Dietary Polyphenols for Active and Healthy Ageing

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Abstract

The prolongation of lifespan is a desired condition, strictly depending from several factors, including genetics and environmental factors. In this context, nutrition can be a powerful tool, useful to modulate ageing. In particular, polyphenols constituents, widely distributed in edible vegetables and fruits, can act on specific intracellular markers, among which the enzyme sirtuin-1 (SIRT1) and several kinases, mainly AMPK, mTOR and MAPK/ERK and then contribute to reduce proinflammatory and fibrotic processes typical of the ageing; therefore inhibiting the progression of age-related pathologies, including neurodegenerative, cardiovascular and cancer. Indeed polyphenol family is very big and includes numerous subgroups of chemical constituents, ranging from rather elementary substances, such as phenolic acids and stilbenes, to complex polymerized molecules, such as tannins. They are different for distribution in the natural king and for bio-pharmacological profile. In this chapter the role played from polyphenols in the senescence has been evaluated.

Keywords

Ageing · Polyphenols · Lifespan · Health · Diet

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7.1 Introduction

The increase in life expectancy, in industrialized as well as developing countries, raises the number of age-related pathology incidences, such as cardiovascular, metabolic and neurodegenerative diseases, to a point beyond social and economic sustainability, making ageing an important and worldwide topic (Dilberger et al. 2019; Pray 2017; Tzioras et al. 2018). Several studies have demonstrated that healthy ageing depends on several factors, such as genetics and environmental factors; therefore, nutrition can be a powerful tool to modulate ageing (Mico et al. 2017).

Senescence is a process in which cells stop proliferating and become dysfunctional and secrete proinflammatory molecules, reactive oxygen species (ROS) and extracellular matrix components that cause inflammation in the surrounding tissues, responsible for a low-grade systemic inflammation and oxidative stress (Franceschi et al. 2018). Indeed, it is well known that an accumulation of cellular damage and a reduction in protective stress response pathways are at the basis of age-related diseases. In particular, the accumulation of genetic damage, including nuclear mutations, telomere attrition and epigenetic changes, can accelerate the shortening of the lifespan (López-Otín et al. 2013).

In addition, NF-κB is implicated as a key transcription factor in the development of chronic inflammation; in fact, NF-κB is implicated in the initiation of tissue-specific stress responses throughout the body (Aggarwal et al. 2004; Sethi et al. 2008). NF-kB is the principal supporter of the senescence-associated secretory phenotype (SASP), which is characterized by the production and secretion of proinflammatory cytokines, thereby sustaining the chronic inflammation typical of ageing (Queen and Tollefsbol 2010).

Another intrinsic age-related state observed in numerous organisms is the accumulation of toxins at the level of cells and organs; in neurodegenerative conditions, such as Alzheimer's disease (AD), β and γ secretases are critical for the production of insoluble amyloid proteins, known to play a role in Alzheimer's disease (Glukhov et al. 2008; Sebai et al. 2009).

Moreover, another event associated with ageing and the development of age-related diseases is mitochondrial dysfunction (Wagner et al. 2009; Modrick et al. 2009). A decline in mitochondrial function, and the commensurate loss of a sufficient energy production, supposedly plays a key role during ageing. Indeed, the free radical theory proposes that an age-related progressive loss of mitochondrial function is associated with ROS production (Green et al. 2011). However, the reduced efficiency of mitochondrial bioenergetics with ageing can result from reduced biogenesis of organelles, in which the transcriptional cofactor PGC1α, regulated through SIRT1, is crucial (Sahin and DePinho 2012). Therefore, developing ways to prevent mitochondrial dysfunction can prove a potent strategy to counteract adverse effects associated with ageing (Ikonomovic et al. 2009; Anisimov et al. 2009; Weinreb et al. 2004; Levites et al. 2003).

7.2 Targets Responsible for the Anti-Ageing Effects of Polyphenols

Polyphenols are natural compounds that are widely produced by plants, endowed with antibiotic and antifungal properties (Leiro et al. 2004) and moreover are well known for their antioxidant activity. However, in addition to promoting specific antioxidant and anti-inflammatory activities, polyphenols have garnered considerable interest for their role in the modulation of a plethora of targets.

New findings point to the possibility that polyphenols have suitable properties for treatment of several disease states in humans, and a combination of these may hold therapeutic benefits not yet realized (Cheynier 2005).

7.2.1 Sirtuin-Isoform 1 (SIRT1)

The role of sirtuin in the protecting against cellular senescence has mainly been investigated with mammalian sirtuin isoform 1 (SIRT1), which is a species-conserved NAD^+-dependent protein deacetylase that targets acetylated lysine residues in substrate proteins. It plays a crucial role in many cell signalling pathways (Heger et al. 2019); indeed, its overexpression has been shown to extend the lifespan of lower eukaryotes, such as yeast and worms, and to reduce senescence in several cell types, particularly when exposed to oxidants (Sasaki et al. 2006). In addition, the reduction of SIRT1 promotes premature senescence-like phenotypes in endothelial cells (Ota et al. 2007).

Taken together, these results support the idea that SIRT1 plays a role in cellular senescence. In vitro evidence shows that SIRT1 is capable of deacetylating a wide variety of proteins, including AMP-activated protein kinase (AMPK), p53, mechanistic target of rapamycin (mTOR) NF-κB, HSF-1, FOXO1, FOXO3, and FOXO4, and PGC-1α by directly activating them (Chaudhary and Pfluger 2009; Saunders and Verdin 2009), highlighting the complex network involved in longevity (Lee et al. 2019).

7.2.2 AMPK

AMPK is a pivotal energy sensor that alleviates or delays the process of fibrogenesis. Therefore, considering that fibrosis is a common process characterized by excessive extracellular matrix accumulation after inflammatory injury, AMPK is considered a crucial player that orchestrates ageing and the main diseases of the heart, liver, kidney and lung (Jiang et al. 2017; Hardie 2007; Steinberg and Kemp 2009; Mihaylova and Shaw 2011; Reznick et al. 2007).

Notably, Reznick et al. demonstrated that the ageing process is associated with a decline in AMPK, suggesting a reduced capability of organisms to respond to age-related stress (Reznick et al. 2007). Accordingly, several studies have highlighted that upregulated AMPK expression may be associated with a prolonged lifespan in lower organisms (Ulgherait et al. 2014; Stenesen et al. 2013).

7.2.3 mTOR

mTOR is a serine-threonine kinase that senses and integrates diverse environmental and intracellular signals, such as those initiated by growth factors and nutrients, to direct cellular and organismal responses (Saxton and Sabatini 2017). It is evolutionarily conserved, its name is derived from the first inhibitor rapamycin found to affect this signal transduction pathway, which is identified in the 1970s (Pazoki-Toroudi et al. 2016).

mTOR has been recognized as a regulator of lifespan of stem cells in the nematode *Caenorhabditis elegans* (Vellai et al. 2003), in the fruit fly *Drosophila melanogaster* (Kapahi et al. 2004) and in the yeast strain *Saccharomyces cerevisiae* (Kaeberlein et al. 2005). The inhibition of mTOR by rapamycin doubles the lifespan of these simple organisms and in more developed animal species, including rodents; suggesting that also mTOR network can be considered as a regulator of ageing and lifespan (Harrison et al. 2009; Selman et al. 2009).

Moreover, recently, a main role of mTOR in the promotion of SASP has been suggested, leading to hypotheses implicating its role in inflammation and in the increase in mitochondrial mass and markers of mitochondrial activity (Weichhart 2018).

7.2.4 MAPK/ERK

The mitogen-activated protein kinase (MAPK) signalling pathway is shared by four distinct cascades, which have been named accordingly to their components: extracellular related kinase (ERK1/2), Jun amino terminal kinase (JNK1/2/3), p38 MAPK and ERK5. These enzymes are activated through a sequential phosphorylation cascade that amplifies the signals transduced from the cell membrane to the nucleus. Depending on the duration and magnitude of its expression and its subcellular localization, ERK regulates various cell responses, such as proliferation, migration, differentiation and death (Ramos 2008). In particular, the activation of the ERK pathway can induce senescence; indeed, an increase in β-galactosidase activity and an induction of classical senescence-associated genes, including p16 and p21, have been reported (Denoyelle et al. 2006). Recent evidence has revealed that numerous bioflavonoids, obtained from a variety of dietary fruits, plants and medicinal herbal

sources, exhibit protective functions against the development of neurodegenerative diseases, mainly through the modulation of different compartments of the ERK signalling pathway (Farzaei et al. 2018).

7.2.5 Classification of Polyphenols

Polyphenols are one of the most abundant and extensively studied family of chemical entities, naturally produced by the plant kingdom (Bravo 1998). Polyphenols can be found in fruits, vegetables, nuts, seeds, flowers and tree bark. These components are involved in the attraction of pollinators, execution of structural functions, defence against ultraviolet radiation and protection against microbial invasion and herbivores (Manach et al. 2004). A wide number of substances containing numerous hydroxyl moieties on aromatic rings are included in this family. Furthermore, this class of compounds is highly diversified and comprises several subgroups, ranging from rather elementary substances, such as phenolic acids and stilbenes, to complex polymerized molecules, such as tannins (Cheynier et al. 2017). Natural polyphenols are present in nature in conjugated form, with one or more sugar residues associated with a hydroxyl group, although the direct linkage of a sugar unit to an aromatic carbon atom can also occur. Monosaccharides, disaccharides and oligosaccharides are also attached (Bravo 1998). Polyphenols are usually classified on the basis of the number of phenol rings and by the structural components that bind these rings together; therefore, phenolic acids, flavonoids, stilbenes and lignans are naturally produced (Fig. 7.1). Moreover, flavonoids can be further organized into distinctive subgroups, including anthocyanins, flavan-3-ols, flavones, flavanones and flavonols (Fig. 7.2) (Bravo 1998; Manach et al. 2004; Tsao 2010).

With regard to the physical properties of polyphenols, they played a critical role in determining the sensory and nutritional characteristics of foods and, in addition, to pigmentation. Although some volatile polyphenols, such as vanillin and eugenol, are extremely potent odorants; the most common flavour perceptions stimulated by polyphenols are astringency and bitterness, primarily elicited by flavonol polymers (proanthocyanidins or condensed tannins) (Bravo 1998; Lesschaeve and Noble 2005).

7.2.6 Phenolic Derivatives

Oleuropein, a polyphenol typically found in extra-virgin olive oil, in cultured neuroblastoma and in a mouse model of amyloid beta (Aβ) deposition, triggers autophagy through a rapid release of Ca^{2+} from stores, which in turn activates the phosphorylation and activation of AMPK. The link between AMPK activation and mTOR inhibition has also been observed in animal models, supporting the idea that autophagy activation by oleuropein proceeds through mTOR inhibition (Rigacci et al. 2015).

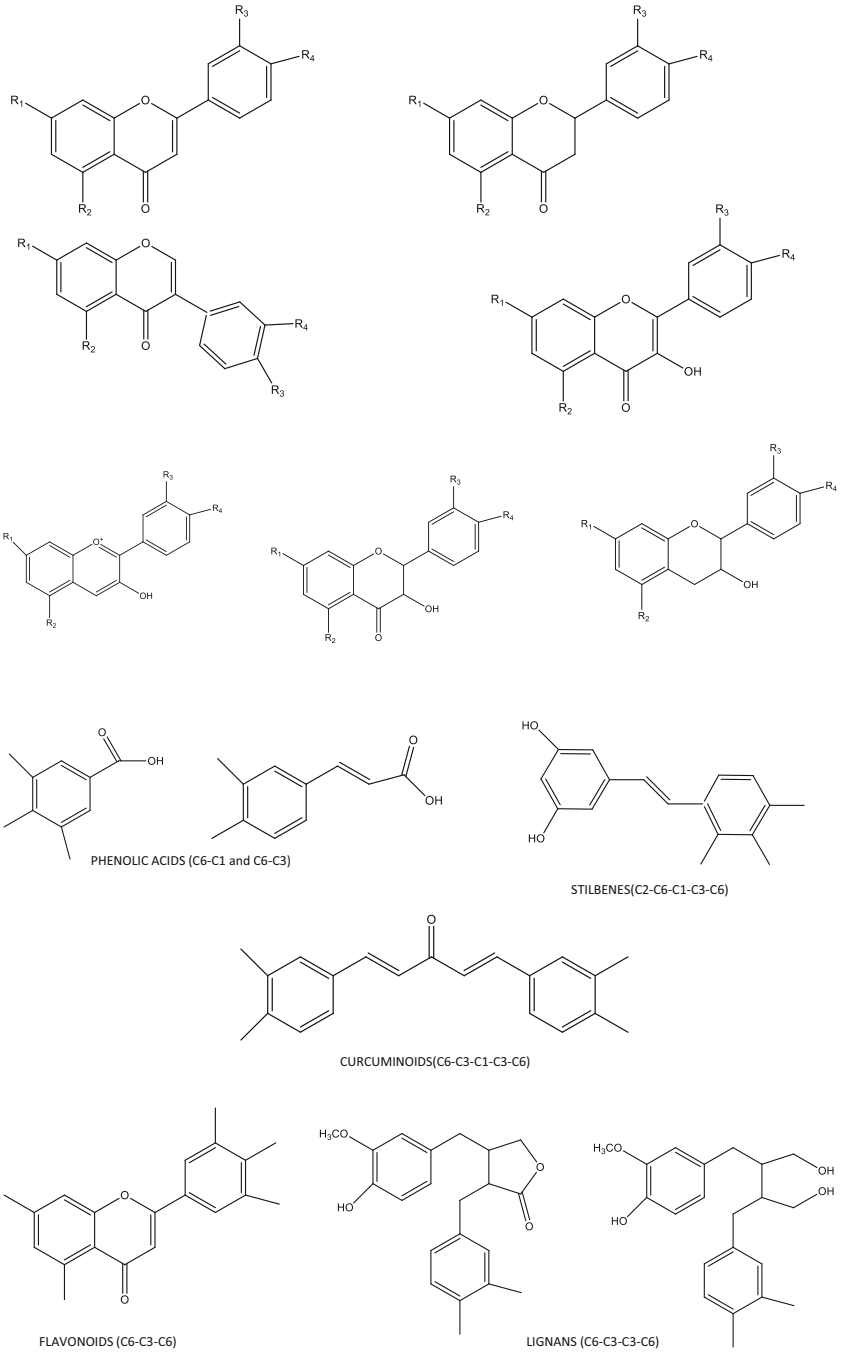

Fig. 7.1 Chemical structures of polyphenols classes

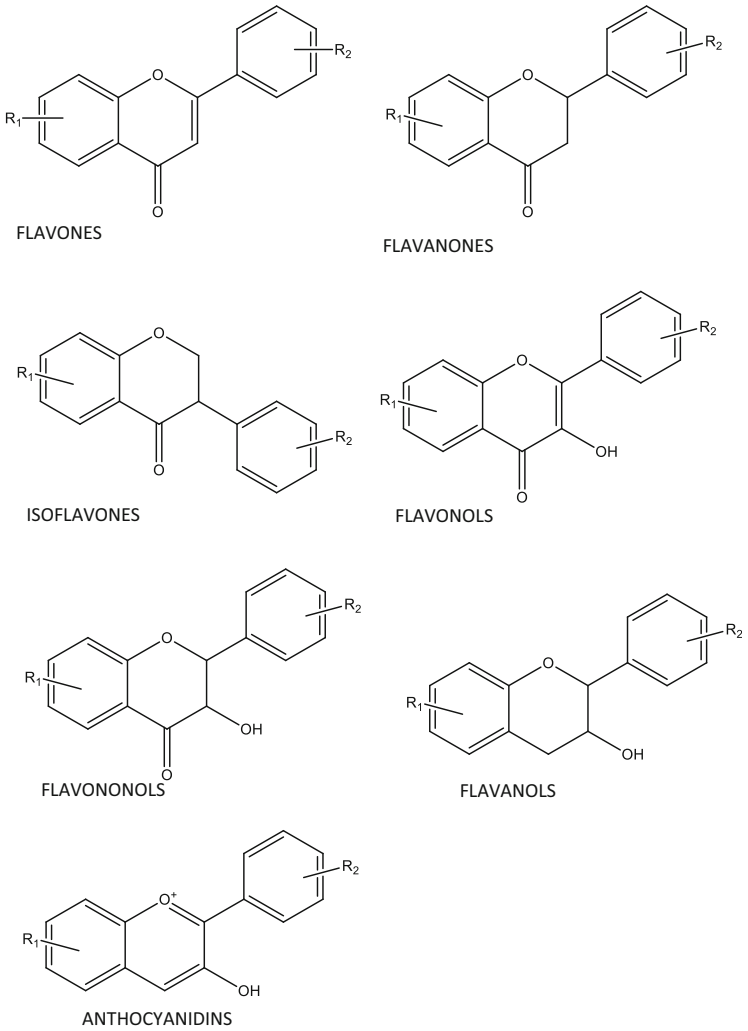

Fig. 7.2 Chemical structures of flavonoids sub-classes

7.2.7 Resveratrol and Other Stilbene Derivatives

A wide body of evidence suggests the positive effects of resveratrol (RSV), a well-known stilbene derivative, for enhancing health through multiple signalling pathways. First, RSV is recognized as a potent activator of the SIRT1 enzyme (Abolaji et al. 2018).

Interestingly, Smith et al. have shown that an innovative formulation of RSV, called SRT501, has a molecular profile similar to that observed under calorie-restricted conditions in both genetically and diet-induced obese mice. Recently,

other polyphenols structurally similar to RSV can activate SIRT1, as demonstrated in in vivo investigations, producing effects very similar to those of calorie restriction (Smith et al. 2009). Furthermore, RSV is able to induce AMPK, even in SIRT1-knockout mice, ensuring additional effective protection against ageing (Cheng et al. 2019). In zebrafish, retinal is involved in the same signalling pathways, and it has been hypothesized that RSV inhibits mitochondrial dysfunction through this pathway (Wang et al. 2019).

It has been demonstrated that RSV can modulate several mechanisms involved in cognitive decline, including antioxidant, anti-inflammatory and anti-apoptotic processes and autophagy regulation; however, it also increases blood flow and enhances the plasticity of synaptic pathways, suggesting that these functions can be, at least in part, the means through which RSV can be leveraged to support healthy ageing (Fontana 2009). Moreover, RSV activates the transmembrane protein α-secretase, which is associated with the formation of a soluble, non-amyloidogenic—non plaque-forming—protein from the amyloid precursor protein (APP) located in the membrane of neuronal cells. Interestingly, when soluble APP is produced, any neuritic plaque, a hallmark feature of AD, is formed. Indeed, APP is modified through a pathway that involves two additional enzymes, β- and γ-secretase, which sequentially process the APP protein, leading to the formation of insoluble, amyloidogenic oligomers or fibrils. Under these conditions, neuritic plaques are formed, suggesting the crucial role of RSV for understanding the aetiology of AD (Adlard et al. 2009; Mandel et al. 2008; Rao et al. 2020).

In addition, Benitez et al. have suggested that RSV may exert anti-proliferative and apoptotic effects by mediating the inhibition of NF-κB, as observed during in vitro studies of human prostate cancer cells (Benitez et al. 2009).

Moreover, RSV, in fish gut, reverses senescence-associated β-galactosidase activity, downregulates the levels of proinflammatory cytokines, IL-8 and TNFα, and upregulates the expression of the anti-inflammatory cytokine IL-10. Furthermore, RSV increases SIRT1 expression and inhibits NF-κB by decreasing RelA/p65, Ac-RelA/p65 and p-IκBα levels and by increasing the interaction between SIRT1 and RelA/p65. Moreover, it reverses the decline in intestinal epithelial cells (IECs) and intestinal stem cells (ISCs) in fish gut caused by ageing (Liu et al. 2018).

Interestingly, RSV alone or in combination with exercise significantly increases the expression of phosphorylated AMPK and SIRT1, decreases the expression of acetyl P53 and the Bax/Bcl-2 ratio in aged rats, showing significant improvement in gastrocnemius muscle morphology and ultrastructure and having possible positive effects in sarcopenia, an age-related syndrome characterized by progressive loss of muscle mass and function (Liao et al. 2017). Recently, RSV has been correlated with an improvement in the osteogenic differentiation of mesenchymal stem cells in bone through the activation of the AMPK signalling pathway (Zhou et al. 2019).

7.2.8 Curcumin

Curcumin (CRM) is a ferulic derivative obtained from the rhizome of *Curcuma longa*, commonly used as a spice (curry and turmeric) and yellow food dye (E100). It has a pleiotropic profile due to its ability to interact simultaneously with many receptors, growth factors, kinases, transcription factors, enzymes, adhesion molecules, apoptotic regulators, proinflammatory cytokines and other compounds (Bielak-Zmijewska et al. 2019). Furthermore, CRM upregulates and downregulates different kinds of miRNA and participates in epigenetic changes, such as the regulation of histone acetyltransferases and histone deacetylases (Gupta et al. 2013; Boyanapalli and Kong 2015; Remely et al. 2015; Reuter et al. 2011). Several in vitro and in vivo preclinical studies have demonstrated the potential therapeutic value of CRM against ageing-associated disorders, including atherosclerosis, hypertension, diabetes, neurodegenerative diseases, osteoporosis and cancer. In fact, it is the object of clinical trials for the treatment of these disorders (Kumar et al. 2018).

In particular, CRM reduces amyloid burden, rescues neuronal damage and restores normal cognitive and sensory motor functions in different animal models of neurodegenerative diseases (Maiti and Dunbar 2018). In this regard, CRM binds Aβ plaques, reducing their neurotoxicity and initiating their degradation; CRM injected intraventricularly in Aβ1–42-expressing rats reduces the cognitive decline and promotes hippocampal regeneration (Voulgaropoulou et al. 2019). At the vascular level, CRM increases the level of sirtuins and AMPK in vascular smooth muscle cells undergoing replicative senescence (Grabowska et al. 2016). Finally, mice and rats receiving CRM supplements showed enhanced effects from exercise in terms of time until exhaustion and prevention of fatigue, most likely because of an increased level of AMPK and SIRT1 expression and/or activation in muscles (Huang et al. 2015; Ray Hamidie et al. 2015).

7.2.9 Classification of Flavonoids

Flavonoids are abundantly present in plants as secondary metabolites. The basic chemical structure of flavonoids is represented by two benzene rings (A and C) connected by a pyran ring B (Fig. 7.2). One of the benzene rings (A) is fused with the pyran ring, while the other benzene ring (C) is attached as a substituent to the pyran ring. Various derivatives of flavonoids are produced, depending on the pattern of substitution on the benzene rings and of the oxidation and saturation status of the pyran ring.

Therefore, isoflavones present a benzene ring (C) attached to position 3 of the pyran ring and are typical of various natural products, mainly soybean (Wang and Murphy 1994).

Neoflavonoids have a benzene ring (C) attached to position 4 of the pyran ring (Donnelly and Boland 1995).

Flavones contain a double bond in the pyran ring between positions 2 and 3 and hydroxyl substituents in both aromatic rings (Fukui et al. 1968).

Flavonols differ from the flavones in the hydroxyl group at position 3 of the pyran ring; indeed they are the alcoholic derivatives of flavones and generally, they are known as 3-hydroxyflavones.

Flavanones, saturated flavones, are also known as dihydroflavones. They differ from flavones and flavanones for the absence of a double bond between positions 2 and 3. Flavanones are characteristic, but not exclusive, to the *Citrus* genus.

The flavanonols are 3-hydroxy flavanones and are also called dihydroflavonols. They present a saturated pyran ring, a hydroxyl group at position 3 and a carbonyl group at position 4.

Finally, flavanols, also called flavan-3-ol, are lacking of a carbonyl group at position 4. The pyran ring is saturated and disubstituted at positions 2 and 3. This chemical characteristic leads to four possible diastereomers of the flavanol. In flavanols, the benzene ring (C) is attached to position 2, while the hydroxyl groups are attached at position 3 of the pyran ring (Ayaz et al. 2019).

7.2.10 Evidence of Anti-Ageing Properties of Flavonoids

Several flavonoids have been demonstrated to inhibit the progression of age-related neurodegenerative pathologies and to alleviate cognitive deficits in numerous normal and transgenic preclinical animal models. Indeed, flavonoids are recognized as inhibitors of cholinesterases, including acetylcholinesterase and butyrylcholinesterase; β-secretase; and free radicals and considered possible modulators of the signalling pathways implicated in cognitive and neuroprotective functions. Moreover, flavonoids can to interact with various signalling protein pathways, including ERK and PI3-kinase/Akt, to modulate their actions, thereby leading to beneficial neuroprotective effects. Finally, they enhance vascular blood flow and stimulate neurogenesis, particularly in the hippocampus (Macready et al. 2009; Spencer 2010; Zhang et al. 2019a).

7.2.10.1 Anthocyanidins

Berry fruits, which contain high amounts of flavonoids, especially anthocyanidins, have received particular attention for preventing age-related cognitive decline. In particular, blueberry supplements has been shown to improve memory and learning. Moreover, a long-term prospective study on neurologically healthy elderly people emphasized that increased intake of berry anthocyanidins is associated with a slower rate of cognitive decline and delays in the onset of deficits by approximately 2.5 years (Bakoyiannis et al. 2019).

7.2.10.2 Flavanols

A number of preclinical and clinical evidence points to the beneficial effects of flavanols in age-related disorders, particularly neurodegenerative and cardiovascular disorders. Cocoa and green tea contain high amounts of flavanols, among which are epicatechin, catechin and their derivatives (Ottaviani et al. 2018).

Evidence suggests that cocoa flavanols can benefit brain function via mechanisms that include enhanced neuronal plasticity and cerebrovascular function. For example, epicatechin has been found to enhance the retention of spatial memory in male C57BL/6 mice (8–10 weeks old), particularly in combination with exercise, and catechins of green tea administered to 14-month-old female mice for 6 months prevented spatial learning and memory decline (Yevchak et al. 2008; Mastroiacovo et al. 2015; Alonso-Alonso 2015). An increase in hippocampal brain-derived neurotrophic factor has also been observed in adult C57BL/6 mice treated with 4 mg/day of epicatechin (Stringer et al. 2015). Cocoa flavanol intake for 2 weeks improved flow-mediated dilatation in both the young and elderly patients included in the clinical study, where it enhanced arteriolar and microvascular vasodilator capacity and decreased systolic blood pressure (Heiss et al. 2015). More recently, cocoa flavanol consumption was found to improve the endothelial functional integrity in healthy humans, thereby decreasing endothelial microparticle levels, a marker inversely correlated with flow-mediated dilation (Gröne et al. 2019).

7.2.10.3 Citrus Flavanones

Recently, the citrus flavonoids naringenin (NAR) and hesperetin (HSP) have been reported to prevent senescence. In particular, Da Pozzo and colleagues demonstrated that a juice obtained from *Citrus bergamia*, Rizzo, called bergamot, (BJ) was able to induce antioxidant effects and to inhibit the expression of senescence markers (β-galactosidase, p16 and p21) in cardiomyoblasts subjected to damage following treatment with doxorubicin or hydroxyperoxide. Moreover, BJ upregulated SIRT1, Nrf2 and FOXO3 expression in 12-month-old mice that had received it as a supplement for 3 months (Da Pozzo et al. 2018).

NAR is well known for the anti-ischemic cardioprotective profile it confers to adult rats, which is mediated by stimulation caused by large-conductance calcium-activated potassium channels in mitochondria (Martelli et al. 2013). Later, Testai et al. confirmed that this profile is maintained in older animals (12 months), suggesting that NAR could be considered a valid supplement that benefits elderly patients (Testai et al. 2017).

Interestingly, Testai and colleagues recently demonstrated that NAR is endowed with anti-senescence activity, which it confers through the activation of the SIRT1 enzyme. Indeed, NAR presented a similar profile to that presented by BJ with respect to senescent doxorubicin-treated cardiomyoblasts, showing a reduction in β-galactosidase and in p21 and p16; moreover, these researchers demonstrated that NAR administered to 12-month-old mice for 6 months inhibited oxidative stress, chronic inflammation and fibrosis processes at the myocardial level (Da Pozzo et al. 2017). It is noteworthy that NAR slowed the progression of degenerative processes in a retinitis pigmentosa model (Piano et al. 2019).

HSP has antioxidant properties that are not limited to its radical scavenging activity; in fact, HSP exhibits a pivotal role in senescence processes by enhancing cellular antioxidant defences via the ERK/Nrf2 signalling pathway (Parhiz et al. 2015; Kim et al. 2006). Of note, HSP-glycoside (hesperidin) can inhibit ROS production in *Saccharomyces cerevisiae*, as demonstrated by the reduction in SOD gene expression. This effect seems to be correlated with an increase in Sir2 activity (homologue of the mammalian SIRT1 enzyme) (Sun et al. 2012). HSP also significantly reduces the secretion of inflammatory cytokines, including IL-1β and IL-6, and downregulates the phosphorylation of ERK/MAPK pathway components during LPS-induced neuroinflammation involving BV2 cells (Jo et al. 2019).

7.2.10.4 Flavonols

Quercetin (QRC) is the main flavonol in the daily human diet, and most of the quercetin in plants is in the glycoside form. QRC has been demonstrated to modulate sirtuins and to protect against several chronic diseases; in particular, this flavonol stimulates the SIRT1 enzyme both in vitro and in vivo models through direct and indirect mechanisms (Howitz et al. 2003; Trevino-Saldana and Garcia-Rivas 2017). Notably, the role of QRC is not restricted to SIRT1; in fact, it also upregulates SIRT2 expression in vivo (Peredo-Escarcega et al. 2015), and similar to kaempferol, it can inhibit SIRT6 (Rahnasto-Rilla et al. 2018). In this regard, through molecular docking approaches the mechanisms involved in the modulation of the SIRT6 enzyme by QRC and its derivatives have been investigated. The authors of these studies observed that diquercetin preferred a binding site in the nicotinamide (NAM) moiety, whereas 2-chloro-1,4-naphthoquinone-quercetin preferred to dock at a substrate binding site, leading to speculation that different interaction sites are involved in QRC activity; indeed, diquercetin competes with nicotinamide adenine dinucleotide (NAD^+), whereas 2-chloro-1,4-naphthoquinone-quercetin competes with the acetylated substrate in the catalytic site of SIRT6 (Papaevgeniou and Chondrogianni 2018).

A short treatment with QRC *plus* caloric restriction (but not alone) is effective to counteract t age-related accumulation of oxidative macromolecular damage, including the decline in SOD and catalase activity, counteract, in 21-month-old Wistar rats (Alugoju and Periyasamy 2018). An interesting reaction in which antioxidant defences were ameliorated has also been observed in mice with D-galactose-induced neurotoxicity. The administration of QRC at 20 and 50 mg/kg for 8 weeks improved mouse learning and memory compared to the memory and learning observed in the control mice. QRC also prevents changes in neuronal cell morphology and apoptosis rate in the hippocampus, and it increases the expression of Nrf2, HO-1 and SOD in D-galactose-treated mice. Finally, the abolition of these effects in the presence of a Nrf2 inhibitor corroborates the involvement of the Nrf2-ARE signalling pathway in the beneficial action of QRC (Dong et al. 2017).

Sarubbo et al. reported in vivo effects of long-term QRC administration in 18-month-old Sprague-Dawley rats when administered in combination with silymarin and naringenin (20 mg/kg/day i.p., 4 weeks). The restorative effects of QRC on cognition and motor coordination were consistent with the biochemical and

molecular results. In addition, polyphenols increased SIRT1 levels and decreased NF-κB levels in the hippocampus, confirming it is a valuable potential therapeutic for attenuating inflammation and brain function decline (Sarubbo et al. 2018).

Fisetin is another flavonol with a promising senotherapeutic profile; indeed, an acute or intermittent fisetin treatment of progeroid and aged mice reduced senescence markers in multiple tissues in a dose-dependent manner (Yousefzadeh et al. 2018).

Of note, fisetin suppresses markers of senescence in vivo in transgenic mice characterized by accelerated accumulation of senescent cells but not in wild-type mice, suggesting that this natural compound intriguingly can confer specific health benefits to elderly patients (Yousefzadeh et al. 2018).

Furthermore, Wistar rats that received fisetin supplements had modulated membrane transporters, namely, calcium-ATPase, sodium potassium-ATPase and sodium hydrogen exchanger, during senescence-induced by D-galactose and during natural ageing. Fisetin also protected against oxidative modifications in rat ageing (Singh et al. 2019).

7.2.10.5 Flavones

Chrysin, an abundant flavone present in honey and propolis, at a dose of 10 mg/kg significantly protects against age-related memory decline, attenuating the increase in ROS levels and the inhibition of SOD, CAT and GPx action in aged mice. Moreover, chrysin markedly mitigates the decrease in brain-derived neurotrophic factor (BDNF) levels in prefrontal and hippocampal regions (Souza et al. 2015). Generally, chrysin supplementation for 8 weeks, protected against oxidative damage from with the exposure to D-galactose, as confirmed by histopathological evaluation (Anand et al. 2012).

More recently, Farkhondeh et al. observed that chrysin was effective in attenuating age-related lipid abnormalities, glucose elevation and inflammation, in young (2-month-old) and old (20-month-old) rats (Farkhondeh et al. 2019).

7.2.10.6 Isoflavones

Anti-senescence activity has also been demonstrated by genistein, an isoflavone, in human umbilical vein endothelial cells. This effect seems to be associated with induced autophagy through the involvement of the SIRT1/AMPK pathway (Zhang et al. 2019b). Similarly, formononetin (another isoflavone) has been associated with cardioprotective effects in a model of ischaemia/reperfusion injury in the hearts of aged rats, which was also induced through enhanced autophagy (Huang et al. 2018).

7.2.11 Bioavailability of Polyphenols: A Limit to or an Advantage for Clinical Efficacy?

A body of evidence on human disease models demonstrates beneficial effects of polyphenolic compounds, however, the development of new and effective treatments greatly depends on obtaining a greater understanding of the

bioavailability and metabolism of polyphenols (Cheynier et al. 2017). After oral intake, polyphenols are rapidly hydrolysed into the aglycones by lactase-phlorizin hydrolase or cytosolic β-glucosidase in the small intestine or by bacterial glycosidases in the colon. The plasma concentrations in humans after intake of polyphenol-rich food can reach to a maximum on the order of several μM (Murota et al. 2007; Mullen et al. 2006). The aglycones are further metabolized through phase reaction into glucuronides by UDP-glucuronosyltransferase and/or sulphates by sulfotransferase, and those with the catechol moiety can also be methylated by catechol-O-methyltransferase (COMT) (Nemeth et al. 2003; Murota and Terao 2003; Kawai 2018). Indeed, phase reactions are generally recognized as responsible for production of more polar, hydrophilic, and biologically inactive molecules that are more readily excreted in urine.

Most recently, the interactions between polyphenols and intestinal microbiota have been considered crucial to gaining greater knowledge of the metabolic destiny of these natural compounds. Indeed, recent evidence suggests the existence of reciprocal relationship between polyphenols and microbiota. On the one hand, microbiota, in the gastrointestinal tract, can influence the absorption and bioavailability of polyphenols in ingested food, and on the other hand, the microbiota can also influence the metabolism of polyphenols, leading to the production of propionic and acetic derivatives, also known as short chain fatty acids (SCFAs). Interestingly, SCFAs are thought to greatly modulate the local immune system and intestinal permeability and are critical to the microbiota composition. Therefore, SCFAs have been suggested to have the ability to stimulate mitochondrial biogenesis and metabolism; specifically, it has been hypothesized that, despite the low bioavailability of polyphenols, significant beneficial effects can be mediated by their microbiota-produced metabolites. In light of this hypothesis, a substantial impact on the potential benefits of polyphenols has been correlated with the intestinal microbiota population (Kumar Singh et al. 2019). Further work is required to fully understand the complex interactions between polyphenols and the microbiota and to determine the exact nature of their subsequent local and systemic health benefits, particularly in humans.

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