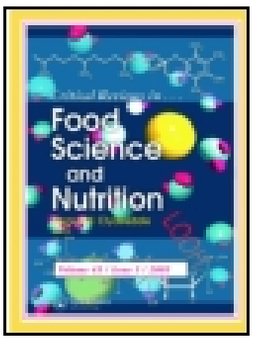

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REVIEW

Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiota

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ABSTRACT

Naturally occurring compounds polyphenols are secondary metabolites of plants, comprised several categories, namely, flavonoids, phenolic acids, lignans and stilbenes. The biological aging process is driven by a series of interrelated mechanisms, including oxidative stress, inflammation status, and autophagy function, through diverse signaling pathways. Moreover, the crucial role of gut microbiota in regulating aging and health status was widely demonstrated. In recent years, the potential anti-aging benefits of polyphenols have been gaining increasing scientific interest due to their capability to modulate oxidative damage, inflammation, autophagy, and gut microbiota. This review highlights the influence of polyphenols in preventing aging disorders and augmenting lifespan based on the influence of oxidative stress, inflammation, autophagy, and gut microbiota, and encourages research on novel polyphenol-based strategies and clinical trials to develop a nutrition-oriented holistic anti-aging therapy.

KEYWORDS

polyphenol; aging; oxidative stress; inflammation; autophagy; gut microbiota

Introduction

Polyphenols are secondary metabolites produced by plants as defense against ultraviolet radiation, mechanical damage, or certain pathogens and predators (Serra, Almeida, and Dinis 2018). A wide variety of polyphenols with high chemical diversity is present in dietary sources, such as fruits, coffee, tea, black beans, cocoa powder, vegetables, and wine (Serra, Almeida, and Dinis 2018). Polyphenols are also known as active principles of plant-derived nutraceutical and herbal medicinal products. Numerous studies suggest that polyphenols have antioxidant, anti-inflammatory, antibiofilm, and antimicrobial properties. These properties are implicated in the reduced risk of various age-related diseases, such as neurodegeneration, obesity, osteoporosis, cancer, and cardiovascular diseases (Gowd et al. 2019). Moreover, many works have correlated dietary polyphenols with the aging process. However, the exact action mechanisms in delivering the anti-aging effects of polyphenols remain unclear. We systematically searched the relative articles from 2015 to 2020 published in English in ScienceDirect, PubMed and Google Scholar databases. The titles and abstracts of approximately 200 studies were reviewed to be selected eligible studies, and then grouped into six groups: polyphenols, aging, oxidative stress, inflammation, autophagy, and gut microbiota. This review explores the emerging influence and the interrelationship of oxidative stress, inflammation response, autophagy function, and gut microbiota on the aging process using complex signaling networks or related molecules linked to the aging process. The evidence of the potential of various polyphenols in mitigating different facets in aging processes and the possible molecular and therapeutic targets are subsequently enumerated. These works were prepared by review articles and research articles, including animal experiments, controlled clinical trials, epidemiological studies, meta-analyses and in vitro studies.

Classification of polyphenols

Polyphenols naturally occur in the following forms: free forms (i.e. aglycones), derivatives (i.e. acylated, esterified or glycosylated aglycones), polymers or oligomers (i.e. macromolecules). To date, over 8000 members of polyphenols have been identified (Karim et al. 2018). Polyphenols represent a broad group of heterogeneous compounds marked by hydroxylated phenyl and are classified into four categories according to their carbon skeleton: flavonoids, phenolic acids, lignans, and stilbenes. The basic skeleton and their represent examples in classes of polyphenols are shown in Figure 1. Flavonoids contain a phenyl benzopyran skeleton (C6–C3–C6) and two benzene rings (A and B) linked through a heterocyclic pyran ring (ring C). Flavonoids are the most abundant classes of polyphenol in dietary foods, with over 6000 identified classes (Karim et al. 2018). According to the differences in the pyran ring, flavonoids can be further subdivided into eight subgroups: flavones, flavonols, flavanones, dihydroflavonols, chalcones, flava-3-ols,

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anthocyanidins, and isoflavones. Flavones are the most basic structure of flavonoids, which contain a keto group in C4, a double bond between C2 and C3, and a B ring attached to C2. Compounds, such as luteolin, apigenin, tangeretin, and nobiletin, are the major representatives of flavones. Flavones are also uncommon in foods but can be found in herbs and vegetables, such as celery, parsley, artichokes, plantain, and thyme. Flavonols, which include kaempferol, quercetin, myricetin, and isorhamnetin, are flavones hydroxylated in C3. Flavonols, as the most commonly occurring group of flavonoids, are found in diverse vegetables (e.g. onions, kale, artichokes, Chinese cabbage), fruits (e.g. berries, cherries, apples), and tea. In flavanones, ring C presents a saturated pyrane group (i.e. no double bond between C2 and C3) and possesses the keto group in C4. The major aglycones of flavanones are naringenin, eriodictyol, and hesperitin, which are commonly found in grapes, lemons, oranges, tomatoes, and certain aromatic plants (e.g. mint). Dihydroflavonols have a similar chemical structure to flavanones, but the former contains OH in C3. Some examples of dihydroflavonols are taxifolin and ampelopsin, which are found in considerable amounts in citrus fruits, juices, and herbs, such as *Mexican oregano* and peppermint. Chalcones are characterized by the absence of ring C in the basic flavonoid skeleton structure, thus termed as "open-chain flavonoids". Chalcones (e.g. phloretin, chalconaringenin, and phloridzin) are derived from several foods, including strawberries, pears, tomatoes, bearberries, and wheat products. Flavanones, dihydroflavonols, and chalcones are considered minor flavonoids due to their scarcity in nature. Flavan-3-ols contain an OH in C3 and lack the double bond among C2, C3, and oxo group in C4. Flavan-3-ols are rarely found in glycoside forms, which include simple monomers (e.g. (+) catechin and (−) epicatechin) and their derivatives (e.g. (−) epigallocatechin and (+) catechin gallate), oligomeric flavonoids (i.e. condensed tannins, such as proanthocyanidins), and polymeric flavonoids (hydrolyzable tannins, such as ellagitannins). High amounts of flavan-3-ols are found in green tea, vegetables, some fruits (e.g. grapes, blackberries, and apricots), chocolate, red wine, and nuts. Anthocyanidins do not present a keto group in C4 and possess an OH in C3 and two double bonds in ring C. Thus, anthocyanidins are considered to be the only ionic flavonoids due to these structural characteristics (Sinopoli, Calogero, and Bartolotta 2019). Common anthocyanidins include cyanidin, pelargonidin, malvidin, and delphinidin. Anthocyanidins generally occur as hydrosoluble plant pigments rich in colored fruits and vegetables, especially grapes and small berries. Isoflavones are flavones with a B ring attached to C3 instead of C2. This structural feature allows isoflavones to function as phytoestrogens, which possess mild estrogenic activity. The main isoflavones include daidzein, genistein, and glycitein, which are specifically found in the legume family, particularly in soybean (Rodriguez-Garcia, Sanchez-Quesada, and Gaforio 2019).

The nonflavonoid group phenolic acids contain a single phenyl group substituted by one carboxylic group and one or more OH groups. Phenolic acids can be further categorized into two distinctive groups: hydroxybenzoic (basic skeleton C6–C1) and hydroxycinnamic (basic skeleton C6–C3) acids. The two groups differ in the length of the chain containing the carboxylic group (McDougall 2017). Some examples of hydroxybenzoic acids are salicylic gallic, syringic, vanillic, and protocatechuic acid, while hydroxycinnamic acids include caffeic, ferulic, p-Coumaric, and sinapic acids. Phenolic acids account for almost one-third of dietary polyphenols and are highly distributed in vegetables, fruits, grains, seeds, and some beverages, especially coffee and tea. Lignans, which are formed by two phenylpropanoid units (C6–C3–C3–C6), typically present in foods as secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol, and its glycosylated form is secoisolariciresinol diglucoside. Large amounts of lignans are also found in flaxseeds, brassica vegetables, asparagus, broccoli, garlic, apricots, prunes cereals, and nuts. Stilbenes have a C6–C2–C6 skeleton, which is characterized by a double bond connecting the phenolic rings. This subgroup is mainly represented by resveratrol, which is rich in red wine and grape. Other natural stilbenes include rhapontigenin, desoxyrhapontigenin, piceatannol, and pterostilbene, all of which are abundant in grapes, berries, nuts, teas, some rhubarb plants, and the Chinese herb *Gnetum cleistostachyum*.

Molecular mechanisms of polyphenols on the aging process

Overview of the link between polyphenols and aging

Biological aging is a dynamic and chronological process characterized by the gradual accumulation of cellular damage and progressive loss of structural, functional, and physiological integrity. This deterioration is the primary risk factor for major human pathologies, including atherosclerosis, cancer, diabetes, and neurodegenerative and cardiovascular diseases, which eventually lead to death (Luo et al. 2020). In 2013, (Lopez-Otin et al. 2013) outlined a series of criteria that defined the hallmarks of aging, including mitochondrial dysfunction, cellular senescence, altered intercellular communications, and loss of proteostasis. The aging process is driven by a series of interrelated mechanisms as follows: the accumulation of cell damage due to free radical-induced oxidative stress and mitochondrial dysfunction, the altered intercellular communication among aging cells due to the tendency of senescent cells to secrete pro-inflammatory cytokines, and the accumulation of unfolded and misfolded proteins to form aggregates because of the deregulation of autophagy function with cell aging (Smita et al. 2016). Thus, a series of signaling pathways, such as the MAPK and NF-κB pro-inflammatory signaling pathways, as well as AMPK/mTOR and PI3K/AKT/mTOR pathways responsible for the regulation of autophagy process, also play pivotal roles in the above mechanisms. Moreover, in recent years, the crucial role of the microbial community inhabiting the gastrointestinal tract (referred to as gut microbiota) in regulating health status and lifespan was widely demonstrated, the composition of gut microbiota substantially changed with aging and related disease outcomes (Vaiserman, Koliada, and Marotta 2017). Therefore, targeting

gut microbiota is considered to be a novel potential therapeutic avenue for the aging process.

Aging is a multidimensional process involving the interaction among the genes and the environment and lifestyle factors, particularly the diet. Plant polyphenols are identified as potential anti-aging agents due to their capability to modulate some aging hallmarks enumerated by Lopez-Otin et al. (Russo et al. 2020). The progressive impairment of physiological homeostasis and the resultant aging always occurs at the cellular, tissular/organic, and organismal levels. At cellular levels, polyphenols are found to reverse the aging process by reducing damages on cellular components, including DNA and proteins, and inhibiting the senescent cells to develop the senescence-associated secretory phenotype (SASP) (Russo et al. 2020). Subsequently, many studies have been conducted to ascertain the anti-aging effects of polyphenols on the tissular/organic levels. Polyphenols improve intercellular interactions to alter the aging of organ systems, such as the nervous, immune, cardiovascular, and reproductive systems, as well as that of the brain, liver, and skin. The brain contains abnormally high proportions of polyunsaturated fatty acids and reactive species, making this organ a common target for oxidative stress and diverse damage response. Sustained damage induces neuronal death by apoptosis or necrosis, which is associated with the pathology of brain aging, cognitive decline, and age-related neurodegenerative disorders (Castelli et al. 2018). Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and spinal muscular atrophy.

Polyphenol-containing extracts or isolated polyphenol monomers have recently gained considerable attention from the scientific community due to their capability to extend the lifespan of several non-mammalian models at certain concentrations. Resveratrol, which is the most extensively studied polyphenol, could extend lifespans of the yeast (*Saccharomyces cerevisiae*) (10 μM) (Howitz et al. 2003), fruit fly (*Drosophila melanogaster*) (60 mg/kg diet) (Abolaji et al. 2018), flatworm (*Caenorhabditis elegans*) (100 μM) (Wood et al. 2004), and fish (*Nothobranchius guentheri*) (200 μg/g food) by 70%, 41.86%, 20%, and 23%, respectively (Liu et al. 2018). However, the effectiveness of resveratrol in high-order species is reduced (Hector, Lagisz, and Nakagawa 2012). Many other polyphenols, such as anthocyanin (Wang et al. 2016), epigallocatechin-3-gallate (EGCG) (Xiong et al. 2018), and 4,4′-dimethoxychalcone (Carmona-Gutierrez et al. 2019), which increased the lifespans of *Drosophila melanogaster* (10 mg/mL), *Caenorhabditis elegans* (200 μM), and worms (41.6 µM) and flies (200 µM) by 16%, 17%, and 20%, respectively. In mammalian model studies, the lifelong intake of lemon polyphenols with 200 mg/kg/day increased the lifespan in the senescence-accelerated mouse prone 1 (SAMP1) by approximately 4% (Shimizu et al. 2019). Meanwhile, the administration of 500 mg/kg fisetin to old wild-type mice reduced age-related pathology and extended median and maximum lifespans (Yousefzadeh et al. 2018). These varying results from different dietary polyphenols can be ascribed to the composition and dose of polyphenols, the genetic background of experimental animals, administration, and environment. The capability of polyphenols to extend the lifespan is also evident in human bodies. Polyphenols are important components in the Mediterranean diet, such as those from grains, vegetables, fruits, extra virgin olive oil, chocolate, and beverages (e.g. red wine, tea, and coffee). Epidemiological studies and controlled clinical trials have extensively indicated that the Mediterranean diet, along with the high daily intake of polyphenols, increased life longevity while lowering overall mortality. Related studies also suggested that polyphenols possessed other benefits, including lowering cancer risk, preventing cardiovascular and metabolic diseases, and improving type-2 diabetes mellitus (Roman et al. 2019).

Despite the constant exploration of the mechanisms involved in the aging process, accumulated evidence suggests that the activation of oxidative stress, maintenance of systematic low-grade inflammation, and dysfunction of autophagy are the heart of biological aging. Based on the above discussion, this review summarizes the recent findings supporting the potential benefits of different structural classes of polyphenols against aging, focusing on the role of oxidative stress, inflammation response, autophagy function, and gut microbiota.

Polyphenol defense against the aging process as suppressors of oxidative stress

Several theories have been proposed to explain the process of aging. Among them, the free radical theory of aging proposed by Harman in 1956 is the most widely accepted theory. This theory postulated that the constant accumulation of damage due to the free radicals in cellular components, such as DNA, proteins, and lipids, is the main determinant of organism lifespan (Harman 1956). Free radicals, including reactive oxygen species (ROS) and reactive nitrogen species, are crucial in cellular damage. Under normal physiological conditions, an intracellular homeostatic balance exists between free radical generation and quenchin. This balance is beneficial in maintaining cellular homeostasis and physiological function of an organism. When this balance is disrupted by excessive production of ROS, the oxidative stress and resulting oxidative damage ensues. Oxidative stress results not only from the imbalance during the formation of ROS but also from the limited endogenous defense systems (Castelli et al. 2018). The endogenous defense systems are divided into enzymatic and non-enzymatic antioxidants. Antioxidant enzymes, such as quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), peroxiredoxins (Prxs), and glutathione reductase (GRx), maintain the oxidative equilibrium in the first line (Zhang and Tsao 2016). The second line of defense against ROS involves non-enzymatic antioxidants, which comprise endogenous (metabolic) and exogenous (nutrient) antioxidants. Dietary polyphenols are one of the most important groups of exogenous natural antioxidants. The antioxidant roles of polyphenols are as follows: neutralizing the free radicals via transfer electron and/or

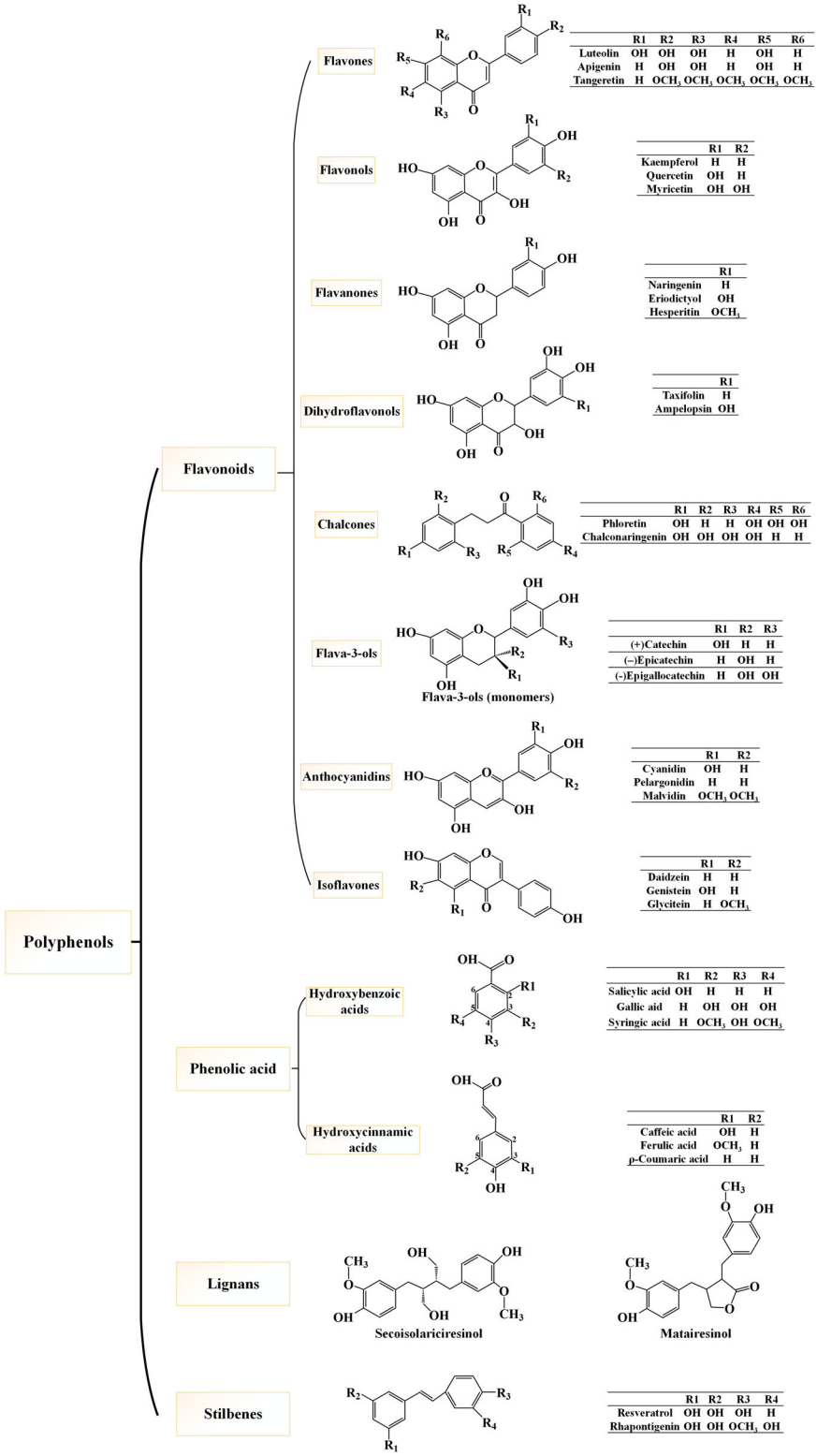

Figure 1. The classes of polyphenols and their basic chemical structures.

hydrogen atom, reducing the formation of metal-dependent hydroxyl radicals through chelation mechanism, decreasing cell apoptosis through modulation of mitochondrial dysfunction, and evoking endogenous antioxidant enzymes by activating the nuclear factor erythroid 2-related factor 2 (Nrf2).

The phenolic groups can transfer electron and/or hydrogen atom to form relatively stable phenoxyl radicals during free radical neutralization. The capability of polyphenols to scavenge radicals largely depends on the number and position of the OH groups attached to the aromatic ring (Castelli et al. 2018). High numbers of OH groups in the aromatic ring result in improved antioxidant properties. Myricetin with six OH groups exhibits better antioxidant properties than quercetin, which has five OH groups, and

kaempferol with four OH groups is less effective than quercetin (Figure 2). In flavonoid, the OH group in the C3 position increases the stability of formed flavonoid radicals once the compound acted as a radical scavenger. For example, blocking the 3-OH group in the C ring of quercetin as a glycoside in rutin or removing the 3-OH group in luteolin decreases the antioxidant activity (Figure 2). Other groups, especially when two or more methoxy groups are located in the *ortho* position relative to the OH groups, also deliver satisfactory antioxidant properties of monophenols, which probably leads to the better antioxidant activity of sinapic acid than that of ferulic acid) (Figure 2) (Halake, Birajdar, and Lee 2016). Moreover, the scavenging radical activities of phenolic compounds are associated with the degree of hydroxylation, oligomer chain length, stereochemical features, and the number and position of additional functional groups, such as alkyl hydrocarbon chains, alkyl chains containing carbon-carbon double bonds, and C=O carbonyl groups (Zhang and Tsao 2016). The antioxidant activity of polyphenols not only neutralizes the free radicals but also inhibits the oxidation process due to their capability to chelate and/or reduce metal ions (Russo et al. 2020). The oxidation process rapidly proceeds under the presence of ionic metals, such as copper and iron; this process promotes the decomposition of hydroperoxides or participates in the production of hydroxyl radicals in the Fenton reaction (Craft et al. 2012). Polyphenolic compounds with two or more groups (e.g. OH, –SH, –COOH, $–PO_3H_2$, C=O, $–NR_2$, –S–, and –O–) can increase chelate metal ions, especially when the *ortho* position of these groups enhances the chelation capability (Santos, Alvarenga Brizola, and Granato 2017). Given that the antioxidant property of polyphenols is dependent on their molecular structure (i.e. the presence of suitable substituents on specific OH groups and their positions), these micronutrients provide the synthesis direction or screen high-efficiency polyphenol antioxidants.

In 1972, Harman revisited free radical theory of aging and stated that mitochondria are the main source of free radicals. Consequently, the theory was subsequently renamed as mitochondrial free radical theory of aging. Bulks of ROS are generally produced by the mitochondrial electron transport chain (ETC) during normal oxidative respiration (Elfawy and Das 2019). The high ROS levels harm the mitochondrial DNA and respiratory chain complex proteins. Such damage accumulates over time and thus induces mitochondrial dysfunction and cellular senescence. This phenomenon leads to cellular apoptosis due to the suppression of the anti-apoptotic protein Bcl-2 and the release of pro-apoptotic proteins, such as cytochrome c, Bax, and p53 (Figure 3) (Sanchez-Rodriguez et al. 2018). Mitochondrial dysfunction intensifies with the increase in age. The antioxidant effects of polyphenols directly or indirectly protect against mitochondrial dysfunction. For instance, oral supplementation with polyphenols (i.e. mixture of tannic acid, resveratrol, quercetin, rutin, gallic acid, and morin at 100 mg/Kg body) protected age-related neuronal death caused by the downregulation of pro-apoptotic Bax, cytochrome c, and p53 in female rat cochleae (Sanchez-Rodriguez et al. 2018). In addition, resveratrol attenuated mitochondrial dysfunction and cell apoptosis by reducing Bax expression and the elevation on Bcl-2 expression in SN4741 cells (Zeng et al. 2017). Mitochondria are responsible for the efficient production of ATP by cells via the mitochondrial respiration chain (Figure 3). A clinical trial revealed that resveratrol treatment (150 mg/day, 30 days) in non-obese post-menopausal women induced a caloric restriction-like effect on the ATP levels, which positively affected the lifespan (de Ligt, Timmers, and Schrauwen 2015). Similarly, catechins (10 mg/kg for 21 days)

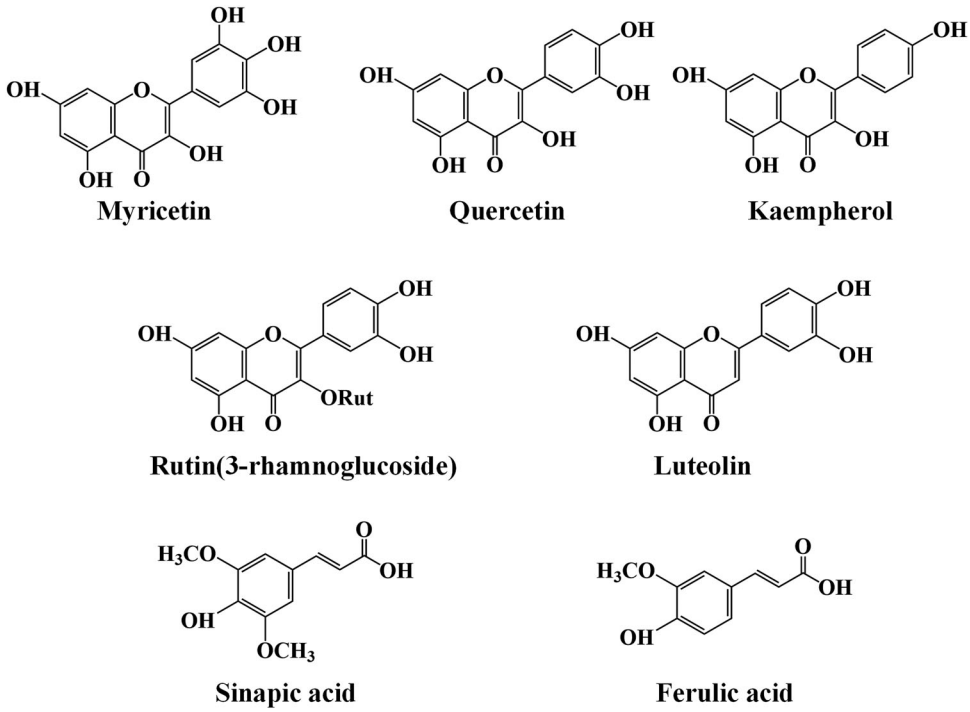

Figure 2. Chemical structures of different phenolic compounds.

(Yamazaki et al. 2014) and quercetin (10 mg/kg for 14 days) (Punithavathi and Stanely Mainzen Prince 2010) could lower the high levels of ATP in rats, suggesting the strong lifespan-extending potential of polyphenols.

As previously mentioned, endogenous antioxidant defense systems play an important role in the first part of ROS-induced stress events. In this regard, Nrf2 is a major transcriptional regulator of numerous detoxification and antioxidant enzymes, which are structurally and functionally conserved from insects to humans. Under basal conditions, Nrf2 is kept transcriptionally inactive because these activators are sequestered in the cytoplasm as it forms a protein complex with its repressor protein, namely, the Kelch-like ECH-associated protein 1 (Keap1). In response to oxidative stress, Nrf2–Keap1 dissociates and causes Nrf2 to translocate into the nucleus, where the latter heterodimerizes with small Maf proteins (Zhou, Kreuzer, et al. 2019). The formed heterodimer binds the antioxidant response element (ARE) sequence in the promoter regions of the genes, thereby inducing detoxifying proteins and antioxidant enzymes (Figure 3) (Davinelli et al. 2018). The Nrf2 pathway is the major mechanism by which polyphenols activate detoxifying and antioxidant enzymes. Caffeic acid, farrerol, apigenin, and tangeretin could inhibit the binding of Keap1 to Nrf2 by decreasing the expression of the former, thereby activating the latter. The initiation of Nrf2 through the polyphenols subsequently upregulated the detoxifying and antioxidant enzymes, such as NQO1, SOD, CAT, GPx, and GRx; these enzymes help reduce oxidative damage and protect against aging in various tissues, such as nerve, brain, skin, liver, and heart (Zhou, Kreuzer, et al. 2019).

The antioxidant polyphenols are one of the most important dietary components and have been ascribed to scavenge ROS directly or improve mitochondria dysfunction indirectly and stimulate the enzymatic antioxidant defense to reduce ROS. Consequently, polyphenols increase the resistance of cells to stress and senescence. These advantages render polyphenols as attractive building blocks for the development and utilization of novel antioxidants and potential anti-aging agents. However, two important aspects should be considered when dealing with either natural or synthetic polyphenol antioxidants. First, polyphenols with different functional moieties can be profoundly diverse in terms of chemical structure and mode of action on oxidative stress. Therefore, identifying the appropriate polyphenol to be used as an antioxidant is recommended to improve the specific pathological condition. Second, recent studies indicated that polyphenols are strong antioxidants as radical

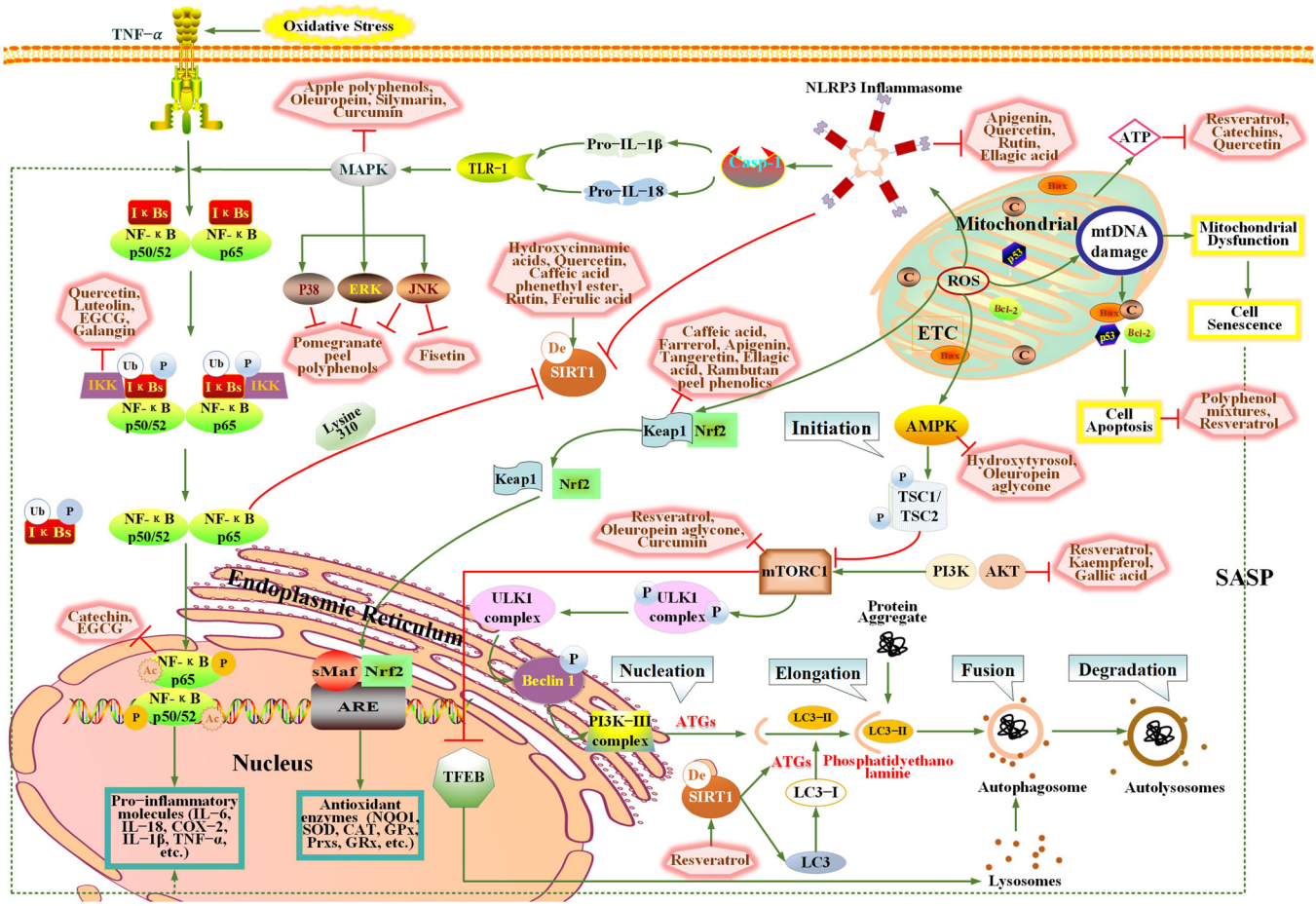

Figure 3. Summary of related cellular pathways over inhibition of oxidative stress and inflammation response, induction of autophagy by polyphenols. mtDNA, mitochondrial DNA; C, cytochrome c; Ub, ubiquitination; Ac, acetylation; P, phosphorylation; De, deacetylation. Arrows indicate activation, whereas perpendicular lines show inhibition.

scavengers in vitro; such actions might exhibit some drawbacks because polyphenols can act as prooxidants at high doses (Olszowy 2019). Therefore, the validity doses for the determination of the effects of polyphenols as antioxidants on human health should be considered.

Polyphenol defense against the aging process as suppressors of inflammation response

ROS-induced damage can accelerate cell senescence, and an excessive accumulation of senescent cells is involved in the biological aging of organisms. Senescent cells develop the SASP, thereby secreting abnormal levels of interleukins (ILs), matrix metalloproteinases, monocyte chemotactic proteins, and growth factors and inducing inflammation and senescence in neighboring cells (Russo et al. 2020). The link between aging and inflammation is accurately coined in the term "inflamm-aging," which denotes the upregulation of certain pro-inflammatory molecules at old ages (Siard, McMurry, and Adams 2016). Consequently, organism aging is always accompanied by a low-grade systemic inflammation, which may be a consequence of the onset and/or progression of age and age-related diseases. With the increase in age, an enhancement in the expressions of pro-inflammatory molecules, such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-2, IL-6, IL-8, and IL-12), and inflammatory mediators (such as NO, inducible NO synthase (iNOS), and cyclooxygenase-2 (COX-2)), has been characterized in various animal models, including mice (Sun et al. 2019), rats (Barrientos et al. 2015), and horses (Siard, McMurry, and Adams 2016). Epidemiological studies demonstrated that the serum levels of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8, are higher in aged individuals than those in young ones. Similarly, patients with AD, PD, atherosclerosis, type 2 diabetes, osteoporosis, and cancer demonstrated enhanced pro-inflammatory molecules (Chung et al. 2009; De Martinis et al. 2006). The aforementioned findings suggest that the elevated pro-inflammatory molecules can act as aging indicators of organisms. However, the reason why older organisms experience inflammatory states and the specific mechanisms that connect inflammation with age-related diseases remain unclear.

The increased oxidative stress to cells prompts the release of TNF-α. Binding of TNF-α to the cell surface TNF-α receptors activates the NF-κB pathway, which is one of the most important signaling pathways in inflammation response. NF-κB comprises a heterodimeric complex of p50/p52 and p65 proteins. In the cytoplasm, NF-κB heterodimer joins the inhibitory IκB proteins (IκBs) in an inactive non-DNA-binding state (Ghizzoni et al. 2011). After the stimulation, the IκBs are phosphorylated by the IκB kinase (IKK), thereby allowing successive ubiquitination and consequent degradation. The released NF-κB p50–p65 subunits then translocate into the nucleus and bind the DNA as a transcription factor at specific promoter regions. Following acetylation and/or phosphorylation, NF-κB prompt the expression of the target genes, including IL-6, COX-2, IL-1β, IL-2, IL-8, and TNF-α (Nam 2006). Consequently, the released molecules can reactivate the NF-κB and thus mediate the inflammatory damage in the tissues through cascade reaction (Figure 3). The overactivation of this NF-κB pathway is considered to be a major driver of the SASP. As a widely acknowledged anti-inflammatory agent, numerous phenolic compounds exhibit a remarkable negative regulation of the NF-κB cascade pathway. For example, quercetin, luteolin, EGCG, and galangin modulated the NF-κB activation cascade at the early phases by blocking the IKK activation to stop the phosphorylation or degradation of the IκBs and the nuclear translocation of p50/p65, resulting in the reduction of SASP. Furthermore, catechin and EGCG blocked the DNA binding of NF-κB during the late phases, leading to the inactivation of the NF-κB pathway. Polyphenols can remarkably inhibit the NF-κB cascade pathway at different steps, which may be due to the different chemical structures of polyphenol monomers (Zhang and Tsao 2016). This phenomenon suggests that the combination of different phenolic compounds can effectively suppress the NF-κB signaling pathway. However, future studies should explore if these polyphenols act independently, synergistically, additively, or even antagonistically.

Extracellular mediators regulate NF-κB by activating different signaling cascades involved in inflammation and further determining the organism lifespan. Among these mediators, mitogen-activated protein kinase (MAPK) plays an important role in the aforementioned functions. MAPK is a highly conserved family of serine/threonine protein kinases, which include the following three subtypes: p38-MAP kinase (p38), extracellular signal-related kinases (ERK) and c-Jun amino-terminal kinases (JNK) (Figure 3). Evidence showed that this MAPK-NF-κB cascade pathway can be extensively inhibited at various levels by different polyphenols. For example, pomegranate peel polyphenols (abundant in punicalagin and ellagic acid) downregulated TNF-α, IL-1β, IL-6, iNOS, and COX-2 expression attributable to suppressing the p38, ERK, and JNK phosphorylation levels via the MAPK signaling pathway in LPS-induced RAW264.7 macrophages (Du et al. 2018). However, administration fisetin (25 mg/kg/day for 7 months) in senescence-accelerated mice was found to decrease brain inflammation only through inhibition of JNK phosphorylation in MAPK signaling pathways (Currais et al. 2018). These results question the capability of the anti-inflammatory activity of polyphenols in restraining the phosphorylation levels of all three subtypes (p38, ERK, and JNK) via MAPK signaling pathway and its superiority to that which only inhibits one of the subtypes of MAPK. Thus, polyphenols endowed with superior anti-inflammatory properties can be identified, and a series of mechanistic studies on the effects of specific polyphenols on the human aging process can be conducted.

Another key node that crosslinks the signaling cascades between redox and inflammation response is NLRP3 inflammasome, which is activated upon the overproduction of ROS. Structurally, NLRP3 inflammasome contains three domains: the leucine-rich repeat-containing receptors, the nucleotide-binding and oligomerization, and the pyrin domains (Cordero, Williams, and Ryffel 2018). Formed

NLRP3 further prompts the release of cytokine pro-IL-1β and pro-IL-18 following caspase-1 activation and then activates Toll-like receptor (TLR)-1. The induction of TLR-1 triggers MAPK kinase cascade and NF-κB signaling transductions, producing cytokines, such as IL-1β, IL-18, IL-6, and TNF-α. This series of reactions finally leads to the amplification of inflammatory events resulting in systemic inflammation in organisms (Figure 3) (Zhang and Tsao 2016). The NLRP3 inflammasome also increased in aging-related diseases, especially in the neurodegenerative diseases. On the contrary, the genetic deletion of NLRP3 in mice extended the lifespan (Youm et al. 2013). Hence, the NLRP3 inflammasome is a crucial driver of many physiological processes associated with aging and a target in age-dependent diseases. Numerous in vivo and in vitro studies have recently shown that dietary polyphenols have protective effects on inflammation through modulation of NLRP3. For example, apigenin inhibited LPS-induced IL-1β and IL-6 production by disruption of the NLRP3 inflammasome assembly and subsequently inhibited caspase-1 activation; this phenomenon led to ERK1/2 and NF-κB pathway inactivation in human THP-1-induced and mouse J774A.1 macrophages (Zhang et al. 2014). Similarly, supplementation with quercetin (Wang et al. 2012), rutin (Aruna, Geetha, and Suguna 2014), and ellagic acid (Tang et al. 2015) in various models of rats inhibited NLRP3 inflammasome activation and restrained the aforementioned associated inflammation pathways.

In addition to the above correlative upstream targets for NF-κB, reports have shown that sirtuins 1 (SIRT1) also interact with NF-κB signaling transductions. The sirtuins (SIRTs) constitute a class of proteins with nicotinamide adenine dinucleotide-dependent deacetylase or adenosine diphosphate-ribosyltransferase activity. In mammals, SIRTs comprise seven members (Sirt1 to Sirt7) (Hou et al. 2016). SIRT1 can deacetylate and inhibit transcription of the p65 subunit of NF-κB at lysine 310, thus attenuating NF-κB-mediated inflammatory signaling transductions (Figure 3). Activation of SIRT1 by several polyphenols, such as hydroxycinnamic acids (Gerardi et al. 2019), quercetin (Sarubbo et al. 2018), caffeic acid phenethyl ester (Li et al. 2018), rutin (Na et al. 2016), and ferulic acid (Hou, Zhang, and Yang 2019) in rats or in cultured cells, were identified to protect against SASP development via NF-κB pathway repression. Among SIRTs, the best-characterized SIRT1 is the closest homolog to yeast silent information regulator 2 (Sir2), which is involved in the yeast replicative aging process. Extra copies of Sir2 increased yeast replicative lifespan by 30%, whereas ablation of the Sir2 gene caused opposite effects on lifespan reduction by 50% (Kaeberlein, McVey, and Guarente 1999). Acting as an agonist on SIRT1, resveratrol extended the lifespan of yeast, *Caenorhabditis elegans*, flies, and mice, by mimicking the beneficial effects of calorie restriction in a Sir2-dependent manner (Hou et al. 2016). In addition, the knockdown of SIRT1 in endothelial cells enhanced NLRP3 inflammasome activation, while SIRT1 stimulation inhibited NLRP3 (Li et al. 2016). However, mechanistic studies indicated that the inactivation of the NLRP3 inflammasome by polyphenols via activation of SIRT1 remains to be identified. Thus, dietary polyphenols play a diverse role in attenuating the risk of inflammatory disorders and enhancing tissue/organ functions during aging by interfering with different cellular signaling pathways. Interestingly, an additional inflammatory source is the gut microbiota, in which the members of microbiota *Clostridium cluster XIVa*, *Bifidobacterium spp.*, and *Faecalibacterium prausntzii* possess anti-inflammatory potential, while *Streptococcus spp.*, *Staphylococcus spp.*, *Enterococcus spp.*, and *Enterobacter spp.* are pro-inflammatory (Russo et al. 2020). Owing to the unique role of cellular signaling pathways during the inflammatory process, thus understanding the influence of these gut microbiota on inflammatory response through the modulation of the above signaling pathways, such as NF-κB, MAPK, Sirt1, and NLRP3 inflammasome may be a remarkable advantage for the contributions of inflammation and gut microbiota to aging.

Polyphenol defense against the aging process as inducers of autophagy function

Recent evidence suggests the unique role of the autophagy process for the aberrant aggregate clearance, protein quality control, aging and age-associated diseases (Ren and Zhang 2018). Interestingly, oxidative stress and autophagy are connected by several crosstalk pathways. Of these pathways, the canonical ways are the mechanistic target of rapamycin complex 1 (mTORC1), an autophagy inhibitor, and the AMP-activated protein kinase (AMPK), which is an autophagy inducer (Russo et al. 2020). The first stage of "initiation" describes the on/off switch of autophagic signaling pathways. The overproduction of ROS interacts with AMPK, which phosphorylates and activates the TSC1/TSC2 complex to suppress mTORC1. Consequently, the ULK1 complex is phosphorylated and activated. The active ULK1 complex translocates to the endoplasmic reticulum to phosphorylate Beclin 1 (Pena-Oyarzun et al. 2018). This translocation induces the formation of the PI3K-III complex, which recruits autophagy-related proteins (ATGs) implicated in the autophagome formation (nucleation process). Then, the "elongation stage" refers to the extension of the autophagosome membrane assisted with LC3, a protein that is cleaved proteolytically to form inactive LC3-I. Meanwhile, LC3-I is conjugated with several ATGs and phosphatidylethanolamine to generate lipidated active form, that is, LC3-II, which is incorporated into the autophagosome (Rockenfeller et al. 2015). LC3-II is widely known as an autophagy marker because it localizes at the autophagosome membranes. Finally, the autophagosome is fused with lysosomes to form autolysosomes ("fusion"), allowing degrading and removing long-lived and/or damaged cellular organelles and protein aggregates ("degradation") (Figure 3) (Pena-Oyarzun et al. 2018). Various studies demonstrate that activation of autophagy could extend the lifespan of mutant organisms in *C. elegans* (Zhou, Kreuzer, et al. 2019), *D. melanogaster* (Aparicio, Rana, and Walker 2019), and mammals (Grzesiak et al. 2018; Wang, Kandadi, and Ren 2019). Functioning autophagy is vital for the healthy organism, but autophagy gradually subsides in old organisms (Wong et al. 2020).

Autophagy deficiency impairs the effective elimination of aggregates and damaged mitochondria, leading to their accumulation and increasing their toxicity and oxidative stress. These conditions are central events in neurodegenerative age-related diseases, such as AD and PD.

Mounting evidence showed that the polyphenol consumption activated autophagy via the AMPK-mTOR signaling pathways further preserved the health by delaying aging in various model organisms. For example, treatment with hydroxytyrosol in neuronal cells and oleuropein aglycone in TgCRND8 Alzheimer's disease model mice for eight weeks could induce autophagy through the activation of AMPK and inhibition of mTOR1 (de Pablos et al. 2019; Rigacci et al. 2015). As previously mentioned, autophagy induction is largely mediated via mTOR1, a ubiquitously expressed serine/threonine kinase in mammalian cells. Moreover, the upstream and downstream regulators are responsible for controlling the activity of mTOR1. Of these regulators, the protein kinase B (AKT) and phosphatidy linositol 3 kinase (PI3K) are the well-known upstream activators of mTOR1 (Figure 3) (Xiang et al. 2020). Several polyphenols, resveratrol (in rats) (Wan et al. 2016), kaempferol (in human endothelial cells) (Che et al. 2017), gallic acid (both in CCD-18Co cells and in rats) (Kim et al. 2017) up-regulated autophagy process via inhibiting PI3K/AKT/mTOR pathway. In addition, the nuclear transcriptional factor EB (TFEB), a direct downstream target of mTOR1, plays an important role in the regulation of lysosomal biogenesis. Upon mTOR1 inhibition, dephosphorylated TFEB translocates to nucleus and promotes the transcription target genes of TFEB that are crucial in autophagy process (Figure 3) (Zhang, Wang, et al. 2016). Recent culture cell findings indicated that resveratrol (Zhou, Kreuzer, et al. 2019), oleuropein aglycone (Miceli et al. 2018), and curcumin (Zhang, Wang, et al. 2016) enhanced autophagy via suppression of mTOR1 to increase transcriptional activity of TFEB. Although the above pathways are primarily known to induce autophagy in an mTOR1-dependent manner, Sirt1 regulates autophagy mostly through (de)-acetylation processes. This deacetylase was shown to promote longevity directly mediated by deacetylation of autophagic-related proteins, such as ATG5, ATG7, ATG8, and LC3, to induce autophagosome formation (Vellai et al. 2009). Resveratrol, the representative agonist of SIRT1, modulated the deacetylation status of ATG5, ATG7, ATG8, and LC3 to restore autophagy in various animal models (Ma et al. 2016). Based on the core regulator of SIRT1 in the link between the autophagy process and the inflammation response, studies regarding the role of SIRT1 deacetylation in the aging process are necessary.

These results generally provide renewed insight into the molecular modes of delaying aging by polyphenols, which is likely to be at least mediated not only by their potent antioxidant and anti-inflammatory effects but also through modulation of autophagic processes to remove the aberrant protein aggregates. This pro-autophagy effect is caused by the modulation of several pathways, including the AMPK/mTOR and PI3K/AKT/mTOR axis, and the activation of autophagy gene expression mediated by TFEB or SIRT1. In particular, the autophagy-related kinases, such as mTOR, AKT, PI3K, and AMPK, play pivotal roles in autophagy induction. Thus, these kinases can be used as breakthrough points of autophagy intervention. However, the recent occurrence of drug resistance of autophagy-related kinase inhibitors/activators is a formidable obstacle to surmount because of factors, such as gene mutation, kinase upregulation, compensatory mechanisms, and bypass effects (Xiang et al. 2020). Acting as bioactive compounds from natural plants, polyphenols have some advantages, such as safety, extensive sources, and more targets, compared with several chemical synthesis drugs. Thus, understanding the mechanisms of polyphenol as autophagy-related kinase activators targeting the related pathways opens up new directions to revolutionize ways to slow down the onset and development of age and age-dependent degeneration.

Reciprocal interaction between polyphenols and gut microbiota on aging

A growing body of studies has strongly implicated that natural polyphenols enhanced human health, prolonging the lifespan and lowering the risk of age-related diseases. Nevertheless, concluding the bioactivities of polyphenols is challenging because of their poor bioavailability and inter-individual variances (Marin et al. 2015). Once polyphenols are ingested, they encounter the gut microbiota, resulting in a reciprocal interaction, the gut microbiota catabolizes polyphenols into metabolites and polyphenols modulate gut microbiota composition (Figure 4) (Dey 2019). Next, the influence of the two-way interaction on the organism aging and health is described below.

Biotransformation of polyphenols by gut microbiota

Following transition into the gastrointestinal tract, the minority of free and simple polyphenols are hydrolyzed by lactase-phlorizin hydrolase (LPH) in the brush border of the small intestine epithelial cells, and the resulting aglycones enter the enterocyte by passive diffusion. However, the absorption of polyphenols in the small intestine is low (5–10%), and the remaining 90–95% polyphenols, together with those recycled aglycones, accumulate at the colon wherein microbial degradation facilitates the absorptivity (Dey 2019). Abundant microbes (approximately 10^{14} bacteria) reside within the gastrointestinal tract, with the majority of 10^{12} inhabiting the colon. The gut microbiota performs the following three major catabolic processes: hydrolysis (O-deglycosylations and ester hydrolysis), cleavage (C-ring fission, delactonization, and demethylation), and reduction (dehydroxylation and double-bond reduction) reactions (Braune and Blaut 2016). Therefore, the resulting aglycones may be conjugated into metabolites (i.e. glucuronides, O-mehtylethers, and sulfates) by phase II enzymes and possibly degraded to simple phenolic derivatives by gut microbiota, ultimately facilitating absorption in the body. It is highly variable in the biotransformation of polyphenols in the body and dependent on the structure of polyphenols and gut microbiota composition.

Next, polyphenols that are known to be metabolized by gut microbiota, which results in bioactive metabolites, are investigated (Figure 4 and Table 1). A prototypical example of flavonoids is catechins from green tea, which comprises EGCG, (−)-epigallo-catechin (EGC), (−)-epicatechin gallate (ECG), and (−)-epicatechin (EC). Studies have shown that some unchanged EGCG and ECG are absorbed in the small intestine. The majority of catechins reach the colon, first transformed into 1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol (2,4,6-THPL) by *Eggerthella lenta*, and then the latter was converted into 5-(3,4-dihydroxyphenyl)-γ-valerolactones (3,4-DHPL) and 4-hydroxy-5-(3,4-hydroxyphenyl)valeric acid (3,4-HPVA) by *Flavonifractor plautii*. Additional microbial metabolites, such as 3,4-dihydroxyphenylacetic acid (3,4-DHPAA), 4-hydroxyphenylacetic acid (4-HPAA), 3-O-methylgallic acid (3OMGA), and hippuric acid, were also detected after green tea intake (Santangelo, Silvestrini, and Mancuso 2019). Another notable example is quercetin, which is conjugated to sugar moieties, such as rhamnose or rutinose, resulting in the corresponding glycoside quercitrin and rutin. The sugar moiety cannot be hydrolyzed by intestinal β-glucosidases; thus, they encountered gut microbiota, including *Bacteroides*, *Enterococcus*, and *Blautia*, and underwent deglycosylation to yield quercetin aglycon. Then, quercetin occurred ring–fission reactions into dominant phenolic acid derivatives 3,4-DHPAA, as well as homoprocatechuic acid, 3-(3-hydroxyphenyl)propionic acid (3HPPA), 3,4-dihydroxybenzoic acid (3,4-DHBA), and 4-hydroxybenzoic acid (4-HBA). The bacterial strains *Clostridium perfringens*, *Bacteroides fragilis*, *Enterococcus gilvus*, *Escherichia coli*, *Lactobacillus acidophilus*, *Stretococcus lutetiensis*, and *Weissella confuse* were responsible for the transformation of quercetin into the aforementioned metabolites (Santangelo, Silvestrini, and Mancuso 2019). Isoflavone daidzein, another major classification of flavonoid found in soybean, is structurally similar to endogenous estrogens. Daidzein was first hydrolyzed by LPH to produce the corresponding aglycons. The aglycons were then reduced into dihydrodaidzein under *Coprobacillus* strain MRG-1, and the dihydrodaidzein underwent hydrogenation into equols by *Eggerthella* strain Julong 732 (Murota, Nakamura, and Uehara 2018). Large molecule polyphenols, such as ellagitannins (hydrolysable tannins), are esters of hexahydroxydiphenic acid (HHDP) and glucose. In the intestinal lumen, the hydrolysis of the ester bonds by the hydrolases released HHDP, which then underwent spontaneous cyclization to yield ellagic acid. The ellagic acid was catabolized through de-lactonization (lactone ring opening and decarboxylation) to form urolithin M5 by *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae*. The sequential removal of hydroxyls from urolithin M5 attained the end products urolithin A, isourolithin A, and urolithin B by *Ellagibacter isourolithinifaciens* (Gowd et al. 2019).

Phenolic acids are mainly structured during ring-fission reactions of flavonoids and may be released from the food matrix. A prime example is chlorogenic acid, which is a

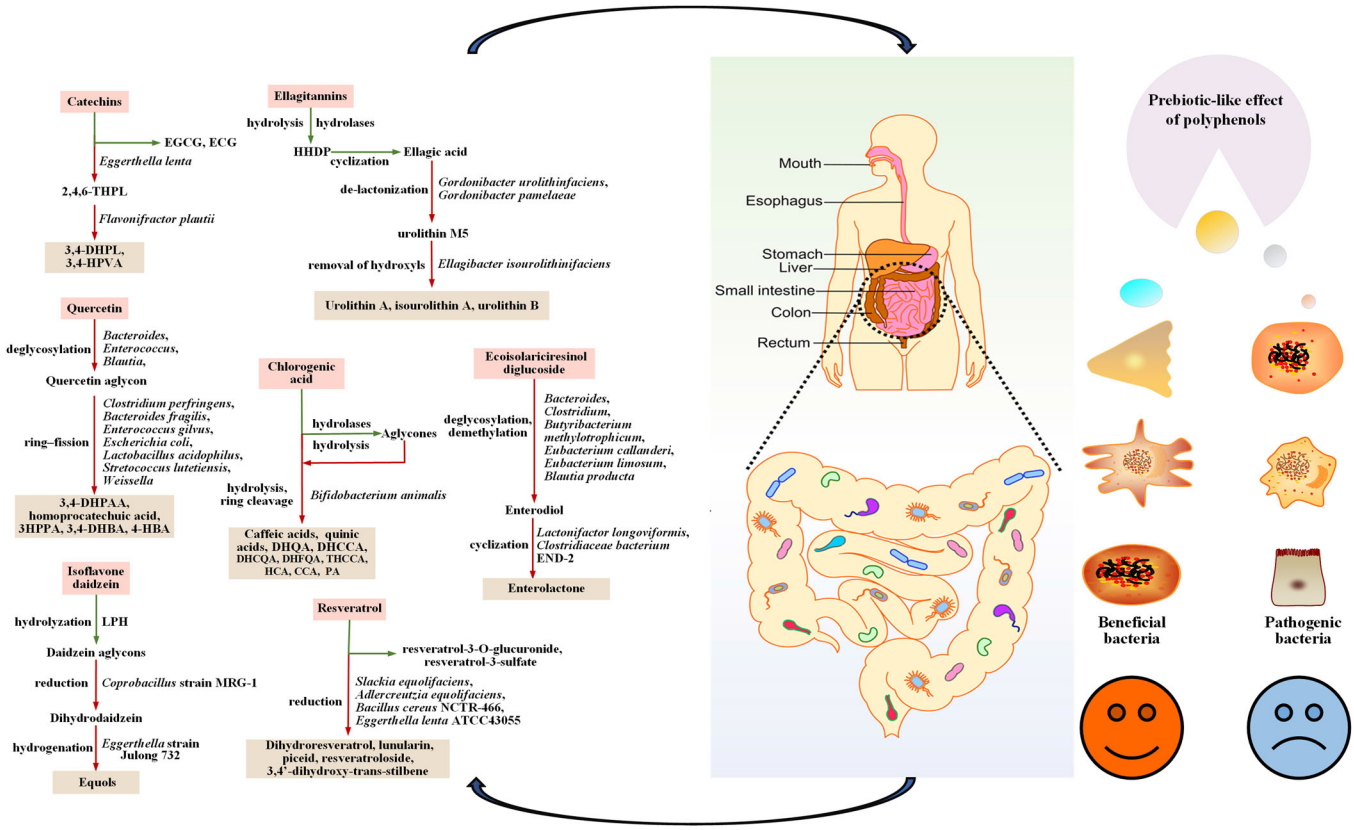

Figure 4. Reciprocal interaction between polyphenols and gut microbiota. On the one hand, polyphenols encounter gut microbiota to undergo extensive metabolism into small-molecule derivates. Green arrows indicate the bioconversion reactions of polyphenols in the small intestine, and red arrow indicate the bioconversion reactions of polyphenols to produce metabolites by gut microbiota in the colon. On the other hand, ingested polyphenols act as "prebiotics", promoting the growth of beneficial bacteria and inhibiting the growth of pathogenic bacteria.

Table 1. Polyphenols metabolism by gut microbiota in humans.

Polyphenol	Models	Bacteria	Metabolites	References
Catechins	Human fecal fermentations, Human intervention studies	*Eggerthella lenta*, *Flavonifractor plautii*	3,4-DHPL, 3,4-HPVA, 3,4-DHPAA, 4-HPAA, 3OMGA, hippuric acid	(Santangelo, Silvestrini, and Mancuso 2019)
Quercetin	Human fecal fermentations	*Clostridium perfringens*, *Bacteroides fragilis*, *Enterococcus gilvus*, *Escherichia coli*, *Lactobacillus acidophilus*, *Stretococcus lutetiensis*, *Weissella confuse*	3,4-DHPAA, homoprocatechuic acid, 3HPPA, 3,4-DHBA, 4-HBA	(Santangelo, Silvestrini, and Mancuso 2019)
Daidzein	Human fecal fermentations	*Coprobacillus* strain *MRG-1*, *Eggerthella* strain Julong 732	equols	(Murota, Nakamura, and Uehara 2018)
Ellagitannins	Human fecal fermentations	*Gordonibacter urolithinfaciens*, *Gordonibacter pamelaeae*, *Ellagibacter isourolithinifaciens* (CEBAS 4A)	urolithins	(Gowd et al. 2019)
Chlorogenic acid	Bacterial strains culture, Human fecal fermentations	*Bifidobacterium animalis*	caffeic acids, quinic acids, DHQA, DHCCA, DHCQA, DHFQA, THCCA, HCA, CCA, PA	(Naranjo Pinta et al. 2018)
Resveratrol	Human fecal fermentations, In vitro culture, Rats in vivo	*Slackia equolifaciens*, *Adlercreutzia equolifaciens*, *Bacillus cereus* NCTR-466, *Eggerthella lenta* ATCC43055	dihydroresveratrol, lunularin, piceid, resveratroloside, 3,4′-dihydroxy-trans-stilbene	(Shen and Ji 2018)
Ecoisolariciresinol diglucoside	Human fecal fermentations	*Bacteroides*, *Clostridium*, *Butyribacterium methylotrophicum*, *Eubacterium callanderi*, *Eubacterium limosum*, *Blautia producta*, *Lactonifactor longoviformis*, *Clostridiaceae bacterium* END-2	enterolactones	(Clavel et al. 2007; Shen and Ji 2018)

general term used for the esters of quinic and caffeic acids rich in coffee. Part hydrolysis of chlorogenic acid occurred in the small intestine through the hydrolases. Most of the chlorogenic acids, together with the aglycones, arrived in the colon, where hydrolysis occurred and ring cleavage yielded the following: caffeic and quinic acids, dehydroquinic acid (DHQA), dihydroxycyclohexane carboxylic acid (DHCCA), dihydrocaffeoylquinic acid (DHCQA), dihydroferuloylquinic acid (DHFQA), trihydroxycyclohexanecarboxylic acid (THCCA), hydroxycyclohexanecarboxylic acid (HCA), cyclohexane carboxylic acid (CCA), and protocatechuic acid (PA) (Naranjo Pinta et al. 2018). These catabolism reactions were conducted under *Bifidobacterium animalis* and other specific bacteria strains that must be further identified. Resveratrol is a well-known polyphenol of stilbene-based phytochemicals. Once absorbed into the enterocyte, resveratrol was conjugated into resveratrol-3-O-glucuronide and resveratrol-3-sulfate. Resveratrol and its metabolites could be further metabolized in the colon, wherein they were converted into dihydroresveratrol via reduction reactions considering *Slackia equolifaciens* and *Adlercreutzia equolifaciens*. Additional metabolites of resveratrol include lunularin, piceid, resveratroloside, and 3,4′-dihydroxy-trans-stilbene, which are related to bacterial species *Bacillus cereus* NCTR-466 and *Eggerthella lenta* ATCC43055 (Shen and Ji 2018). Lignans typically present in foods include ecoisolariciresinol diglucoside, which underwent deglycosylation and demethylation reactions to form enterodiol. *Bacteroides* and *Clostridium* strains were capable of this O-deglycosylation, while *Butyribacterium methylotrophicum*, *Eubacterium callanderi*, *Eubacterium limosum*, and *Blautia producta* were capable of demethylation. The enterodiol then went through cyclization (dehydrogenation) to form a lactone ring leading to enterolactone, which is catalyzed by *Lactonifactor longoviformis* and *Clostridiaceae bacterium* END-2 (Clavel et al. 2007).

Although polyphenols have multiple bioactivities as demonstrated in vivo and vitro, they exhibit low bioavailability and absorptivity. Once ingested, polyphenols encounter gut microbiota to undergo extensive metabolism into small-molecule derivates, which are endowed with higher absorptivity, bioactivity, and bioavailability. Some microbial metabolites exerted similar bioactivities compared with their precursor polyphenols, such as vasodilatory effect of 3HPPA and chlorogenic acids (Najmanova et al. 2016), anti-lipid peroxidation and anti-proliferative effects on tumor cells of piceid and resveratrol (Shen and Ji 2018). More importantly, some other metabolites tended to be more bioactive than their parent polyphenols, such as equols and 3,4-DHPAA possessed stronger antioxidant activity than that of daidzein and quercetin, respectively (Davinelli et al. 2018; Peng et al. 2014). Urolithins exerted stronger anti-inflammatory activity than ellagitannins by modulating MAPK/NF-κB signaling

pathways (Larrosa et al. 2010). As the most abundant metabolites of catechins, 3,4-DHPL had stronger anti-adhesion and antioxidant activity than catechins via phosphorylation of IKK and IκB and downregulating NF-κB transcription (Unno et al. 2003). More importantly, urolithins were detected in human urine with a maximum excretion at 32 h and persisted up to 80 h after the intake of ellagitannin-containing food. The maximum excretion of 3,4-DHPAA was observed at 48 h, which was also the case for valerolactone 5-(3′,4′,5′-trihydroxyphenyl-γ-valerolactone) and 3-hydroxyphenylacetic acid produced from proanthocyanidins (Williamson and Clifford 2017). These findings suggest that microbial-derived metabolites of polyphenol show a longer persistence in human body circulation and thus can exert biological effects for longer periods than their parent polyphenols. Overall, these results lead to the assumption that microbial metabolites not only improve the absorptivity and bioavailability of the parent polyphenols but are also primarily responsible for the health-promoting potential at the tissue level. However, not all individuals are capable of producing the bioactive microbial-derived metabolites and are subject to high inter-individuality possibly due to interpersonal variations of gut microbiota composition. Therefore, stratification in clinical trials according to the metabotypes of individuals is necessary to fully understand the health effects of polyphenols. Despite numerous detected polyphenol biotransformation of many bacterial strains, additional mechanistic studies are encouraged to detect additional species. Particularly, these studies characterize the enzymes catalyzing the polyphenol bioconversion, aiming to lay a basis for potential microbial production of additional bioactive metabolites. Furthermore, the evidence supports that the bioactivity of polyphenol-derived microbial metabolites is limited. Thus, additional studies are required to compare the absorptivity, bioactivity, and bioavailability with parent polyphenols.

Modulatory effect of polyphenols on gut microbiota

Gut microbiota has recently emerged as a key regulator of the aging process of organisms, but its precise role remains unclear. A dysbiosis of gut microbiota has been reported to shorten lifespan in invertebrate models (*Drosophila melanogaster* and *Caenorhabditis elegans*) (Clark and Walker 2018), while fecal microbiota transplantation from young to old individuals could enhance lifespan in vertebrate models (progeroid mouse (Barcena et al. 2019) and African turquoise killifish) (Smith et al. 2017). Among the elderly, a decrease in the diversity of gut microbiota was observed, with reduced numbers of *Bifidobacteria*, *Blautia coccoides-Eubacterium rectal*, *Bacteroidaceae*, *Coprococcus*, *Clostridium cluster* XIV, and the ratio of *Firmicutes* to *Bacteroidetes* (F/B), whereas a large presence of *Bacilli*, *Odoribacter*, *Butyricimonas*, *Enterobacteriaceae*, and *Oscillospira* was found. Meanwhile, the short-chain fatty acids (SCFAs) also declined in the elderly possibly due to the reduced abundance of SCFA-producing bacteria, including *Lachnospiraceae*, *Ruminococcaceae*, *Barnesiella*, *Roseburia*, and *Faecalibacterium* prausnitzii (Rondanelli et al. 2015; Vaiserman, Koliada, and Marotta 2017). SCFAs (acetate, propionate, and butyrate) are essential metabolites produced by gut microbiota in the colon, helping to maintain the gut barrier functions and inhibit the inflammatory cytokine production and endowed with anti-inflammatory and anti-cancer capabilities (Riviere et al. 2016). Some similar alterations of gut microbiota are also found in patients with age-related diseases, such as neurodegeneration, cognitive decline, obesity, diabetes, and cardiovascular diseases. However, data on changes in gut microbiota are characterized by high inter-individual variability, especially in old adults.

The classical concept of "prebiotic," which induces the growth of *Lactobacilli* and *Bifidobacteria*, has been recently reevaluated. A novel definition states that prebiotic are non-digestible compounds that modulate the composition and/or diversity of the gut microbiota through its metabolization by gut microbiota, thus conferring a beneficial physiological effect on the host (Bindels et al. 2015). The microbiota-targeted dietary polyphenol interventions have favorably affected the host health and aging. These selected dietary polyphenols not only act as the classical "prebiotics" to promote the growth of *Lactobacilli* and *Bifidobacterial* but also enhance specific beneficial bacteria and inhibit pathogenic bacteria proliferation (Fig. 4). For instance, several polyphenols have been identified to promote the growth of health-promoting groups (e.g. *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Christensenellaceae*, and *Verrucomicrobia*), such as lemon (Shimizu et al. 2019), mango (Kim et al. 2020), and non-extractable polyphenols (González-Sarrías, Espín, and Tomás-Barberán 2017). Moreover, diet consumption of anthocyanins (Peng et al. 2020) or red wine polyphenols (Moreno-Indias et al. 2016) could augment the number of SCFA-producing bacteria (*Barnesiella*, *Faecalibacterium prausnitzii*, *Odoribacter*, *Roseburia*, *Ruminococcaceae*), thus promoting the production of SCFAs. In addition, green, oolong, and black teas (Sun et al. 2018), neohesperidin (Gong et al. 2019), and resveratrol combined with curcumin (Sreng et al. 2019) significantly restrained the proportions of some representative pathogenic bacteria, such as *Clostridiumm*, *Desulfovibrionaceae*, *Prevotella*, and *Proteobacteria*. Another prime indicator of organism dysbiosis is the ratio of F/B, which is positively correlated with the development of obesity and metabolic syndrome. Interestingly, (Guo et al. 2017) found that the F/B ratio was reduced after feeding with 0.1%(w/w) tea polyphenols in C57BL/6J mice for three weeks. Meanwhile, (Li, et al., 2020) reported that the F/B ratio was increased following feeding with 1.92% g/kg diet tea polyphenols in canines for 18 weeks. The inconsistency in the results of gut microbiota alterations may be attributed to the species and nutrient status of animals, the composition and concentration of polyphenolic compounds in the diets, and the treatment method and length of time. The recent studies related to the modulatory effects of polyphenols on gut microbiota and the corresponding metabolic outcomes are summarized in Table 2. The health benefits of most polyphenols are partly derived from an interplay between the reshaping of gut microbiota to a healthy composition and the modification of the microbial metabolites bioavailable to the host. However, whether the reshaping of gut microbiota is determined by microbial-derived polyphenolic

Table 2. Summary of the studies related to the effects of polyphenols on gut microbiota and the corresponding metabolic outcomes.

Models	Time	Polyphenols	Dose	Altered bacteria	Metabolic outcomes	Reference
In vitro						
Fecal samples fermentation	36 h	Green tea, oolong tea and black tea	1% (w/v)	↑*Bifidobacterium* ↑*Lactobacillus/Enterococcus spp.* ↓*Bacteroides-Prevotella* ↓*Clostridium histolyticum*	↑SCFAs	(Moreno-Indias et al. 2016)
Fecal samples fermentation	48 h	Date palm polyphenol extract	150 mg/ml	↑*Bifidobacteria* ↑*Bacteroides*	↑Acetate	(Eid et al. 2014)
Fecal samples fermentation	72 h	Mango *Mangifera indica L.* peel polyphenols	70 g	↑*Bifidobacterium* ↑*Lactobacillus*	↑SCFAs	(Sayago-Ayerdi, Zamora-Gasga, and Venema 2019)
Fecal samples fermentation	24 h	Purple sweet potato anthocyanins	1% (w/v)	↑*Bifidobacterium* ↑*Lactobacillus/Enterococcus spp.* ↓*Bacteroides-Prevotella* ↓*Clostridium histolyticum*	↑SCFAs	(Zhang, Wang, et al. 2016)
In vivo						
SAMP1 male mice	8 weeks	Lemon polyphenols	0.1% (w/v)	↑F/B ratio ↑*Lactobacillus*	↑Lifespan ↓Aging-related scores	(Shimizu et al. 2019)
C57BL/6 male mice	12 weeks	Anthocyanins from *Lycium ruthenicum Murray*	200 mg/kg/day	↑*Barnesiella* ↑*Alistipes* ↑*Eisenbergiella* ↑*Coprobacter* ↑*Odoribacter*	↑Antioxidant status (T-AOC, T-SOD, CAT, GSH, GSH-Px) ↑Intestinal barrier ↓Anti-inflammatory status (iNos, Cox-2, TNF-α, IL-6, IL-1β)	(Peng et al. 2020)
C57BL/6J-APC$^{min/+}$ transgenic mouse	12 weeks	Neohesperidin	100 mg/kg	↑*Firmicutes* ↑*Proteobacteria* ↓*Bacteroidetes*	↓Colorectal tumorigenesis	(Gong et al. 2019)
C57Bl/6J hyperglycemic male mice (HFD: 72% fat, 28% protein and $<$1% carbohydrate)	5 weeks	Resveratrol	60 mg/kg/day	↑*Anaerotruncus* ↑*Firmicutes/Bacteroidetes* ↑*Ruminococcaceae* ↓*Proteobacteria* ↓*Rikenellaceae* ↓*Peptostreptococcaceae* ↓*Alistipes* ↓*Clostridium* XI	—	(Sreng et al. 2019)
C57BL/6J human flora-associated male mice (60 kcal% Fat)	3 weeks	Green tea polyphenols	0.1% (w/w)	↑*Bacteroidetes* ↑*Proteobacteria* ↑*Ruminococcaceae* ↓*Veillonellaceae* ↓ F/B ratio	—	(Guo et al. 2017)
HFD-induced obesity male canines ($\geq$45 g/kg)	18 weeks	Green tea polyphenols	1.92% g/kg diet	↑F/B ratio ↑*Acidaminococcus* ↑*Succinivibrio* ↑*Citrobacter* ↓*Fusobacteria* ↓*Anaerobiospirillum*	↓Weight gain ↓Intestinal inflammation (TNF-α, IL-6, IL-1β)	(Li, et al., 2020)
Koi carp (*cryprinus carpio*)	8 weeks	Tea polyphenols	1000 mg/kg diet	↑*Proteobacteria* ↑*Vibrio* ↑*Citrobacterium* ↑*Enterobacter* ↑*Raoultella* ↑*Fusobacteria* ↓*Cetobacterium*	↓Immune response (serum IL-1β, IL-6)	(Zhang et al. 2020)

(*continued*)

Table 2. Continued.

Models	Time	Polyphenols	Dose	Altered bacteria	Metabolic outcomes	Reference
HFD-fed male Wistar rats (4.7 kcal/g, 45kcal% fat)	8 weeks	Resveratrol Sinapic acid	400 mg/kg 200 mg/kg	↑*Blautia* ↑*Dorea* ↓*Bacteroides* ↓*Desulfovibrionaceaesp*	↓Body weight ↓Oxidative stress (ROS, MDA)	(Yang et al. 2019)
HFD-induced C57BL/6J male mice (61% of kilocalories)	13 weeks	Concord grape polyphenols	1%	↑*Akkermansia muciniphila* ↓F/B ratio	↑Intestinal barrier function ↓Weight gain, ↓Adiposity ↓Serum/intestinal inflammatory markers (TNFα, IL-6, LPS, iNOS) ↓Glucose intolerance	(Roopchand et al. 2015)
HFHS-fed C57Bl/6J male mice	21 weeks	Cranberry extract	200 mg/kg	↑*Akkermansia muciniphila* ↑*Barnesiella spp.* ↓F/B ratio	↑Hepatic steatosis ↓Pro-inflammatory genes (COX-2, TNF-α)	(Anhe et al. 2017)
HFD-induced obesity in C57BL/6 J male mice	12 weeks	Blueberry polyphenol extract	200 mg/kg bw/day	↑*Bifidobacterium* ↑*Proteobacteria* ↑*Flexispira* ↓*Lactococcus* ↓*Coprobacillus* ↓*Prevotella* ↓*Clostridium*	↓Weight gain ↓T-CHO, TG	(Jiao et al. 2019)
C57BL/6 male mice	6 weeks	Black raspberries	10% w/w	↑*Barnesiella* ↓F/B ratio ↓*Clostridium*	—	(Gu et al. 2019)
HFD-induced C57BL/6N mice	9 weeks	*Lonicera caerulea L.* berry polyphenols	1%	↑*Parabacteroides* ↑*Bacteroidales* ↑*Rikenellaceae* ↓*Staphylococcus* ↓*Lactobacillus* ↓*Ruminococcus* ↓*Oscillospira* ↓F/B ratio	↓Serum IL-2, IL-6, MCP-1, TNF-α, ↓Endotoxin	(Wu et al. 2018)
Clinical trails						
Patients with mild IBD aged 18–75 years	8 weeks	Mango polyphenols	200–400 g	↑*Lactobacillus spp.* ↑*Lactobacillus. plantarum* ↑*Lactobacillus. reuteri* ↑*Lactobacillus. lactis*	↑Butyric acid ↓Pro-inflammatory cytokines (IL-8, GRO, GM-CSF)	(Kim et al. 2020)
Men with metabolic syndrome aged 45–50 years	30 days	Dealcoholized red wine	272 mL/day	↑*Bifidobacteria* ↑*Lactobacillus* ↑*Faecalibacterium prausnitzii* ↑*Roseburia* ↓*Escherichia colia* ↓*Enterobacter cloacae* ↓F/B ratio	—	(Moreno-Indias et al. 2016)
		Hypercholesterolemic adults aged 46–67 years	3 weeks	Virgin olive oil phenolic compounds	25 mL/day	↑*Bifidobacteria*
↓Seric ox-LDL	(Martin-Pelaez et al. 2017)					
Healthy subjects aged 18–45 years	7 days	Orange juice	500 mL/day	↑ Mogibacteriaceae ↑*Tissierellaceae* ↑*Veillonellaceae*	—	(Brasili et al. 2019)

				↑*Odoribacteraceae* ↑*Ruminococcaceae*		
Overweight-obese subjects (BMI > 27 kg/m^2)	3 weeks	Pomegranate extract	656 mg	↑*Odoribacter* ↑*Bacteroides* ↑*Faecalibacterium* ↑*Butyricicoccus* ↑*Butyricimonas* ↓*Parvimonas* ↓*Metanobrevibacter* ↓*Metanosphaera*	↓ LBP	(Gonzalez-Sarrias et al. 2018)

T-AOC, total antioxidant capacity; T-SOD, total superoxide dismutase; APC, adenomatous polyposis coli; HFD, high fat diet; w/v, weight/volume; HFHS, high fat, high sucrose; w/w, weight/weight; bw, body weight; LPS, lipopolysaccharide; T-CHO, serumtotalcholesterol, TG: triglycerides; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; IBD, inflammatory bowel disease; GRO, monocyte growth-regulated oncogene; GM-CSF, granulocyte macrophage colony-stimulating factor; ox-LDL, oxidant low density lipoprotein; BMI, body mass index; LBP, lipopolysaccharide binding protein.

metabolites or the parent compounds alone is initially unclear. Therefore, precise microbiome studies are urgently needed in this area to provide novel insights for future clinical diet interventions. Second, given that the dynamic and delicate interactions amongst dietary polyphenols, host metabolome, and gut microbiota are personal, understanding this complex network of interactions requires the novel use of large datasets and the implementation of machine learning algorithms and artificial intelligence.

Conclusions

Overall, dietary polyphenols are increasingly envisaged as a novel strategy in the prevention and delay of the aging process. This review explained this strategy not only through the actions of polyphenols (and/or their metabolites) to reduce the oxidative stress and systematic inflammation and improve autophagy function but also to modulate the gut microbiota. Thus, polyphenols are promising nutraceuticals to combat age and age-related diseases. Although extensive knowledge has been gathered on the potential effect of polyphenols on the aging process, many important questions remain unanswered. These questions might generally be grouped into three categories. First, defining the individual roles of each polyphenol monomers in aging is difficult because of the variations in the consumption patterns (pure compounds or extracts containing different percentages of the compounds, dosage, and duration of the treatment), structure diversity and pleiotropy of polyphenols used in the study, food matrix, and the individual differences in gut microbiota diversity and the related metabolism. Second, the challenge for the future lies in the effective understanding of molecular mechanisms triggered by different anti-aging approaches as a proof-of-concept to design appropriate clinical trials whose current limitation represents the bottleneck in the field. Thus, although polyphenols are the best candidates as anti-aging agents, studies for the risk assessment and safety evaluation to determine the effective dosage of polyphenols must be prioritized. Additional research is needed to study the relationship between the chemical structure of polyphenols and their potential target on aging to find the active sites of phenolic compounds by computational chemistry methods, such as molecular docking and molecular dynamics simulation. Eventually, targeting gut microbiota has been considered to be a novel potential therapeutic avenue for the aging process. Despite the possible benefits of polyphenols for human health through microbiome modulation, studies are scarce and several limitations are found. The association of the microbiome analysis with other omics, such as genomics, transcriptomics, proteomics, and metabolomics, will clarify the biological effects of the polyphenol-microbiota interactions.

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