# Chapter 11
# Plant Polyphenols in Healthcare and Aging


**Kanti Bhooshan Pandey and Syed Ibrahim Rizvi**

**Abstract** Aging is characterized by a progressive inability of organs of biological systems to defend against environmental stressors. Oxidative stress, a state of imbalance between cellular production of oxygen free radicals and reactive oxygen species (ROS) and their removal by antioxidants, has emerged as a critical player in aging process. Indeed, oxidative stress status is observed during aging and in numerous age-related diseases. The accumulation of deleterious oxidative damages occurring in cells with advancing age would induce damage of the vital cellular macromolecules, lipids, proteins, and DNA, which can potentially lead to cell dysfunction and death. Hence, organs and tissues accumulate free radical damage over time under conditions in which their endogenous antioxidant defenses are overwhelmed, resulting in overall cellular redox imbalance and impaired organ physiology. Dietary antioxidants are bioactive molecules, which can scavenge ROS and decrease the incidence of oxidative stress-induced damage. Plant antioxidants, including polyphenols, have been extensively studied for their beneficial health effects in human. There is evidence that populations consuming diets rich in polyphenols are less susceptible to oxidative damage and diseases during aging. The present chapter deals with the free radical theory of aging, providing current evidence of dietary interventions aimed at limiting the aging process. This chapter also describes the biological activities of some abundantly occurring polyphenols and their possible roles in healthcare as well as in prevention and treatment of age-related diseases.

**Keywords** Oxidative stress • Dietary antioxidants • Polyphenols • Healthy aging

K.B. Pandey • S.I. Rizvi (✉)
Department of Biochemistry, University of Allahabad,
Allahabad 211002, India
e-mail: sirizvi@gmail.com



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## 11.1 Introduction

The process of aging is characterized by a progressive inability of organs and tissues of biological systems to defend against environmental stressors that leads to alterations in the normal functioning of organism over time and an enhanced susceptibility to many diseases (Rattan 2006; Donato et al. 2015). The free radical theory of aging hypothesizes that oxygen free radicals generated during cellular metabolism and respiration are responsible for the age-related damage of organs and tissues in aerobic organisms (Harman 1956, 2006). Free radicals and other reactive oxygen species (ROS) damage mitochondrial DNA, which in turn induce mutations and alter mitochondrial function, including adenosine triphosphate (ATP) production (Sanz and Stefanatos 2008). Hence, cells accumulate free radical damage over time under conditions in which their antioxidant defenses are overwhelmed, resulting in overall cellular redox imbalance, organ dysfunction, and chronic diseases (Valko et al. 2007). Exhaustive research on the aging population repeatedly reports decrease in plasma antioxidant capacity with age (Pandey and Rizvi 2010b; Moreira et al. 2014).

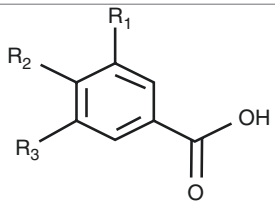
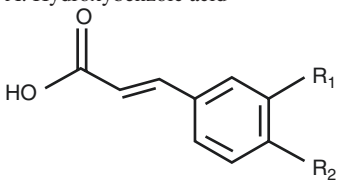
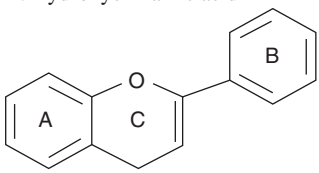
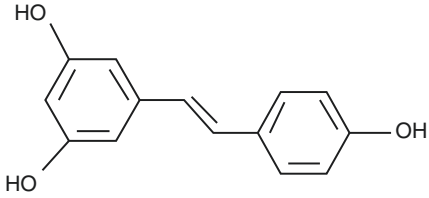
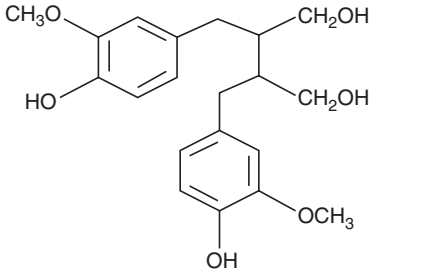
Natural antioxidants, including polyphenols, are abundantly present in many plants and their products. Polyphenols are synthesized in plants as secondary metabolites in times of adversity such as exposure to stressors: solar ultraviolet (UV) radiation, toxic heavy metals, and free radicals generated during the photosynthetic process or during pathogens attack (Stevenson and Hurst 2007). Polyphenols have been extensively studied for their beneficial pleiotropic biological effects in human health (Scalbert et al. 2005; Pandey and Rizvi 2009a; Moreira et al. 2014). Antioxidants are bioactive molecules, which can scavenge ROS and decrease the incidence of oxidative stress-induced cellular damage. Dietary supplementation with plant-derived polyphenols has emerged as a promising approach to counteract age-associated physiological dysfunction (Queen and Tollefsbol 2010). Clinical, nutritional, and epidemiological studies indicate that populations consuming diets rich in polyphenols are less susceptible to many age-associated pathologies such as cardiovascular disease (CVDs), diabetes, and cancer (Pandey and Rizvi 2009b; Khurana et al. 2013; Park and Pezzuto 2015). Considering that plants are major sources of various polyphenolic compounds, this chapter describes the biological activities of some abundantly occurring polyphenols and their possible roles in healthcare as well as in prevention and treatment of age-related chronic diseases.

## 11.2 Polyphenols: Occurrence, Types, and Structure

Polyphenols are the most numerous and widely distributed groups of molecules in the plant kingdom. More than eight thousand polyphenols have been identified in different food sources derived from plants (Pandey and Rizvi 2012a); however, their distribution is not uniform. Insoluble polyphenols such as resveratrol, myricetin, and astringin occur abundantly in cell walls, while soluble phenolics such as gallic

acid, cyanidin, and catechins are present in plant cell vacuoles. Fruits and vegetables are major sources of polyphenolic compounds. Linseed is a major source of lignans, where secoisolariciresinol levels can reach 3.7 g/kg dry weight (Adlercreutz and Mazur 1997). Blueberries, kiwis, cherries, and apples contain 0.5–2 g/kg of phenolic acids. Fresh onions have up to 1.2 mg/kg quercetin. Resveratrol content in red wine varies between 0.1 and 14 mg/L, while dried grape skins contain about 24.06 mg/g

**Table 11.1** Different classes of plant polyphenols with their structure and examples

| | |
|---|---|
| 1. *Phenolic acids*<br>Phenolic acids comprise about one third of total polyphenols known and are further divided into two subclasses: hydroxybenzoic acid and hydroxycinnamic acids. Phenolic acids generally do not exist in free form in nature but occur as glycosylated or ester derivatives<br>Examples: gallic acid, protocatechuic acid, caffeic acid, and ferulic acid |  <br>A. Hydroxybenzoic acid<br>  <br>B. Hydroxycinnamic acid |
| 2. *Flavonoids*<br>Flavonoids consist of two aromatic rings that are bound together by three carbon atoms that form an oxygenated heterocycle. Based on the variations in the type of heterocyclic involved, flavonoids are further divided into six subclasses<br>Examples: quercetin, myricetin, catechins |  <br>Divided in six subclasses:<br>Flavonols, flavones, flavanones, flavanols, anthocyanins, isoflavones |
| 3. *Stilbenes*<br>Stilbenes contain two phenyl moieties connected by two-carbon methylene bridges. They are synthesized in response to infections or injury<br>Examples: resveratrol, piceids, astringins |  |
| 4. *Lignans*<br>Lignans are diphenolic compounds that contain a 2,3-dibenzylbutane structure that is formed by the dimerization of two cinnamic acid residues. Several lignans, such as secoisolariciresinol, are considered phytoestrogens<br>Examples: secoisolariciresinol, matairesinol |  |

of resveratrol (Burns et al. 2002). Red wine and green tea contain up to 45 mg flavonoids/L (Pandey and Rizvi 2009c).

Although different polyphenols vary in their structures, they all stem from a common intermediate phenylalanine or a close precursor, shikimic acid (Spencer et al. 2008). Based on the number of phenol rings and the structural moieties that bind these rings to one another, polyphenols are classified into four major classes: phenolic acids, flavonoids, stilbenes, and lignans. Hydroxybenzoic acid and hydroxycinnamic acids are subclasses of phenolic acids since they are derived from two different precursors: benzoic acid and cinnamic acid. Flavonoids are further divided into six subclasses, flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones (Table 11.1), on the basis of the type of heterocycle involved (Pandey and Rizvi 2009c).

## 11.3 Antiaging Effect of Plant Polyphenols

Polyphenols are reported to contribute to the human health benefits associated with consumption of diets rich in fruits and vegetables or plant-derived beverages. Plant polyphenols protect against oxidative damage and can extend life span in multiple species. Green tea polyphenols, mainly epigallocatechin gallate (EGCG) and epigallocatechin (EGC), have been reported to extend life span by almost 6% in the C57BL/6 mouse strain, possibly by mechanisms related to caloric restriction and hormesis (Kitani et al. 2007). Quercetin has also been reported to extend the life span of the nematode *Caenorhabditis elegans* (Saul et al. 2008). Quercetin is able to prevent the oxidation of lipids, proteins and DNA while also restoring the diminished antioxidant status in different types of cells such as erythrocytes and hepatic and endothelial cells in many organisms including humans (Pandey and Rizvi 2009b; Boots et al. 2008; Pandey et al. 2010). Likewise quercetin and caffeic acid can extend life span of nematodes by increasing antioxidative capacity in vivo and reducing oxidative damage (Pietsch et al. 2011). Population-based observational studies indicate that consumption of polyphenol-rich foods reduced mortality rates and the incidence of CVDs and cancer (Stevenson and Hurst 2007). Other evidence supporting the antiaging effect of polyphenols is the fact that consumption of red wine (Baur and Sinclair 2006) or green tea (Khan and Mukhtar 2013) is associated with reduced rates of mortality. Furthermore, polyphenols have also the potential to counteract age-associated diseases including cancer, based on their ability to modulate master regulatory molecules involved in various disease states (Novelle et al. 2015).

## 11.4 Antioxidant Effect of Specific Plant Polyphenols

Epidemiological studies report that dietary polyphenols enhance plasma antioxidant capacity and protect biological systems from oxidative injury during the aging process (Khurana et al. 2013, Singh and Rizvi 2015). Importantly, the antioxidant

effect of specific plant polyphenols, mainly catechins, curcumin, and resveratrol, was the subject of considerable studies.

### *11.4.1 Catechins*

Green tea catechins are the most widely studied natural polyphenols, particularly because of their pleiotropic biological effects (Khan and Mukhtar 2013). Rats receiving green tea extract exhibit higher levels of antioxidant enzymes including glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) (Skrzydlewska et al. 2005). A study in humans demonstrated that consumption of two cups of green tea containing about 250 mg of total catechins for 42 days significantly improved plasma total antioxidants while also reducing peroxide levels (Singh et al. 2008). Catechins decrease the impact of oxidative burden by inhibiting the expression of xanthine oxidase, a key enzyme for the generation of free radicals in the body (Bickford et al. 2000). Catechins protect the oxidation of lipids in the aging brain and liver (Skrzydlewska et al. 2005). Various mechanisms have been proposed through which catechins elicit antioxidant activities including chelation of metal ions such as Fe (II) and Cu (II). Ultra-rapid transfer of electrons to ROS-induced radical sites on DNA is another mechanism by which catechins can act as antioxidants (Singh et al. 2008). Moreover, oxidation of catechins by ROS results in a dimerized product, which has the ability to scavenge superoxide ($^{\bullet}O^{2-}$) free radicals (Singh et al. 2008).

### *11.4.2 Curcumin*

Curcumin in micro molar concentration scavenges ROS in both in vitro and in vivo studies (Joe and Lokesh 1994; Singh and Rizvi 2015). Altered ion homeostasis and enhanced osmotic fragility, which is an index of membrane integrity, have been reported during aging in the study carried out on 91 normal healthy subjects of both sexes (59 males and 32 females) between the ages of 18 and 80 years (Pandey and Rizvi 2013, 2014a, b). Glutathione plays an important role in antioxidant defenses either by reacting directly with ROS or by acting as cofactor for GPx. Curcumin has the potential to reduce myocardial lipid peroxidation by increasing glutathione content and GPx activity (Venkatesan 1998). Experimental studies using several cell models document that curcumin protects the cellular integrity and homeostasis by preventing the peroxidation of lipids and oxidation of proteins (Kolodziejczyk et al. 2011). It is important to note that treatment with 0.1–10 μM curcumin reduces the intracellular ROS levels in many types of cells during adverse conditions such as inflammation, oxidative stress, and neuronal disorders (Singh et al. 2008; Kim et al. 2007; Singh and Rizvi 2015).

### *11.4.3 Resveratrol*

Resveratrol, a natural compound with anti-inflammatory and antioxidant properties (Bo et al. 2013), has been reported to prevent CVDs, diabetes mellitus, and neurodegenerative disorders (Smoliga et al. 2011). Significant increases in plasma antioxidant level and reductions in lipid peroxidation occur after consumption of resveratrol-rich diets (Wenzel et al. 2005). Oxidation of low-density lipoprotein (LDL) particles is strongly associated with the risk of developing CVDs and myocardial infarction during aging (Baur and Sinclair 2006). Resveratrol prevents oxidation of LDL and hence provides protection against myocardial infarction (Urpí-Sardà et al. 2005). Resveratrol reduces glycated albumin in serum and 8-hydroxyguanosine in urine, both markers of oxidative stress, in stroke-prone spontaneously hypersensitive rats (Mizutani et al. 2001). Resveratrol (10–100 μM) decreases the expression of the superoxide-producing enzyme NADPH oxidase 4 (Nox4) and, at the same time, increases protein expression of ROS scavenging antioxidant enzymes, SOD 1 and GPx, in human endothelial cells (Spanier et al. 2009). It has been also reported that resveratrol provides protection against lipid peroxidation, protein carbonylation, and sulfhydryl group oxidation in erythrocytes during aging in humans (Pandey and Rizvi 2013).

## 11.5 Activation of Plasma Membrane Redox System by Polyphenols

The impairment of cellular homeostasis during aging is well described (Radak et al. 2011; Sohal and Orr 2012). There is a mounting realization that the structural and functional damage-based hypothesis of aging process actually involves a shift in cellular redox states (Sohal and Orr 2012; Rizvi and Jha 2011). A group of oxidoreductase enzymes known as plasma membrane redox system (PMRS) exist in the plasma membrane of the eukaryotic cells; these enzymes play a crucial role in maintaining the redox state of the cell (Hyun et al. 2006; Pandey and Rizvi 2010a). The PMRS transfer reducing equivalents from intracellular donors such as ascorbate and nicotinamide adenine dinucleotide reduced (NADH) to extracellular acceptors that are used to maintain homeostasis though several mechanisms (Rizvi et al. 2009; VanDuijn et al. 1998).

The PMRS along with the enzyme ascorbate free radical (AFR) reductase recycles ascorbate in the plasma. The role of PMRS becomes very significant since ascorbate acts as a primary antioxidant in the body and also serves as a cofactor in many important enzymatic reactions (Harrison and May 2009). Activation of the PMRS along with AFR reductase is hypothesized to be a compensatory mechanism operating in the body to minimize the redox imbalance that occurs during aging (Pandey and Rizvi 2012a; Rizvi et al. 2009). An enhancement of PMRS is a mechanism by which caloric restriction may counteract mitochondrial dysfunction and

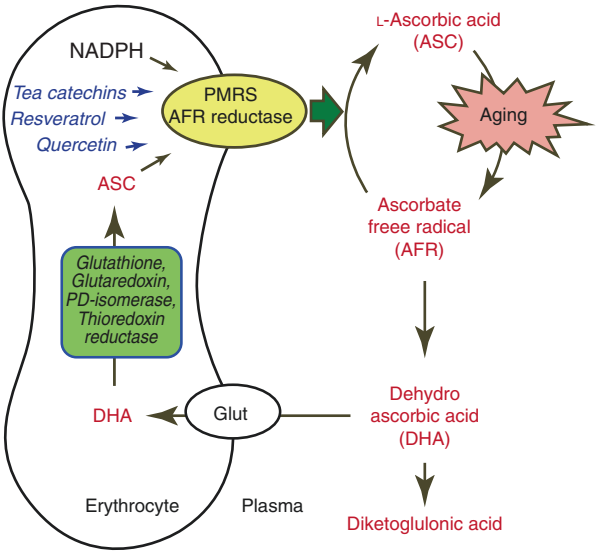



**Fig. 11.1** Schematic representation of the role of polyphenols in maintaining intra- and extracellular redox states in human erythrocytes. *PMRS* plasma membrane redox system, *NADH* nicotinamide adenine dinucleotide, *Glut* glucose transporter

oxidative stress in the brain during aging (Hyun et al. 2006). Upregulation of PMRS is considered as an effective antiaging strategy (Rizvi and Jha 2011). Many polyphenols can activate the PMRS and AFR reductase in human cells. A study of 97 human male and female subjects aged between 18 and 82 documents that resveratrol significantly upregulates the redox system and ascorbate recycling during aging (Pandey and Rizvi 2013). It has been proposed that some polyphenols can enter in cells and, once inside, accumulate in higher concentrations compared to their concentration in the plasma. Quercetin and green tea catechins including EGCG and EGC activate the PMRS by accumulating in cells and donating electrons within the intracellular compartment in a dose-dependent manner (Fig. 11.1) (Pandey and Rizvi 2012b; Rizvi et al. 2010).

## 11.6 Caloric-Restriction Mimicking Effect of Polyphenols

Caloric restriction is a reduction in food intake without malnutrition. Studies report that 2–30% reduced caloric intake prolongs life span of various organisms, including yeast, nematodes, rodents, and some nonhuman primates (Colman et al. 2009, 2014; Fontana et al. 2010; Mercken et al. 2012). Caloric restriction has been reported to extend the average and/or maximum life span in *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila*, mice, and rhesus monkeys (Fontana et al. 2010). In both rodents and monkeys, caloric restriction also delays loss of function

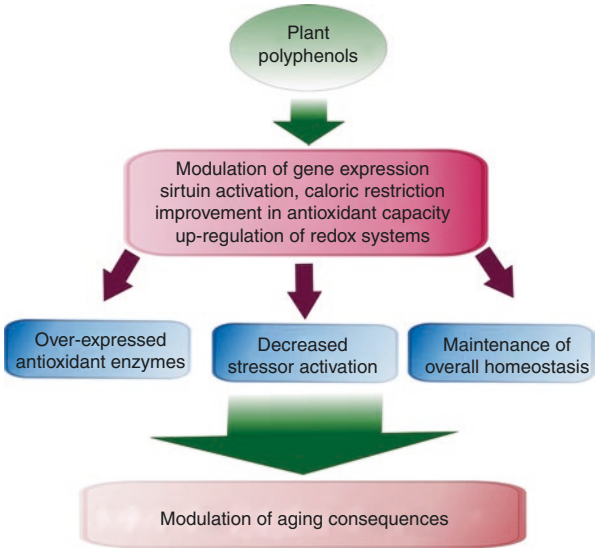



**Fig. 11.2** Diagrammatic representation of role of polyphenols in mitigating aging consequences

and reduces the incidence of chronic diseases, and in humans it causes a reduction in metabolic markers of many diseases such as diabetes, neural problems, cancer, and CVDs (Omodei and Fontana 2011). Recent studies on aging interventions suggest that consumption of polyphenols mimics caloric restriction and may thus mitigate age-dependent diseases (Fig. 11.2).

Studies on resveratrol indicate that the caloric restriction mimicking effect of this stilbene that may underlie its role in extending longevity does so without reducing fecundity in lower organisms (Howitz et al. 2003) or in short-lived invertebrates such as the fruit fly *Drosophila melanogaster* (Wood et al. 2004; Bhullar and Hubbard 2015). Mean life span was extended by up to 70%, 18%, and 29% on treatment of resveratrol in lower organisms, short-lived invertebrates, and fruit flies, respectively. This effect has been attributed to activation of the sirtuin (SIRT) class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases. Seven sirtuins have been identified in mammals, of which SIRT-1 is believed to mediate the beneficial effects on health and longevity of both caloric restriction and resveratrol (Soleas et al. 2001; Orallo 2008).

Resveratrol prolongs mean life span of the short-lived seasonal fish *Nothobranchius furzeri* by up to approximately 56% (Valenzano et al. 2006), retards the expression of age-dependent traits by delaying the age-dependent decay of cognitive performances, and reduces the expression of neurofibrillary degeneration in the brains of *Nothobranchius furzeri* (Valenzano et al. 2006). Resveratrol promotes longevity and improves glucose homeostasis and energy balance and increases mitochondrial function in mice fed with a high-fat diet by stimulating the SIRT1-mediated deacetylation of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Lagouge et al. 2006; Baur et al. 2006). PGC-1α is a key regulator of mitochondria; the targets of its

co-activation are the nuclear receptor family of transcription factors that are involved in multiple aspects of metabolism (Anderson and Weindruch 2012). Glucose restriction triggers 5′ adenosine monophosphate-activated protein kinase (AMPK) activity and activates the gene encoding the NAD synthetic enzyme, Nampt, which is necessary for the activation of the SIRT1. AMPK is also a PGC-1α activator. Many polyphenols modulate kinase pathways including AMPK and thus simultaneously modulate redox signaling and inhibit mitochondrial function (Joven et al. 2014). Therefore, a reduction in stress signaling and a subsequent reduction in ATP production may be predictable outcomes of polyphenol ingestion that suggest important implications for healthy aging.

## 11.7 Anti-inflammatory Effects of Polyphenols

Inflammation is considered as paramount to chronic disease development in modern lifestyle contributing to most age-related chronic diseases including CVDs, cancer, and Alzheimer disease (Joseph et al. 2016). Many in vitro and in vivo studies suggest that certain polyphenols possess anti-inflammatory properties that may be linked with the preventive effect of these secondary metabolites on onset, progression, and complications of inflammatory diseases. Resveratrol may act in vivo as an anti-inflammatory agent by inhibiting inflammatory cytokine expression in response to the lipopolysaccharides in lungs of rats (Birrell et al. 2005). Furthermore, resveratrol treatment decreases the overexpression of both vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 by inhibiting the nuclear factor-kappa B (NF-kB) pathway in tumor necrosis factor alpha (TNFα)-activated endothelial cells (Deng et al. 2011). Resveratrol is proposed to prevent chronic inflammation during obesity through reducing pro-inflammatory cytokine secretion and enhancing adiponectin release from human adipose tissue (Olholm et al. 2010).

Although several mechanisms have been proposed to explain the anti-inflammatory effect of quercetin, primarily it is the activation of signaling pathways involved in NF-kB activation which is considered to be the most important. Quercetin at 10 μM concentration is reported to decrease mRNA and protein levels of TNFα, interleukin (IL)-1β, IL-6, macrophage inflammatory protein-1α, and inducible nitric oxide synthase (iNOS) in various studies (Boesch-Saadatmandi et al. 2011; Andriantsitohaina et al. 2012). Quercetin has pleiotropic effects in apoE-KO mice including reduction of pro-inflammatory markers and enhancement of anti-inflammatory indicators such as endothelial NOS (eNOS) and heme oxygenase-1 expression, suggesting that quercetin at a dose of 64 mg/kg body mass daily could delay the process of atherosclerosis through its anti-inflammatory properties (Loke et al. 2010).

Delphinidin, one of the most studied anthocyanins, has been found to exhibit anti-inflammatory effect by directly interacting with kinases (Kwon et al. 2009). In mouse epidermal cells, delphinidin at concentration of 5–20 μM suppresses cyclooxygenase (COX)-2 promoter activity and COX-2 expression by inhibiting activa-

tor protein-1 and NF-kB pathways. The study reports that these effects shown by delphinidin are a result of the direct binding of this polyphenol to the ATP-binding site in the kinase domain of mitogen-activated protein kinase 4 and to the ATP-binding site of the catalytic domain of phosphatidylinositol-3-kinase (Kwon et al. 2009; Andriantsitohaina et al. 2012). Curcumin has significant anti-inflammatory activity, as reported in studies showing that it can inhibit lipoxygenase and COX-2, suppress iNOS levels, and act as a potent inhibitor of NF-kB (Bengmark 2006).

There is evidence in support for an anti-inflammatory effect of green tea extract, possibly mediated by the ability to scavenge nitric oxide ($NO^{\bullet}$) and peroxynitrite anion (ONOO–) and to inhibit the expression of iNOS (Tedeschi et al. 2004). The iNOS enzyme is expressed in organs including the lungs and intestine, where an overproduction of $NO^{\bullet}$ contributes significantly to many chronic diseases such as inflammatory bowel disease, celiac disease, Crohn's disease, asthma, vascular failure, and end-organ damage during endotoxemia and septic shock (Guslandi 1998; Tedeschi et al. 2004). In aging brain catechins inhibit the expression of neuronal NOS. This effect of catechins is likely to be involved in the suppression of the activation of transcription factor NF-κB as the κB sequence is present in the promoter region of the iNOS gene (Lin and Lin 1997; Chan et al. 1997). Catechins could induce the endothelial isoform eNOS to elicit anti-inflammatory effects (Lorenz et al. 2004; Singh et al. 2008). EGCG acts as anti-inflammatory agent by inhibiting the production of IL-1 and attenuating the IL-1-induced expression of COX-2 (Kim et al. 2007).

## 11.8 Dietary Polyphenols and Endothelial Function

Endothelial dysfunction is an important impairment during aging. Age-associated progressive induction of an endothelial dysfunction in arteries promotes the initiation and development of CVDs during aging (Matz et al. 2000). Endothelial cells play a key role in the regulation of vascular homeostasis in several ways including through the release of potent vaso-protective factors such as $NO^{\bullet}$, prostacyclin (PGI2), and endothelium-derived hyperpolarizing factor (EDHF) (Andriantsitohaina et al. 2012). There is substantial evidence that many polyphenols provide significant vascular protection against progression as well as development of CVDs (Andriantsitohaina et al. 2012; Bollmann et al. 2014). The polyphenol-mediated endothelium-dependent relaxations were first reported by Fitzpatrick and colleagues in 1993, which showed that grape skin extract and grape juice cause endothelium-dependent relaxations in aortic rings; however, direct evidence that polyphenols stimulate endothelial $NO^{\bullet}$ formation was documented by using electron paramagnetic resonance spectroscopy using aortic rings and cultured endothelial cells of rats (Fitzpatrick et al. 1993). There is evidence that red wine polyphenols (3 μg/ml) induce the endothelium-dependent relaxation in porcine coronary artery rings (Ndiaye et al. 2005).

Daily consumption of 10 mg resveratrol for 3 months improves endothelial function as measured by flow-mediated vasodilation in patients with stable coronary artery disease (Magyar et al. 2012). One-month resveratrol treatment (400 mg per day) on endothelial response reduces mRNA levels of inflammatory and adhesion molecule markers commonly associated with atherosclerosis (Agarwal et al. 2013). Resveratrol stimulates eNOS activity to enhance endothelium-dependent vasodilation (Wallerath 2002). The selective inhibition of COX-1 over COX-2 reduces endothelial inflammation and platelet aggregation (Baur and Sinclair 2006). Endothelial dysfunction in porcine coronary arteries due to homocysteine-induced impairment of endothelium-dependent vasorelaxation was reversed by curcumin, possibly by increasing eNOS levels as well as reducing $^{\bullet}O^{2-}$ production (Ramaswami et al. 2004). Curcumin mitigates accelerated aging after irradiation in *Drosophila melanogaster* by reducing oxidative stress (Seong et al. 2015). The study demonstrates that pretreatment with 100 μM curcumin recovered the irradiation-mediated shortened life span of *D. melanogaster*. It has been suggested that vascular protective effect of quercetin is associated with eNOS upregulation (Kukongviriyapan et al. 2012). Studies on rat aortic ring segments show that quercetin treatment for half an hour enhanced relaxation of aortic rings by virtue of NOS and endothelium-derived hyperpolarizing factor. Another study performed by the same group demonstrated that bovine aortic endothelial cells, when incubated with quercetin, exhibited an increase in intracellular calcium, eNOS phosphorylation, and subsequent increase in $NO^{\bullet}$ (Chirumbolo 2012). Taken together, all these results suggest that quercetin-induced phosphorylation of eNOS can increase availability of $NO^{\bullet}$, thereby inducing protective vascular effects during aging.

## 11.9 Conclusions

The overall decline in organ function plays a crucial role in aging and age-associated diseases. Oxidative stress, a state of imbalance between cellular production ROS and their removal by antioxidants, has emerged as a critical player in aging process. Oxidative stress status is observed during aging and in numerous age-related diseases. Hence organs and tissues accumulate ROS damage over time under conditions in which their endogenous antioxidant defenses are overwhelmed, resulting in overall cellular redox imbalance and impaired organ physiology. Plant polyphenols can scavenge ROS and decrease the incidence of oxidative stress-induced damage. There is evidence that populations consuming diets rich in polyphenols are less susceptible to oxidative damage and diseases during aging.

Plant polyphenols have demonstrated potential against progression of many age-associated pathologies in laboratory animal and epidemiological studies through different mechanisms. There is evidence to suggest that dietary polyphenols such as resveratrol, EGCG, and curcumin have the capacity to mitigate age-associated cellular damage induced by excessive ROS production. Caloric restriction mimicking

effect and enhancement of life span are hotly investigated biological activities of some polyphenols. Despite certain gray areas linking consumption of polyphenols and purported healthy and antiaging benefits, the present chapter provides a current understanding of the role of polyphenols in aging and age-associated chronic diseases.

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