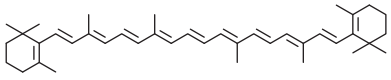
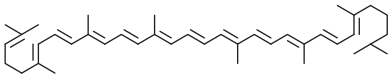
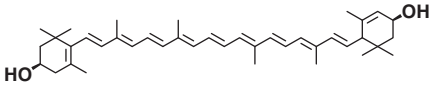
daily food intake. Natural dietary compounds possess broad biological activities including anti-oxidative, anti-inflammatory, detoxification, regulating signaling pathway, modulation of enzyme activity that have been believed as promising approach for anti-aging. Many dietary natural compounds have been demonstrated to have protective action on aging-associated pathology through targeting specific signaling and molecules which involved in cellular metabolism, nutrition sensing, mitochondrial biogenesis, cell survival/death, senescence and stress resistance. Most of them exhibit ability in increasing lifespan and preventing, retarding or improving age-related diseases in experimental organism/animal model. The molecular mechanisms of anti-aging for selected natural dietary compounds are highlighted below.

### 4.1 Carotenoids

Carotenoids are naturally occurring fat-soluble pigments that rich in many plants, fruits and flowers. Carotenoids are known to possess powerful anti-oxidant properties characterized by conjugated double bonds of polyene backbone such as β-carotene, lycopene and lutein. Their potent anti-oxidative activity might provide the mechanism for anti-aging and prevent age-related disease. Among carotenoids, β-carotene is the most abundant carotenoid and anti-oxidant in vegetables and fruits (Table 1). In vitro study shows that β-carotene reduces genotoxicity against $H_2O_2$-induced sister chromatid exchanges in Chinese hamster ovary cells [96]. Diabetic rats feeding with β-carotene reduce lipid peroxidation and increases SOD activity in kidney. The glucose tolerance also improved by β-carotene that indicating the ability of dietary β-carotene on suppression of diabetic symptoms [97, 98]. Researchers have found that diabetes mellitus is a major risk factor for atherosclerosis that causes most morbidity and mortality. Dietary supplemented with β-carotene to patients with diabetes mellitus reduced the susceptibility of LDL oxidation, thus may decrease the pathogenesis of atherosclerosis in diabetic patients [99]. Insulin resistance is a physiological condition and a characteristic in most metabolic syndrome such as obesity which results from excessive inflammatory cytokines production in adipocytes and reduces glucose uptake. β-Carotene increases the gene expression of adiponectin and GLUT4 that against TNF-α-induced insulin resistance in 3T3-L1 adipocytes [100].

Lycopene is a highly unsaturated 40-carbon molecule that contains 11 conjugated and 2 unconjugated double bonds

**Table 1.** Molecular mechanisms of anti-aging/aging-related diseases by carotenoids

| Group | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|
| Carotenoids | β-Carotene |  | Carrots, pumpkin and leafy green vegetables | (i) Against $H_2O_2$-induced chromatin damage | [96] |
| | | | | (ii) Inhibits lipid peroxidation, increases MnSOD activity and improves glucose tolerance in diabetic rats | [97, 98] |
| | | | | (iii) Reduces LDL oxidation in diabetic patients | [99] |
| | | | | (iv) Improves insulin sensitivity in insulin-resistant adipocytes | [100] |
| | Lycopene |  | Tomatoes and papaya | (i) Reduces mitochondrial dysfunction and oxidative stress as well as increases antioxidant in rats | [101, 102] |
| | | | | (ii) Inhibits high-fat diet-induced atherosclerosis in rabbits and reduces foam cells formation induced by ox-LDL | [104, 105] |
| | | | | (iii) Decreases $H_2O_2$-induced p53 expression and oxidative damage in human endothelial cells | [103] |
| | Lutein |   | Spinach and kale | (i) Reduces aortic cholesterol levels, cytokines production and lipid peroxidation in guinea pigs | [106] |
| | | | | (ii) Decreases diabetes-induced lipid peroxidation in cortex in rats | [107] |

that found in tomato, watermelon, papaya and orange grapefruit, and has been believed as potent anti-oxidant. Dietary lycopene is found to have neuropreventive effect by reduction of ROS production and increases of mitochondrial complex and SOD activity that prevent neurodegeneration such as Parkinson's disease [101, 102]. Several in vitro and in vivo studies suggest the anti-atherosclerotic property of lycopene. Lycopene protects $H_2O_2$-induced apoptosis through down-regulation of p53 expression that increases cell survival in human endothelial cells [103]. High-calorie diet is known to increases age-related pathology such as obesity and atherosclerosis. Male rabbits administrated with lycopene reduce atherosclerotic plaque and pathologic changes of the aorta that attributes to decreased ox-LDL, triacylglycerol and foam cell formation [104, 105].

Lutein is widely used to protect against age-related macular degeneration and eye conditions. Supplementation of lutein is found to lower high-cholesterol diet-induced cholesterol and malondialdehyde levels in aortas and reduce atherosclerotic pathology in guinea pigs [106]. Diabetic rats feeding lutein also show a neuroprotective effect by decreasing lipid peroxidation in cortex [107].

### 4.2 Flavonoids and flavonolignans

Flavonoids are ubiquitous in fruits, vegetables, nuts and seeds. They can be classified into seven groups: flavones, flavanones, flavonols, flavanols (catechins), flavanonols, isoflavones and anthocyanidins. Modifications of functional group by hydroxylation, methoxylation or glycosylation provide various pharmacological properties of flavonoids. So far, there are at least 2000 naturally occurring flavonoids identified and many of them exhibit a broad spectrum of biological properties. Epidemiological studies suggest that dietary flavonoids have widespread beneficial effects including that they reduce chronic diseases and improve health (Table 2).

Quercetin, a flavonol is rich in onions, broccoli and leafy green vegetables It has been found to possess many biological activities. Mitochondrial dysfunction is one of causes for cellular senescence. Quercetin protects against $H_2O_2$-induced cell death and increases mitochondrial biogenesis through up-regulation of PGC-1 and SIRT1 that regulates mitochondrial activity and mtDNA, thus may prevent cellular senescence [108, 109]. Feeding quercetin to old mice reduces high-cholesterol-induced Aβ deposits and improves behavioral performance through modulation of AMPK, HMGCR and ACC that may decrease cholesterol levels and prevent age-associated neurodegeneration [110]. Quercetin suppresses osteoclast-like cell formation and differentiation that contributes to prevent bone resorption [111]. In additional, quercetin and kaempferol, another flavonol present in broccoli, tea and various vegetables, both are found to increase lifespan in *C.elegans* by activation FOXO that increases stress-resistance ability to against oxidative stress [112, 113]. Kaempferol is considered to improve diabetic condition by protecting kidney. Kaempferol has been reported to protect against AGEs-induced NF-κB-dependent inflammatory cytokines expression in aged rat kidney [114]. Kaempferol also protects glucose-induced oxidative damage and cell death in pancreatic β cells [115].

Apigenin belongs to flavones and is most prevalent in parsley and celery, is considered to regulate high-glucose-induced dysfunction. Apigenin reduces hyperglycaemia in diabetic mice that attributes to decrease glucose levels and increase insulin in serum by inhibition of hepatic G-6-Pase activity [117]. Moreover, apigenin inhibits high-glucose-induced cell adhesion to endothelial cells through suppression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression that prevents endothelial cells dysfunction and diabetes-associated atherosclerotic pathology [119]. Another flavone luteolin is most often present in thyme and other plants including brussels sprouts, cabbage, onion, broccoli and cauliflower. Luteolin also reveals anti-aging activity such as increasing insulin sensitivity, regulating fatty acid metabolism and anti-atherosclerosis. It modulates insulin-induced relaxation in rat aorta by regulating IRS-1/Akt signaling and increasing NO production, thus improves insulin resistance in endothelium [118]. In addition, luteolin attenuates ox-LDL-induced monocytes adhesion to HUVECs and may prevent endothelial dysfunction-related atherosclerosis [119]. Luteolin strongly decreases lipid accumulation by activation of AMPK and following inhibition of SREBP-1c, a transcription factor involved in regulation of a range of enzymes required for endogenous cholesterol, fatty acid, triacylglycerol and phospholipid synthesis such as fatty acid synthase (FAS) [120].

Nobiletin is a polymethoxyflavone that is rich in citrus peel and with many biological activities. In obese *ob/ob* mice model, leptin-deficient (*ob/ob*) transgenic mice, is known to develop severe type 2 diabetes and hypercholesterolemia. Dietary nobiletin improves insulin resistance by increasing GLUT1 and GLUT4 expression in adipose tissue and muscle [121]. Feeding nobiletin also reduces Western diet-induced atherosclerosis in the aortic sinus through increasing insulin sensitivity and suppression of lipid accumulation via up-regulation of PGC-1α that attributes to enhanced fatty acid oxidation [122]. Baicalein is one of flavones that naturally occurred in the roots of *Scutellaria baicalensis* which displays protective effect against oxidative stress. Pretreatment of neuron cells and retinal pigment epithelium cells with baicalein prevents the $H_2O_2$-induced oxidative damage, mitochondrial dysfunction and cell death that may prevent age-associated eye pathology and neurodegeneration [123, 124]. Diosmetin is a methoxy flavone commonly presented in citrus fruits, reduces AGEs-induced inflammatory cytokines production thus may reduce neuroinflammation [125].

Green tea or black tea is the most popular beverage and has been shown to possess wide health benefits due to their

**Table 2.** Molecular mechanisms of anti-aging/aging-related diseases by flavonoids and flavonolignans

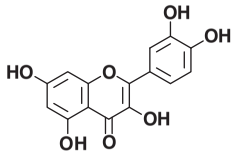
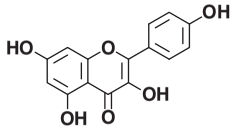
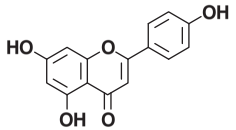
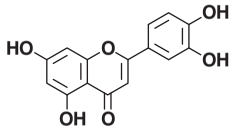
| Group | Sub-class | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|---|
| Flavonoids | Flavonols | Quercetin |  | Onion and broccoli | (i) Reduces $H_2O_2$-induced mitochondrial dysfunction and cellular senescence | [108] |
| | | | | | (ii) Increases mitochondrial biogenesis through up-regulation of PGC-1α, SIRT1 and mtDNA in mouse brain and muscle | [109] |
| | | | | | (iii) Protects high-fat diet induced neurotoxicity by activation of AMPK, increases HMGCR and ACC as well as decreases eIF2α phosphorylation in old mice | [110] |
| | | | | | (iv) Suppresses activation and differentiation of osteoclasts | [111] |
| | | | | | (v) Extends lifespan and increases stress resistance in *C. elegans* through activation of FOXO | [112] |
| | | Kaempferol |  | Broccoli and tea | (i) Decreases oxidative stress and increases survival through activation of FOXO in *C. elegans* | [113] |
| | | | | | (ii) Suppresses aging-associated AGE formation and NF-κB signaling in aged rat kidney | [114] |
| | | | | | (iii) Reduces glucose-induced oxidative cell damage and dysfunction in pancreatic β cells | [115] |
| | Flavones | Apigenin |  | Parsley and celery | (i) Decreases hepatic G-6-Pase activity, lipid peroxidation and increases antioxidant status in diabetic mice | [116] |
| | | | | | (ii) Reduces high glucose-induced adhesion molecule (ICAM-1 and VCAM-1) expression in human endothelial cells | [117] |
| | | Luteolin |  | | (i) Increases insulin sensitivity through modulation of IRS-1/Akt signaling in rat aorta | [118] |
| | | | | | (ii) Attenuates ox-LDL uptake and decreases monocyte adhesion through reducing LOX-1 expression in human endothelial cells | [119] |
| | | | | | (iii) Reduces lipid accumulation through activation of AMPK, ACC-1, CPT-1 and down-regulation of SREBP-1c and FAS | [120] |

**Table 2.** Continued

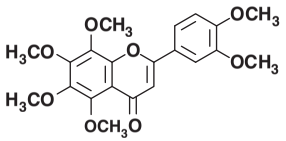
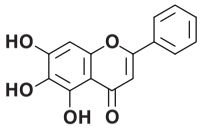
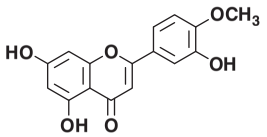
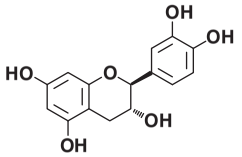
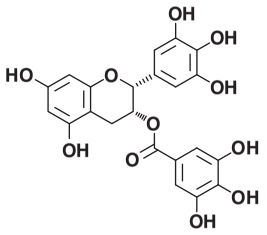
| Group | Sub-class | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|---|
| | | Nobiletin |  | Citrus peels | (i) Reduces hyperglycemia by increasing Glut4 in WAT and muscle in obese diabetic ob/ob mice | [121] |
| | | | | | (ii) Reduces atherosclerosis by up-regulation of PGC-1α that decreases TG accumulation, and increases glucose tolerance in mice | [122] |
| | | Baicalein |  | Baical Skullcap | (i) Protects $H_2O_2$-induced oxidative damage, mitochondrial dysfunction and cell death | [123] |
| | | | | | (ii) Against $H_2O_2$-induced ROS production and increases cell survival in human retinal pigment epithelium cells | [124] |
| | | Diosmetin |  | Citrus lemon | (i) Reduces AGEs-induced NO and TNF-α production | [125] |
| | Flavanols (catechins) | Catechin |  | Tea | (i) Decreases Aβ oligomer formation in hippocampus by down-regulation of PKA/CREB signaling in SAMP8 mice | [127] |
| | | | | | (ii) Reduces brain senescence through decreasing carbonyl proteins and increasing GPx activity in aged SAMP10 mice | [128] |
| | | Epigallocatechin-3-*O*-gallate (EGCG) |  | | (i) Prolongs lifespan through activation of FOXO in *C. elegans* | [129] |
| | | | | | (ii) Reduces Aβ deposits in transgenic *C. elegans* and improves cognitive impairment in Alzheimer transgenic mice | [130] |
| | | | | | (iii) Reduces glucotoxicity-induced pancreatic β cell death and increases insulin sensitivity through AMPK signaling | [131] |
| | | | | | (iv) Improves insulin resistance by up-regulation of AMPK and IRS-1, PI3K/Akt and GLUT4 translocation in skeletal muscle and adipose tissue | [132, 133] |
| | | | | | (v) Up-regulates ACC through LKB1/AMPK signaling in 3T3-L1 cells | [134] |

**Table 2.** Continued

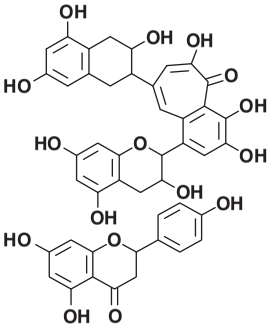
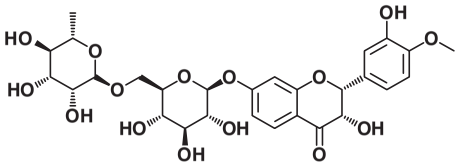
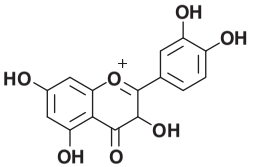
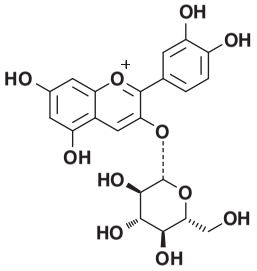
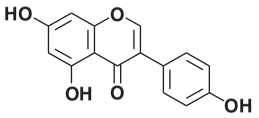
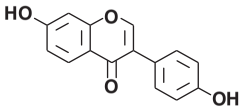
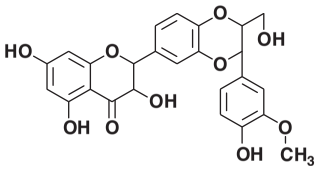
| Group | Sub-class | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|---|
| | | Theaflavin |  | Black tea | (i) Reduces lipid accumulation through LKB1/AMPK medicated decreasing ACC activity and fatty acid synthesis | [135] |
| | | | | | (ii) Attenuates atherosclerotic lesion in aorta through reduction of ROS and inflammation as well as up-regulation of eNOS | [136] |
| | Flavanones | Naringenin |  | Citrus | (i) Reduces high-fat diet-induced atherosclerosis by inhibition of immune cell adhesion in vascular wall in mice | [137] |
| | | | | | (ii) Increases glucose uptake through activation of AMPK in muscle cells | [138] |
| | | | | | (iii) Regulates lipid metabolism by decreasing FAS and HMGR as well as increasing fatty acids oxidation | [139] |
| | | Hesperetin |  | Citrus | (i) Protects $H_2O_2$-induced neuronal apoptosis through up-regulation of PI3K/Akt and ERK1/2 survival signaling | [140] |
| | | | | | (ii) Increases SOD activity and decreases carbonyl content in brains of mice | [141] |
| | Anthocyanidins | Cyanidin |  | Cherries and strawberries | (i) Reduces $H_2O_2$-induced cellular senescence and increases cell viability | [142] |
| | | Cyanidin 3-glucoside |  | | (i) Reduces $H_2O_2$/TNF-$\alpha$ induced insulin resistance and increases glucose uptake in adipocytes | [143] |
| | | | | | (ii) Suppresses high-fat diet-induced insulin resistance through JNK-dependent FOXO1 activation in obese and *db/db* mice | [144] |

**Table 2.** Continued

| Group | Sub-class | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|---|
| | Isoflavones | Genistein |  | Soybean | (i) Increases mitochondrial biogenesis by up-regulation of PGC-1α and SIRT1 | [145] |
| | | | | | (ii) Improves insulin resistance via up-regulation of IRS, JNK and GLUT1 | [146] |
| | | | | | (iii) Increases pancreatic β cell proliferation in diabetic mice | [147] |
| | | | | | (iv) Reduces Aβ-induced mitochondrial damage by increasing SOD expression and decreasing lipid peroxidation | [148] |
| | | Daidzein |  | | (i) Increases mitochondrial biogenesis by up-regulation of PGC-1α and SIRT1 | [145] |
| | | | | | (ii) Increases insulin-stimulated glucose uptake by up-regulation of GLUT4 and IRS1 in adipocytes | [150] |
| Flavonolignans | | Silibinin |  | Milk thistle | (i) Reduces senescence and improves recognition memory by increasing autophagy and decreasing lipid peroxidation in old mice | [151] |
| | | | | | (ii) Reduces Aβ-induced neurotoxicity via decreasing ROS production in SH-SY5Y cells | [152] |
| | | | | | (iii) Protects cardiac myocyte death through decreasing MDA levels and increasing SOD activity as well as up-regulation of SIRT1 | [153] |

bioactive compounds including catechins and theaflavins. In ageing research, senescence-accelerated mouse (SAM) has been successfully developed to investigate the spontaneous aging and age-related diseases that characterized by irreversible advance of senescence, short life span and various aging pathologic phenotype [126]. When SAMP8 mice, a strain of SAM characterized by cognitive impairment and abnormal Aβ accumulation in brain, were giving green tea catechins in drinking water for 6 months resulted in strong decrease of Aβ oligomers in the hippocampus and improvement of learning and memory decline [127]. In addition, green tea catechins administration reduces carbonyl protein levels in the brain of aged SAMP10 mice [128]. Epigallocatechin gallate (EGCG) is the most abundant catechin component in green tea that exhibits longevity effect evidenced by extending lifespan in *C. elegans* via activation of FOXO/DAF-16 transcription factor and its downstream gene, *sod-3* [129]. EGCG also suppresses Aβ deposits and oligomerization in *C. elegans* that prevents neurodegenerative change [130]. Pancreatic β cell dysfunction and insulin resistance in adipocyte and muscle are contributing to diabetes and metabolic disorders whereas EGCG could ameliorate metabolic syndrome through the modulation of AMPK. EGCG protects glucose-induced pancreatic β cell death and up-relation of IRS as well as AMPK signaling that increases insulin sensitivity in rat pancreatic β cells [131]. EGCG also improves insulin resistance through up-regulation of AMPK and PI3K/Akt signalings that promote GLUT4 translocation and glucose uptake in adipocyte and muscle cells [132, 133]. Moreover, EGCG activates LKB1/AMPK pathway and downstream ACC-1 that increases mitochondrial fat oxidation in 3T3-L1 adipocytes and mice liver [134]. Theaflavins include theaflavin (TF-1), theaflavin-3-gallate (TF-2a), theaflavin 3′-gallate (TF2b) and theaflavin-3,3′-digallate (TF-3) are major polyphenols in black tea. Both in vitro and in vivo studies exhibit that black tea theaflavins are able to reduce lipid accumulation by suppression of FAS and ACC activity via activation of LKB1/AMPK that prevents fatty liver and obesity [135]. Dietary feeding black tea theaflavins also attenuates atherosclerosis through protection of endothelial dysfunction caused by ROS and aortic inflammation in mice [136].

Flavanones such as naringenin and hesperetin are rich in citrus fruit and peel and appear to prevent atherosclerotic pathogenesis. In high-fat diet-induced hypercholesterolemia mice, feeding naringenin reduces endothelial dysfunction, smooth muscle cell proliferation and immune cell adhesion and infiltration in the intima that prevented diet-induced atherosclerosis [137]. Naringenin also increases glucose uptake by activation of AMPK in muscle cell [138]. In addition, naringenin promotes lipid metabolism in rat liver by increasing fatty acid oxidation and inhibition of FAS and HMGR that maintain lipid homeostasis [139]. Another citrus flavanone hesperetin displays neuroprotective effect against oxidative stress. Cortical neurons pretreatment with hesperetin have been found to protect against $H_2O_2$-induced apoptosis through increasing survival signals such as PI3K/Akt and ERK1/2 [141]. Mice feeding hesperetin reduces oxidative damage such as carbonyl protein level and activation of catalase and SOD that deceases neurotoxicity in the brain [141].

Anthocyanidins are plant pigment commonly occurred in fruits and vegetables such as blueberries and grapes. Cyanidin has been reported to have anti-oxidant and radical-scavenging actions that contribute to protect $H_2O_2$-induced cellular senescence in vitro [142]. Cyanidin 3-glucoside improves $H_2O_2$ and TNF-α-induced insulin resistance by inhibiting IRS1 and JNK signaling that promotes glucose uptake in adipocytes [143]. Cyanidin 3-glucoside also increases insulin sensitivity by down-regulation of JNK that promotes FOXO1 activation in adipose tissue in high-fat diet fed and *db/db* diabetic mice [144].

Isoflavones such as genistein and daidzein from soybean are a subclass of flavonoids and considered as phytoestrogens that show potentially beneficial effects. Both genistein and daidzein increase mitochondrial biogenesis through activation of PGC-1α and SIRT-1 [145]. Several studies have shown the anti-diabetic effect of genistein. Genistein treatment increases insulin sensitivity through inactivation of IRS-1 and JNK as well as up-regulation of GLUT1 [146]. Otherwise, feeding genistein increases pancreatic βcell proliferation in insulin-deficient diabetic mice [147]. The neuroprotective effect of genistein is documented by in vitro and in vivo studies. Genistein prevents Aβ-induced oxidative mitochondrial damage and increases SOD expression both in PC12 cells and rats and improves learning and memory deficits in rats [148, 149]. Another isoflavone daidzein demonstrates enhancement of glucose uptake through increasing GLUT4 in adipocytes [150].

Silibinin is a flavonolignan and major constituent of the seeds of milk thistle plant *Silybum marianum*. The crude form of silibinin, silymarin, is most known to have potent hepatoprotective effect and largely nontoxic. The anti-senescence efficacy of silibinin has been documented in improvement of memory recognition in aged mice by reducing lipid peroxidation and increasing autophagy [151]. Silibinin also protects Aβ-neurotoxicity by inhibition of Aβ aggregation and $H_2O_2$ production that prevents amyloid plaque formation [152]. In rat cardiac myocytes, treatment with silibinin reduces cytotoxicity by up-regulation of SIRT1 thus blocks mitochondrial death signaling [153].

### 4.3 Isothiocyanates

Isothiocyanates are naturally occurring sulfur-containing compounds found in cruciferous vegetables such as broccoli, cabbage and brussels sprouts. Isothiocyanates including sulforaphane, benzyl isothiocyanate (BITC) and phenethyl isothiocyanate (PEITC) are derived from the hydrolysis of glucosinolates and glucotropaeolin by myrosinase, an

enzyme in plants. Studies demonstrate that isothiocyanates are strong activators of nuclear factor E2-related factor 2 (Nrf2) which involved in induction of phase II enzymes that exerts as promising chemopreventive agents. The decline of Nrf2 has been reported to result in reduced glutathione synthesis and stress resistance in mice during aging process [154] (Table 3). Sulforaphane is effective in protecting various cell types from ROS-induced cytotoxicity. It has been found that sulforaphane protects $H_2O_2$, cytokine or electrophilic stress-induced cell death through activation of Nrf2-dependent phase 2 enzymes that increases stress resistance in primary neuronal cells, aortic smooth muscle cells and human chondrocytes [155–157]. In addition, PEITC displays anti-osteoclastogenesis effect by blocking receptor activator of NF-κB ligand (RANKL), a member of the tumor necrosis family, –triggered downstream MAPK signaling that promotes the differentiation of hematopoietic cells into bone-resorbing osteoclasts, thus prevents bone resorption [158].

### 4.4 Terpenoids

Terpenoids are natural substances occurring in many types of leaves, flowers and fruits. Monoterpenes such as limonene, and menthol consist of two isoprene units, and are major constituent of essential oils obtained from citrus fruits, cherries, spearmint dill, caraway, apricots and grapes. Rats supplemented with d-limonene result in reduced high-fat diet-induced hepatic lipid level, lipid peroxidation, increased phase II enzymes activities, and decreased liver and pancreas pathology that against metabolic syndrome [159] (Table 3). Menthol is found to suppress bone resorption by inhibition of osteoclastogenesis via interfere with RANKL signaling [160]. Retinoic acid is a diterpene and a major component of vitamin A. It has been known to offer protection against age-related macular degeneration. Retinoic acid also acts on modulation of glucose metabolism by stimulating glucose uptake through activation of AMPK signaling in skeletal muscle cells [161]. In diabetic ob/ob mice, dietary *all-trans* retinoic acid limits obesity and improves insulin sensitivity that could be considered in prevention of obesity-related diabetic mellitus [162]. In experimental diabetic neuropathy model, *all-trans* retinoic acid feeding also restores neuronal function and induces neural regeneration through increases of neural growth factor (NGF) levels [163].

### 4.5 Proanthocyanidins

Proanthocyanidins are also known as condensed tannins that exist as dimers or oligomers of flavan-3-ols linked mainly through C4–C8 bonds. They are a group of polyphenolic secondary metabolites widely present in fruits and berries, seeds, flowers, nuts, cocoa and wine. The varieties of proanthocyanidins structures are depend on the flavan-3-ol skeleton extension, the interflavan bond linkage and location as well as the degree of polymerization. Proanthocyanidins have been demonstrated with variable biological and nutraceutical benefits. Proanthocyanidins in blueberries has been reported to prolong lifespan through increasing stress resistance and slowing aging-related declines in *C. elegans* [164] (Table 4). Proanthocyanidins from persimmon peels exhibit anti-cellular senescence effect caused by $H_2O_2$ and attribute to reduce oxidative DNA adduct formation and increased SIRT1 expression in human fibroblasts [165]. Administration of Oligonol, a product of low-molecular proanthocyanidins from lychees, to SAMP8 mice results in increased lifespan and improved locomotive activity [166]. Rats feeding proanthocyanidin-rich extract from longan flower reduces high-fructose-induced blood pressure and increases insulin sensitivity via activation IRS1 and GLUT4 [167]. In addition, proanthocyanidin extract from grape seed reduces high-fat diet-induced hypercholesterolemia and fatty liver in rats by repression of VLDL and SREBP-1, key regulators of lipogenesis [168].

### 4.6 ω-3 fatty acids

Increased dietary intake of marine ω-3 polyunsaturated fatty acids has been reported to benefit human health associated with preventing coronary heart disease, maintaining cognitive function, regulating lipid metabolism, reducing inflammatory condition and improving insulin resistance. Dietary feeding eicosapentaenoic acid (20:5*n*−3, EPA) to rats significantly increases insulin sensitivity than feeding α-linolenic acid, an ω-3 fatty acid found in plants [169] (Table 4). EPA also increases GLUT1 protein level in rat brain endothelial cells that contributes to enhance glucose transport and may be implicated in the regulation of brain energy metabolism [170]. Both EPA and docosahexaenoic acid (22:6*n*−3, DHA) are found to regulate fatty acid metabolism by suppression of insulin-induced lipogenic enzymes such as FAS and ACC-1 as well as SREBP-1c transcription in primary rat hepatocytes [171]. Feeding a mixture of EPA and DHA in diabetic db/db mice displays decreased triglyceride in kidney which is associated with down-regulated SREBP-1 and contributes to protect renal function during diabetic condition [172]. In another study, diabetic rats administrated with DHA reveals decreased oxidative stress and lipid peroxidation in the cerebral cortex that provides the protective ability for central nervous system in diabetic [107].

### 4.7 Other polyphenolic compounds

Curcumin is the major pigment from dried rhizome of the plant *Curcuma longa* Linn, that has been used as spice and

**Table 3.** Molecular mechanisms of anti-aging/aging-related diseases by isothiocyanates and terpenoids

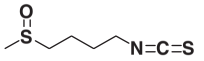
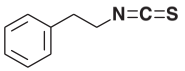
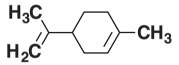
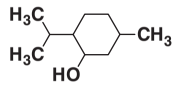
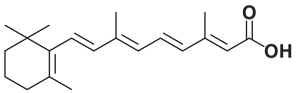
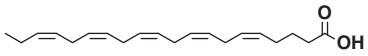
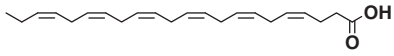
| Group | Sub-class | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|---|
| Isothiocyanates | | Sulforaphane |  | Cabbage, turnips, broccoli, kale, cauliflower, Brussels sprouts | (i) Against cytokine- and $H_2O_2$-induced cell death in human chondrocytes | [156] |
| | | | | | (ii) Protects $H_2O_2$- and paraquat-induced cytotoxicity in primary neuronal cultures of rat striatum | [157] |
| | | | | | (iii) Protects oxidative and electrophilic stress-induced cytoxicity by increasing antioxidant status of mitochondria in aortic smooth muscle cells | [155] |
| | | Phenethyl isothiocyanate (PEITC) |  | | (i) Suppresses osteoclastogenesis through blockage of RANKL-induced signaling | [158] |
| Terpenoids | Monoterpenes | Limonene |  | Citrus fruits, cherries, spearmint dill, caraway, apricots and grapes | (i) Reduces lipid accumulation in liver, lipid peroxidation, plasma insulin and pancreas pathology in high-fat diet-treated rats | [159] |
| | | Menthol |  | | (i) Inhibits bone resorption by repressing formation of osteoclasts | [160] |
| | Diterpenes | Retinoic acid | | Mint | (i) Increases glucose uptake through activation of AMPK and p38 MAPK in skeletal muscle cells | [161] |
| | | All-*trans* retinoic acid |  | | (i) Decreases obesity and serum glucose as well as increases insulin sensitivity in diabetic ob/ob mice | [162] |
| | | | | | (ii) Restores neuronal function and induces neural regeneration in diabetic mice | [163] |

**Table 4.** Molecular mechanisms of anti-aging/aging-related diseases by proanthocyanidins and ω-3 fatty acids

| Group | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|
| Proanthocyanidins | | | Fruits, berries, beans, nuts, cocoa and wine | (i) Prolongs lifespan and increases stress resistance in *C. elegans* | [164] |
| | | | | (ii) Against $H_2O_2$-induced cellular senescence through decreasing 8-OHdG formation and increasing SIRT1 levels | [165] |
| | | | | (iii) Prolongs lifespan and improves locomotive activity in SAMP8 mice | [166] |
| | | | | (iv) Reduces high fructose-induced insulin resistance by increasing IRS-1 and GLUT4 in rats | [167] |
| | | | | (v) Reduces high-fat diet-induced fatty liver by repression of SREBP1 and VLDL | [168] |
| ω-3 fatty acids | EPA |  | Fish oils | (i) Increases insulin sensitivity in male Wistar rats | [169] |
| | | | | (ii) Increases glucose uptake in rat brain endothelial cells by up-regulating GLUT1 protein level | [170] |
| | | | | (iii) Inhibits insulin-induced lipogenesis through repression of SREBP-1c, FAS and ACC-1 expression | [171] |
| | DHA |  | Fish oils | (i) Inhibits insulin-induced lipogenesis through repression of SREBP-1c, FAS and ACC-1 expression | [171] |
| | | | | (ii) Decreases triglyceride levels in kidney by reduction of SREBP-1 in *db/db* mice | [172] |
| | | | | (iii) Reduces glucose-induced oxidative stress and lipid peroxidation in diabetic rat cerebral cortex | [107] |

traditional medicine in Asia for centuries to treat gastrointestinal upset, arthritic pain, parasites, inflammation and other diseases. Studies have shown the potent anti-oxidative activity of curcumin may be one of the mechanisms for anti-aging. Curcumin extends life span in *Drosophila* by reducing oxidative stress and increasing locomotive activity [173] (Table 5). Curcumin also prevents methylglyoxal-induced ROS production and apoptosis in mouse embryonic stem cells and blastocysts [174]. Several in vivo studies show the neuroprotective effect of curcumin that protects against neurodegenerative disorders including Alzheimer's disease. Dietary feeding curcumin to mice improves cognitive function and locomotive activity by increases anti-oxidant status and mitochondrial enzyme complex activities [175]. In an Alzheimer's disease transgenic mouse model, treatment with curcumin reveals increased telomere length and decreased micronucleus formation that contribute to maintain genomic stability during aging pathology [176]. Evidence exhibits that curcumin reduces lipid accumulation in various cell types and displays anti-atherosclerotic and anti-obesity activities. Curcumin inhibits the translocation of SREBP-1 to nuclei in vascular smooth muscle cells thus suppresses ox-LDL-induced cholesterol accumulation and reduces atherosclerotic lesions in mice [177]. Curcumin also increases fatty acid oxidation, and reduces adipogenesis and lipogenesis in adipocytes as well as high-fat diet-treated mice that lowers obesity [178]. In addition, curcumin activates LKB1/AMPK pathway that increases glucose uptake and insulin sensitivity both in L6 myotubes and diabetic rats caused by high-fat diet [179].

**Table 5.** Molecular mechanisms of anti-aging/aging-related diseases by other phenolic compounds

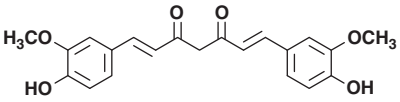
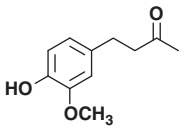
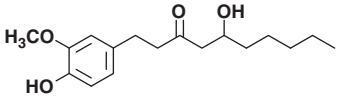
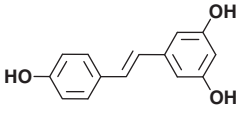
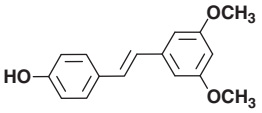
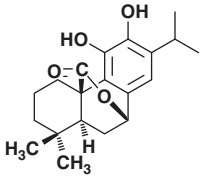
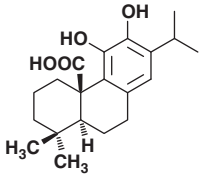
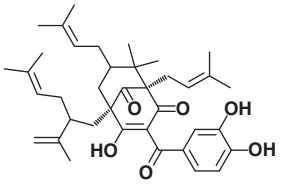
| Group | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|
| Other phenolic compounds | Curcumin |  | Turmeric | (i) Extends lifespan by against oxidative stress in *Drosophila* | [173] |
| | | | | (ii) Protects methylglyoxal-induced ROS production and apoptosis | [174] |
| | | | | (iii) Against senescence through improving cognitive function, increases antioxidant status and restores mitochondrial enzyme complex activities in mice | [175] |
| | | | | (iv) Reduces micronucleus formation and increases telomere length in AD transgenic mice model | [176] |
| | | | | (v) Reduces ox-LDL-induced cholesterol accumulation through inhibition of SREBP-1 nuclear translocation in vascular smooth muscle cells | [177] |
| | | | | (vi) Inhibits adipocytes differentiation and high-fat diet-induced obesity in mice through modulation of lipid metabolism | [178] |
| | | | | (vii) Increases glucose uptake and improves insulin resistance by activation of AMPK in L6 myotubes form diabetic rats | [179] |
| | Zingerone |  | Ginger | (i) Suppresses ROS production and age-related NF-κB signaling in aged rats | [180] |
| | [6]-gingerol |  | Ginger | (i) Against Aβ-induced ROS production and apoptosis by up-regulation of HO-1 and Nrf2 in SH-SY5Y cells | [181] |
| | Resveratrol |  | Grapes and red wine | (i) Extends lifespan through up-regulation of Sir2 and AMPK in *Drosophila* and *C. elegans* | [183] |
| | | | | (ii) Extends lifespan through SIRT1-dependent autophagy in *C. elegans* | [182] |
| | | | | (iii) Reduces endothelial cellular senescence and dysfunction by inhibition of S6K signaling and ROS production | [184] |
| | | | | (iv) Against cellular senescence through deacetylation of p53 | [185] |
| | | | | (v) Protects mitochondrial function through activation | [186] |

**Table 5.** Continued

| Group | Compound | Structure | Dietary source | Mechanisms | Ref. |
|---|---|---|---|---|---|
| | | | | of LKB1/AMPK, SIRT1 and PGC-1α in hepatocytes and mice | |
| | | | | (vi) Extends lifespan and improves health through increasing insulin sensitivity, mitochondrial biogenesis via activation of AMPK and PGC-1α in high-fat diet mice | [34] |
| | | | | (vii) Increases Aβ metabolism by activation of AMPK and induction of autophagy via inhibiting mTOR in neuronal cells | [187] |
| | | | | (viii) Reduces ox-LDL-induced smooth muscle cells proliferation through blockage of PI3K/Akt/mTOR/p70S6K signaling | [188] |
| | | | | (ix) Prevents endothelial progenitor cells senescence through increasing PI3K/Akt-dependent telomerase activity | [189] |
| | | | | (x) Prevents osteoarthritis by decreasing chondrocytes apoptosis and NO levels in the synovial fluid in experimental osteoarthritis of rabbit | [190] |
| | Pterostilbene |  | Blueberries | (i) Reduces smooth muscle cells proliferation through blockage of Akt signaling | [191] |
| | Carnosol |  | Rosemary, sage | (i) Reduces neurotoxicity by decreasing apoptosis and up-regulation of ERK1/2 survival signaling in dopaminergic cells | [192] |
| | Carnosic acid |  | Rosemary, sage | (i) Reduces obesity in high-fat diet-treated mice and decreases adipogenesis in ob/ob mice | [193, 194] |
| | Garcinol |  | *Garcinia indica* | (i) Prevents NO accumulation in astrocytes and promotes neuronal attachment and neurite extension in primary neuron | [195] |

There are several pungent substances such as gingerols, shogaols, paradols and zingerone found in the rhizome of *Zingiber officinale* that has been extensively used as a spice (Table 5). Among those pungent substances, zingerone exhibits anti-oxidative effect on suppression of ROS production and age-related inflammation via down-regulation of NF-κB-medicated inflammatory enzymes expression in aged rat kidney and endothelial cells [180]. [6]-gingerol is a major pungent ingredient in ginger that has been reported to protect Aβ-induced ROS production and apoptosis through activation of Nrf2-medicated heme oxygenase-1 (HO-1) expression in SH-SY5Y cells that may prevent Alzheimer's disease [181].

Resveratrol (3,5,4′-trihydroxystilbene), a compound found largely in the skins of red grapes, exerts positive health effects. Dramatic advances in various organism and animal models have verify the potential of resveratrol on longevity promotion and anti-aging that attributes to the involvement of resveratrol in the modulation of multiple pathways such as insulin/IGF, LKB1/AMPK, mTOR, mitochondria and SIRT. Resveratrol extends lifespan both in *Drosophila* and *C. elegans* through activation of AMPK and Sir2 as well as induction of autophagy [182, 183] (Table 5). Resveratrol also exerts anti-senescence property in endothelial and human fibroblasts by interfering with mTOR/S6 K signaling-mediated ROS production as well as deacetylation of p53 [184, 185]. In addition, studies show that treatment of resveratrol activates LKB1/AMPK, SIRT-1 and PGC-1α in hepatocytes and mice that associates with the attenuation of oxidative stress-caused mitochondrial dysfunction [186]. In a high-fat diet animal model, dietary resveratrol extends lifespan, reduces organ pathology and improves health through increasing insulin sensitivity, mitochondrial biogenesis via activation of AMPK and PGC-1α[34] In neuronal cells, resveratrol increases AMPK-modulated Aβ metabolism through suppression of mTOR and triggers autophagy to reduce Aβ accumulated [187]. Moreover, the anti-atherogenic effect of resveratrol is evidenced by suppression of ox-LDL-induced smooth muscle cell proliferation through blockage of PI3K/Akt/mTOR/p70S6K signaling that reduces DNA synthesis [188]. Resveratrol also involved in regulating telomerase activity that prevents endothelial progenitor cell senescence by maintaining genomic stability [189]. In experimental osteoarthritis model, dietary feeding resveratrol to rabbits reduces chondrocytes apoptosis and NO levels in the synovial fluid that decreases cartilage destruction [190].

Pterostilbene (*trans*-3,5-dimethoxy-4′-hydroxystilbene) is a dimethyl stilbene structurally related to resveratrol found in blueberries (Table 5). The study shows the anti-atherosclerotic effect of pterostilbene by decreasing smooth muscle cell proliferation through blockage of Akt signaling [191]. Rosemary (*Rosmarinus officinals L.*) and sage (*Salvia officinals L.*) leaves are commonly used for spices and food flavoring and known as strong anti-oxidants. Both carnosic acid and carnosol are major phenolic diterpenes and anti-oxidant substances extracted from dried leaf of rosemary and sage. Carnosic acid is unstable during processing and storage will transform into other phenolic diterpenes such as carnosol and rosmanol in the presence of oxygen. Carnosol is reported to reduce neurotoxicity by decreasing apoptosis and up-regulation of ERK1/2 survival signaling in dopaminergic cells that contribute to the prevention of Parkinson's disease [192]. Dietary administration of carnosic acid reduces obesity in high-fat diet-treated mice and decreases adipogenesis in obese ob/ob mice [193, 194]. Garcinol is a polyisoprenylated benzophenone derivative isolated from *Garcinia indica* fruit that has been reported to reduce NO accumulation in astrocytes and promote neuronal attachment and neurite extension in primary neuron that exert neuroprotective activity [195].

## 5 Concluding remarks

Although aging is the inevitable process and biggest challenge for all species, clarification and understanding of the causes, pathology, signaling networks and molecular mechanisms linked to aged-related diseases are critical for searching applicable and effective approach for anti-aging. Despite calorie restriction is efficient to prolong lifespan and reduce aged-pathology, numerous scientific in vitro and in vivo studies have suggested that natural dietary compounds may be able to protect against aging-related decline and diseases. These natural dietary compounds exerts many beneficial effects through regulation of multiple pathways includes insulin/IGF, nutrition sensing and stress response signaling that cooperative modulate cellular metabolism, stress resistance, energy homeostasis, genome maintenance, mitochondrial biogenesis and cellular fate. Coordination of these signaling networks by natural dietary compounds provides the potential mechanism to prevent/delay aging and extends lifespan. Notwithstanding most of these natural dietary compounds are yet to be investigated in clinical. Hence, additional extensive research of natural dietary compounds is needed in the future for improving human health and preventing degenerative disorders of aging.

*This study was supported by the National Science Council NSC 98-2313-B-022-002-MY3, 099-2811-B-022-002, and 100-2918-I-022-005.*

*The authors have declared no conflict of interest.*

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