Bee Ling Tan
Mohd Esa Norhaizan

The Role of Antioxidants in Longevity and Age-Related Diseases

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Bee Ling Tan
Department of Nutrition
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Serdang, Selangor, Malaysia

Mohd Esa Norhaizan
Department of Nutrition
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Serdang, Selangor, Malaysia

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Preface

The average life expectancy has increased worldwide over the last decades. Despite the increasing life expectancy reflecting positive human development, new challenges are arising. Aging can be viewed as the progressive loss of organ and tissue function over time. It is characterized as the onset of major underlying causes for age-related diseases such as cancer, neurodegenerative disorders, cardiovascular disease (CVD), type 2 diabetes, arthritis, osteoporosis, stroke, and Alzheimer's disease. It has been recognized that chronic inflammation is a prominent underlying factor for age-related diseases. Oxidative stress is linked to the development of age-related diseases. The vast majority of published work has revealed the potential preventive and/or therapeutic roles of antioxidant in aging and age-related diseases. Ample evidence has suggested that antioxidant can modulate autoxidation by inhibiting the formation of free radicals or disrupting the propagation of free radicals and thus increase health longevity, enhance immune function, and decrease oxidative stress. In fact, oxidative damage is highly dependent on the acquired or inherited defects in enzymes involved in the redox-modulated signaling pathways. In view of the dramatic and recent increase of age-related diseases among the elderly in developed countries, the discovery of interventions that target the aging aspects of these diseases would have a significant public health impact. Based on our knowledge, the literature reported on antioxidants with their biological mechanisms that mediate age-related diseases has not well been compiled in the form of a book/brief. In fact, this disintegrated knowledge needs to be compiled together to deliver information at one point. Hence, this brief/book attempts to clarify several issues linked to antioxidant, aging, and age-related diseases, namely changes in organ systems over the lifespan, age-related oxidative stress-induced redox imbalance, inflammaging, implications of inflammation in aging and age-related diseases, antioxidant and age-related diseases, and future prospects. By summarizing all the literature in a cohesive and lucid manner in one book/brief, it would provide a comprehensive representation of the information on the mode of actions of antioxidants involved in

the prevention of age-related diseases for the readers and allied stakeholders. A better understanding of how chronic inflammation contributes to aging and age-related diseases would provide a new intervention targeting inflammation.

Serdang, Selangor, Malaysia Bee Ling Tan

Contents

Chapter 1
Introduction and Background

Aging is a biological, universal, and unavoidable process that affecting almost all multicellular organisms and probably common in unicellular organisms such as bacteria, yeast, and protozoa (Książek 2010; Lin and Austriaco 2014; Teulière et al. 2020). It is characterized as degenerative in nature, concomitantly with progressive loss of function, and lastly increased mortality rate (Thoma et al. 2020). Among the mammalian species, humans have the longest lifespan and consume more energy throughout their lifespan per weight basis (Ben-Haim et al. 2018). Despite numerous hypotheses that have been proposed to explain the molecular mechanisms of aging, previous studies suggest that aging is caused by an accumulation of molecular damage, giving rise to a unified theory of aging (Niedernhofer et al. 2018; Ogrodnik et al. 2019). The free radical theory of aging has long been established to explain the aging process (Harman 1956). This theory proposed that aging is a consequence of the failure of some defensive mode of action to respond to the reactive oxygen species (ROS)-induced damage, especially at the mitochondria (Theurey and Pizzo 2018).

In the context of thermodynamic, all aerobic organisms are susceptible to the action of a common oxidant, namely oxygen (Matschke et al. 2019). The redox potential of the $O_2/2H_2O$ redox system is positive compared to other biologically relevant redox systems (Gutteridge and Mitchell 1999). Hence, the oxidation by oxygen in organic compounds showed a negative free enthalpy and response spontaneously (Yang et al. 2018). In this regard, structures or organic compounds consisted of them are thermodynamically unstable in an oxygen-containing atmosphere (Granzow 1978). Molecular oxygen in its triplet basal state is unreactive due to the spin restriction (Sadowska-Bartosz and Bartosz 2014). Subsequently, the formation of free radicals or ROS demonstrates potentially deleterious oxidative reactions of oxygen (Sies and Jones 2020). The previous study has revealed that utilization of oxygen by mitochondria of aerobic organisms can lead to the production of reactive radicals, for example, hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet -}$), as well as hydroxyl radical ($HO^{\bullet}$) (Shim and Kim 2013; Xie et al. 2019; Li Puma et al. 2020).

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Furthermore, nitric oxide ($NO^{\bullet}$) produced by mitochondria may further implicate the aging process and age-related diseases (Opatrilova et al. 2018; Somasundaram et al. 2019; Lieu et al. 2020). Another potent source of oxidant production is via phagocytes (Stawski et al. 2019), in which they produce hypochlorous acid (HOCl), $NO^{\bullet}$, $HO^{\bullet}$, H_2O_2, and $O_2^{\bullet-}$ (Misztal et al. 2019). Indeed, HOCl is an inflammatory mediator as well as a strong chlorinating and oxidizing compound that can produce other reactive metabolites including nitrogen dioxide ($NO_2^{\bullet}$) and nitryl chloride (NO_2Cl), in the presence of nitrite (Rayner et al. 2018). A study found that activated human polymorphonuclear neutrophils can convert nitrite into NO_2Cl and $NO_2^{\bullet}$ metabolites, and thereby leading to the formation of harmful compounds (Whiteman et al. 2003). The deleterious effects of chlorinating compounds, ROS, and reactive nitrogen species (RNS) may subsequently contribute to the aging process (Saxena and Batra 2020; Brunetta et al. 2020; Semerád et al. 2020).

Aerobic organisms are protected against oxidative challenges by sophisticated antioxidant defense systems (Rezayian et al. 2019). Oxidative stress triggered by oxidant species occurs when the rate constant of free radicals is higher than the antioxidant defense mechanisms or when the antioxidant defenses are depleted (Simioni et al. 2018). The defense mechanisms decline with age and accelerate oxidative damage and thereby leading to deterioration in physiological function (Ridhima et al. 2018). Indeed, the oxidative damage of biomolecules is increased with age (Kuzmic et al. 2019). This damage has been hypothesized to play a critical role in cellular biochemical senescence (Moldogazieva et al. 2019). A study found that the antioxidant enzymes such as catalase and superoxide dismutase (SOD) are overexpressed in transgenic *Drosophila*, implied that increased antioxidant enzymes could increase maximum and average lifespan and decrease oxidative damage (Milisav et al. 2019). Furthermore, the study also found that aged species have a greater likelihood to generate a significant amount of ROS compared to the younger counterparts (Hekimi et al. 2016). Data from animal studies have shown a strong inverse correlation between the maximum lifespan and the rate of mitochondrial oxidant production in different species (Munro and Pamenter 2019). A study further revealed that animals with high mitochondrial metabolism have a short lifespan due to the high oxygen consumption and thereby leading to higher oxidant production (Venditti and Di Meo 2020). In support of this, Lin et al. (2019) found a strong correlation between SOD activity and maximum lifespan in *Caenorhabditis elegans*. This finding implies that the increase of SOD activity may protect against superoxide radicals (Case 2017), suggesting that lifespan may partly depend on the activity of this enzyme (Leite et al. 2020).

Free radical theory of aging is commonly explaining the oxidative damage theory of aging, which is a primary facet of intrinsic biological instability of living systems (Yegorov 2020). This theory shows that free radicals or other ROS are produced in the course of metabolism and increased concomitantly due to the action of different exogenous factors and the damage of biomolecules, and accumulation of this damage may result in aging and age-related diseases (Luo et al. 2020).

The average life expectancy of the world population has increased rapidly in the recent decades, with an average of 72.0 years in 2016 (World Health Organization

2020a). The world population aged 60 years is projected to live another 20.5 years on average in 2016 (World Health Organization 2020b). Based on the demographics of the global population between 2000 and 2050, the population aged more than 60 years is expected to increase from 605 million to 2 billion people (World Health Organization 2014). The predicted increase in life expectancy would potentially lead to biological and cognitive degeneration, for instance, psychological impairment, physical frailty, and cognitive decline (Garcia et al. 2018; Marzetti et al. 2019).

In the twenty-first century, age-related diseases have become the greatest health threat (Tan and Norhaizan 2019). The interplay among co-factors, antioxidants, and free radicals is crucial in the modulation of age-related diseases, aging, and health (Tan et al. 2018). Age-related diseases are linked to the structural changes in mitochondria, concomitantly with the modifications of biophysical properties of the membranes, for instance, reduced fluidity, modifications in the electron transport chain (ETC) complexes activities, and thereby leading to energy imbalance and mitochondrial failure (Liu et al. 2020). This perturbation destroys the mitochondrial function and cellular homeostasis and increases susceptibility to oxidative stress (Madreiter-Sokolowski et al. 2018). Older people are vulnerable to oxidative stress due to a decrease in the efficiency of endogenous antioxidant systems (Zhang et al. 2015). In particular, organs including hearts and brains, with limited respiration levels and high amounts of oxygen consumption, are susceptible to these phenomena, suggesting that it may contribute to the high prevalence of neurodegenerative disease and vascular disease in the elderly (Takahashi and Takahashi 2013; Cervellati et al. 2020).

Oxidative stress is regarded as a result of an imbalance between anti- and prooxidant species (Dogru et al. 2018). It plays a prominent role in the development of age-related diseases such as osteoporosis, vascular disease, cancer, osteoporosis, dementia, diabetes, and arthritis (Tan et al. 2018). Increased ROS has been linked to the progression and onset of aging (Moldogazieva et al. 2019). Despite ROS may not be an essential factor for aging, they are more likely to aggravate the progression of age-related diseases through interaction with mitochondria and oxidative damage (Kowalska et al. 2020; Luo et al. 2020). The balance between detrimental and beneficial effects of ROS is preserved in the cells by mediating the complex array of enzymatic and non-enzymatic detoxification mechanisms (Bast and Haenen 2015). Antioxidants can counteract the damage induced by ROS in cells, and thus protecting the physiological targets, for instance, proteins, DNA, and lipids (He et al. 2017). Emerging evidence has revealed that natural products possess a unique complex of bioactive compounds. These compounds can improve the immune system and decrease oxidative stress (Alvarez-Arellano et al. 2020; Romiti et al. 2020). Indeed, the interplay between the overall redox system and antioxidants in humans is very complex and is highly dependent on the acquired or inherited defects in enzymes involved in the redox signaling pathways (Łuczaj et al. 2017). Therefore, the role of diet/food high in antioxidant molecules that combat oxidative stress and promote healthy aging is worth discussing further.

According to the best of the authors' knowledge, the literature on antioxidants and their mode of action that modulate age-related diseases has not well been

compiled in the form of a brief/book. Indeed, this disintegrated information needs to be compiled together to deliver knowledge at one point. Therefore, this brief/book explores several issues related to antioxidant, aging, and age-related diseases, including changes in organ systems over the lifespan, age-related oxidative stress-induced redox imbalance, inflammaging, implications of inflammation in aging and age-related diseases, the role of antioxidants on health and age-related diseases, and future prospects.

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Chapter 2
Changes in Organ Systems over the Lifespan

Aging is characterized by the impairment of the regulatory process that provides functional integration between organs and cells (Srivastava 2017). Increasing age caused an interindividual variability of the physiological changes (Kedlian et al. 2019). Aging is not only a single entity but a collective term as the sum of cumulative local effects at the tissue, cellular, and molecular levels (Ashapkin et al. 2019). Indeed, aging is the effect of these underlying changes but not the cause. Despite an all-encompassing definition of aging is not possible; some characteristics have been identified (Mangoni and Jackson 2004). The most consistent is the functional and time-associated loss units (Chen 2019). This unit is the smallest structure that capable to perform certain physiological activities of the organs including neurons, alveoli, and nephrons (Sgarbieri and Pacheco 2017). Another characteristic is a disruption of the regulatory process that provides functional integration between organs and cells (Jeffries et al. 2019). As a result, the ability to counteract external stresses and maintain homeostasis is reduced (Tan et al. 2020). Loss of the functional reserve is linked to the increase in vulnerability and decrease in viability (Vila 2019). Aging is not solely a progressive decline in function but results in physiological and anatomical changes, and thus may lead to the decompensation of the system when they progress beyond a threshold (Larsson et al. 2019).

2.1 Changes in Nervous System

The brain has a limited capacity for repair. During aging, neurons are progressively reduced and cannot be replaced (Li et al. 2019). Aging is linked to numerous neurological diseases, in which the capacity to communicate and transmit signals in the brain decreased (Hertelendy et al. 2019). Reduced brain function is the biggest challenge facing by the elderly such as dementia and Alzheimer's disease (Nelson et al.

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2016; Acosta et al. 2017). Several neurodegenerative diseases, for instance, Parkinson's disease or sudden devastation of a stroke are also increasing with age (Prange et al. 2019; Yousufuddin and Young 2019). Parkinson's and Alzheimer's diseases are progressive neurodegenerative diseases related to aging (Harrison et al. 2019; Trist et al. 2019). Alzheimer's disease is characterized by progressive deterioration of cognition along with the decreased in daily living activities and changed in behaviors (Takeda 2019). Among the neurodegenerative diseases, Alzheimer's disease is the most common type of senile and pre-senile dementia (Armstrong 2016). It causes tissue loss and nerve cell death throughout the brain, in which the cortex in the brain shrivels up and destroys the area involved in remembering, planning, and thinking (Jonathan et al. 2015). Indeed, the shrinkage of the nerve cell is severe in the hippocampus, the area of the cortex that plays an important role in the formation of new memories (Theofilas et al. 2017). Alzheimer's disease leads to an overall misbalance in the elderly by changes in behavior-like depression and personality, aggressiveness, irritability, mood swings, social withdrawal, apathy, and memory loss (Scott et al. 2020; Wu et al. 2020). Defects in protein processing also may cause the deposition of amyloid plaques (Wang et al. 2020). Notably, there is a steady increase in the symptoms of Alzheimer's disease with age, with nearly doubling the incidence for every 5 years of life after 65 years old (Qiu et al. 2009). Such finding implies that there is not a defined syndrome, in which the late-onset could be labeled as a natural aging of the brain (Murman 2015).

2.2 Changes in Cognitive Function

The hippocampus is a brain area deals with memory as well as the initial target for aging-associated physiological and structural impairments (Bettio et al. 2017) that mediate spatial memory decline (Subramaniapillai et al. 2019). Neurotransmission by glutamate, acetylcholine, dopamine, and γ-aminobutyric acid (GABA) interacts to modulate learning and memory abilities (Cai and Ford 2018; Ravichandran et al. 2018; Mohebi et al. 2019). Glutamate is converted to GABA facilitated by glutamate decarboxylase (GAD) (Zhao and Gammie 2014). GAD is widely used for monitoring neuronal function during aging (Jacobson et al. 2008), while choline acetyltransferase (ChAT) is extensively utilized as a marker for cholinergic function in learning and memory (Hawley et al. 2015). The dopamine output of the striatum also plays an important role in age-related cognitive decline (Darvas and Palmiter 2011). Treatment with $_{L}$-Dopa has been demonstrated to benefit age-related memory loss through enhanced dopamine output (Zhao et al. 2017). Indeed, enhancement of neuronal plasticity during the pre-symptomatic period could be a trophic response to the initial neuronal loss (Mazarakis et al. 2005). Likewise, a study in middle-aged gerbils showed a higher level of brain-derived neurotrophic factor (BDNF) in the hippocampus compared to aged and young groups (Hwang et al. 2006). Compared to young and aged rats, the striatum of middle-aged rats has a higher extracellular dopamine concentration (Segovia et al. 1999). Kim et al. (2005)

have also been reported to enhance GluR-1 positive neurons in the frontal cortex of middle-aged rats.

In the context of behavioral response to plasticity in striatal dopamine and GABA, the middle-aged rats showed less anxiety compared to aged groups (Jacobson et al. 2008). A study by Bessa et al. (2005) further supported that middle-aged rats were shown to have less anxious behaviors compared to the aged rats by illustrating the avoidance of open arm entries. Despite limited evidence reported on the role of dopamine in anxiety during brain aging, the previous study has demonstrated that anxiety observed in Parkinson's patients could be attributed to the diminish of striatal dopamine output (Richard 2005).

The most common cognitive decline with aging is memory impairment, especially in short-term, episodic, and spatial memory (Poddar et al. 2019). In a study by Jacobson et al. (2008) focusing on age-associated neuronal degeneration and plasticity in rat models using behavioral tests, the data showed that aged rats performed more working memory errors in the radial arm maze (RAM), made more entries into incorrect arms in the T-maze test, and were more slowly to find the platform in the Morris water maze (MWM), implied that poor performance of aged rats in hippocampus-dependent tasks (Arias-Cavieres et al. 2017).

Mild cognitive impairment (MCI) is a clinical prodrome, which may evolve to overt dementia in advanced age (Mielke et al. 2017). Neurodegeneration may occur before a clear decrease in function, a model that has been depicted in other forms of neurodegenerative situation, for instance, Parkinson's disease (Zeng et al. 2018). Indeed, this condition may also happen in pathological brain aging. Older people showed a greater difficulty with memory tasks, particularly involving strategic, effortful, and complex memory tasks (Lee et al. 2018). Such finding indicates that aging reduces the memory functions resulted from impairments of basic cognitive functions (Harman and Martín 2020). The mechanisms underlying the age-related changes are not fully understood, but it is hypothesized that lack of cognitive control, loss of inhibitory functions, decreased processing resources, and general slowing contributes to these phenomena (Luo and Craik 2008).

Based on the general slowing, aging is accompanied by a reduction in processing speed and thereby leading to a decline in cognitive functions such as memory performance (Shim et al. 2020). Processing speed plays a crucial role in several cognitive functions. In this regard, complex tasks involving multiple types of processing may gradually slow down, indicating that greater age-related declines (Monteiro et al. 2020). Nonetheless, substantial evidence highlights that this view is primarily derived from path analysis data. It has remained obscure how the hypothesis accounts for some experimental analyses. For instance, (1) age-related declines have been demonstrated in several tasks including free recall that does not need a speed component (Dunlosky and Salthouse 1996); (2) unlimited processing time does not decrease memory problems in the elderly but improves performance in young people (Luo and Craik 2008); and (3) aging is linked to differential effects on tasks which do not involve different levels of processing (Luo and Craik 2008).

During aging, older people experience a reduction in cognitive function such as memory loss (Appel et al. 2020). According to Flexner et al. (1962, 1963, 1967),

changes in the amount of protein synthesis in the brain may affect some of the cognitive effects of aging. When more and more brain-specific proteins and the putative roles were discovered, it became evident that the individual protein expression could decrease or increase with age, and the rates of change across the lifespan may differ between proteins (Tong et al. 2020). In view of the discovery that *de novo* protein synthesis is required for the establishment of long-term information storage, substantial studies were performed to evaluate the translation of individual proteins in restricted areas of the brain, and in response to artificial or cognitive stimulation (Wegmann et al. 2019). Indeed, the regulation of transcription undergoes age-related changes, and that decreases or increases in translation, transcription, or both determine the expression of certain proteins at any stage during the lifespan (Baehr et al. 2017).

Several studies found that the amounts of brain protein synthesis increased during the development of rodents, in which it reaches maximum amounts during the first 6 months of age and gradually decline (Dwyer et al. 1980; Ekstrom et al. 1980; Fando et al. 1980; Ingvar et al. 1985; Smith et al. 1995; Filion and Laughrea 1985; Richardson 1981; Richardson and Birchenall-Sparks 1983; Richardson et al. 1983). Likewise, the same effect was also observed in white leghorn chicken (Yang et al. 1977). Nevertheless, not all studies demonstrated such a link. The previous study evaluated the exact time courses of the decline, in which some studies reported a greater rate of decrease in translation during adulthood (Ekstrom et al. 1980; Fando et al. 1980; Ingvar et al. 1985; Smith et al. 1995), and other study showed the greatest rate of decline during senescence (Dwyer et al. 1980). Despite the protein synthesis reduced was observed in several cells and organ tissues including muscle, kidney, and liver, the rates and time courses of the decline are varied among each other (Webster 1985). Although there remain several disagreements on the timing of the acceleration decrease in brain tissues, the data showed that translation is declined with age (Hipp et al. 2019). It is worth highlighting that most of the data evaluated rates of translation in the brains of animals are not manipulated or cognitively stimulated before measurement, or in non-perturbed *in vitro* preparations. Therefore, the findings found from the foregoing studies demonstrate resting rates of synthesis that may or may not reflect rates occurring when the system is stimulated. In another study, Ingvar et al. (1985) evaluated the amount of protein synthesis in a broad spectrum of brain structures during aging, and after a decade followed this study to calculate this level accurately (Smith et al. 1995). The data from the animal study revealed that age-related declines were observed in brain structures, cerebellar white matter, internal capsule, and olfactory cortex that having a role in the extrapyramidal motor, visual, and auditory systems (Muñoz-Moreno et al. 2018). In particular, the protein synthesis is affected in extrapyramidal motor and sensory systems during aging; however, an alternate interpretation of this finding is that activity in sensorimotor circuitry might be decreased when the reduced locomotion in aged animals. Despite Ingvar et al. (1985) suggested that areas required for higher cognitive function are relatively spared, the age-related protein synthesis is reduced in the locus coeruleus, nucleus accumbens, and hippocampal dentate gyrus region, the regions that modulate memory and learning processes.

Many studies reported that protein expression in specific brain structures can be changed during the aging process (Gelfo et al. 2018). In general, the transcriptional activities involved in regulating synaptic function, neural plasticity, and mitochondrial function are downregulated during aging; whereas the genes that mediate the inflammatory/immune responses and stress are upregulated (Schimanski and Barnes 2010). The translation of certain proteins is preceded by transcription of the mRNAs that encode several proteins, in which it can undergo age-related modifications (Browning and Bailey-Serres 2015).

Normal aging is often accompanied by memory impairment (Rosenzweig and Barnes 2003; Burke and Barnes 2006). Despite numerous forms of memory are left intact by the aging process, age-related deficits have been identified in several types of hippocampus-dependent memory such as trace eyeblink conditioning (Weiss and Disterhoft 2015), fear memory (Zhan et al. 2018), and spatial memory (Yamamoto et al. 2019). Notably, this hippocampal function-dependent memory deficit was found across phylogeny, for instance, human, monkey, dog, rabbit, rat, and mouse (Murray et al. 2018). The previous study showed the increased decline rate of spatial memory in aged rats concomitantly with the rapid decay of long-term potentiation (LTP) at the perforant path-granule cell synapse (Barnes and McNaughton 1985). A study by Winocur (1988a) further supported that aged rodents have a greater likelihood of some types of long-term memory deficits compared to short-term memory. The data showed that aged rats demonstrate selective deficits 21 days after training when evaluated for recall of a passive avoidance response (Winocur 1988b). A study by Foster (1999) further demonstrated that a "saw-toothed" manner of performance in aged rats when several swim trials are performed each day for several concurrent days in the Morris water maze.

Several studies reported by Frankland et al. (2004) and Brightwell et al. (2005) evaluated the age-associated changes in cAMP-responsive element-binding protein (CREB) activity in relation to memory impairment in aging. CREB is a transcriptional activity that is required for hippocampal memory consolidation. CREB is active when phosphorylated (Gonzalez and Montminy 1989), and thus can be upregulated through the induction of LTP (Impey et al. 1996; Schulz et al. 1999). The previous study showed that pCREB upregulates the protein expression that promotes the long-lasting forms of memory and synaptic plasticity (Bailey et al. 1996; Yin and Tully 1996). Some studies have revealed that pCREB activity is decreased in aged rodents (Morris and Gold 2012; An et al. 2018).

Epigenetic mechanisms may also affect the age-related changes in synaptic plasticity and memory (Castellano et al. 2012; Kosik et al. 2012; Kwapis et al. 2018). Alteration methylation of the Arc gene has also been observed in aged rats (Penner et al. 2011). It was evident that changes in histone acetyltransferases (HATs) can improve synaptic plasticity and memory in animal models of neurological disorders and normal groups (Karisetty et al. 2020). HATs are co-activator that regulated the CRE-dependent transcription via CREB (Piccirillo et al. 2019). Taken together, these findings indicate that the expression of protein synthesis-dependent synaptic strengthening is reduced in aged rodents. An alteration of signaling pathways and calcium homeostasis could influence the recruitment of the protein synthesis process and induction of synaptic potentiation (Schimanski and Barnes 2010).

2.3 Changes in Skin

Human skin is constantly exposed to environmental pollutants (Poljšak and Fink 2014), solar radiation (Ali et al. 2020), air (Poljšak and Dahmane 2012), as well as chemical and mechanical agents (Rudolf and Cervinka 2011; Wong et al. 2011), and thus inducing the production of ROS (Hepel and Andreescu 2015; Panich et al. 2016). Indeed, ROS are often of little harm if intracellular modes of action that decrease the damaging effects are worked effectively (Trouba et al. 2002). The most important mechanisms involved in this process including nonenzymatic and antioxidative enzymatic defenses as well as repair processes (Herrling et al. 2006; Prasad and Pospišil 2011; Rastogi and Pospísil 2011). Furthermore, the repair processes and endogenous antioxidative mechanisms are reduced with advancing age (Tan et al. 2018). Thus, the skin tends to become finely wrinkled, drier, less elastic, and thinner (Langton et al. 2019). Changes of skin are partly due to elastin and collagen. Less elastin and collagen are produced when people are getting older. Subsequently, the skin tears more easily (Vanzi and Toma 2018).

Several factors developed extrinsic skin damage, for instance, environmental pollution, overeating, poor nutrition, alcohol intake, several psychological and physical stress, ionizing radiation, and exposure to UV radiation (Farage et al. 2008; Naidoo and Birch-Machin 2017). UV triggered the production of ROS in the skin to develop oxidative stress when the formation exceeds the antioxidant defense ability of the target cells (Lin et al. 2019). Acute exposure to UV radiation promotes protein oxidation and decreases the catalase activity in the skin (Svobodová et al. 2011). Among all the environmental factors, UV radiation is accounting for more than 80% in skin aging and the development of skin cancer (Amaro-Ortiz et al. 2014). The predominant mode of action by which UV radiation initiates molecular responses in the human skin is through the mediation of photochemical generation of ROS primarily via the formation of singlet oxygen ($^1O_2$), hydroxyl radical ($OH^{\bullet}$), H_2O_2, and superoxide anion ($O_2^{-\bullet}$) (Pospíšil et al. 2019). UV radiation penetrates the skin and subsequently reaches the cells, which is absorbed by DNA and thus resulted in the formation of photo-products that inactivate the functions of DNA (Ibarz et al. 2015). UV radiation can modulate the skin damage via two different mechanisms including (1) photosensitization mechanisms, in which the light is absorbed by exogenous (endogenous) sensitizers that are excited to the triplet states; and (2) direct absorption of the incident light by cellular components and leading to the excited state formation for a subsequent chemical reaction (Zaheer et al. 2016; Brem et al. 2017; de Jager et al. 2017). In general, the excited photosensitizers can trigger cellular damage via two mechanisms including (1) energy transfer from oxygen to produce reactive excited state, singlet oxygen (Type II) (Bacellar et al. 2015); and (2) hydrogen abstraction and electron transfer processes to produce free radicals (Type I) (Fukuzumi et al. 2003; Amić et al. 2017). The previous study showed that eukaryotic and prokaryotic cells exposed to UV can cause morphological transformation, mutation, chromosome changes, and cell death (Nawkar et al. 2013). In addition to nuclear DNA, UV radiation can trigger oxidative damage to mitochondrial DNA

(mtDNA) (Van Houten et al. 2016). Indeed, aging is a multifactorial phenomenon characterized by increased susceptibility to functional decline and cellular loss, in which mtDNA damage response and mutations play a pivotal role (Höhn et al. 2017). The previous study has revealed that sunlight passing through the skin is not only can lead to DNA damage in white cells circulating through the skin capillaries (Brenner and Hearing 2008), but it can cause the damage of dermal mtDNA (Stout and Birch-Machin 2019). Singlet oxygen produced by UVA light has been reported to cause strand breaks in the mtDNA and leading to the deletions of mtDNA (Schuch et al. 2017). A study reported by Hahn and Zuryn (2019) has revealed that mtDNA serves as the most crucial target of endogenous ROS production because it lies in the inner mitochondrial membrane, which is close to the ETC that produced the freest radicals. Emerging evidence has suggested that mitochondria exert effective DNA repair mechanisms in the last few decades (Kowluru and Mishra 2018). The predominant DNA repair pathway has been reported to actively take place in mammalian mitochondria including the base excision repair pathway (Jang et al. 2019). The data showed that mtDNA is higher in sun-exposed skin compared to protected skin (Berneburg et al. 1999; Birch-Machin et al. 1998). In this regard, avoidance of sporadic and excessive cumulative sun exposure is vital in decreasing skin aging and the risk of skin cancer (Watson et al. 2016). The most frequent mutation is the 4977-base pair deletion or known as common deletion, which is increased in photoaged skin (Berneburg et al. 2004). Collectively, the DNA damage caused by ROS is not a rare phenomenon because the human cell is estimated to sustain about 10^5 oxidative hits per day (Poljšak and Dahmane 2012). Since the DNA is functionally stable, thus the incidence of cancer is expected to be low, by taking into account the high frequency of oxidative hits.

2.4 Changes in Cardiovascular System

Atherosclerosis is regarded as a scourge of increased age, albeit its onset can be traced from a young age (Sarbacher and Halper 2019). In particular, young individuals have a healthy intima with a thin layer of endothelial cells attached with glycocalyx on its luminal surface (Halper 2018). The endothelial cells are tightly linked to the internal elastic lamina and basement membrane (Halper 2018). Nonetheless, increasing age enhanced a repeating cycle of endothelial repair and injury leading to the thickening of tunica intima that may subsequently cause plaque formation and atherosclerosis (Sarbacher and Halper 2019). A significant change has been found in the function and structure of the cardiovascular system in the elderly, for instance, decreased elasticity (Fhayli et al. 2019). Increasing age is related to an elevation of the collagen cross-linking and collagen levels, activation of the fragmentation of the internal elastic membrane, stimulation of vascular smooth muscle hypertrophy, and increased intimal thickness (Lacolley et al. 2017). These microscopic changes are accompanied by the increased arterial stiffness and thickness and progressive elongation and dilatation of arteries. Arterial stiffening is

linked to aging in Western societies even in the absence of cardiovascular disease (CVD) (Kitzman et al. 1988; Vaitevicius et al. 1993). It has demonstrated an increase in pulse wave velocity, widening of blood pressure, and elevation of systolic blood pressure (Kim and Kim 2019; Papaioannou et al. 2019). These changes create early reflected pressure waves that alter the pressure waveform (London et al. 2019). Such effects lead to an elevation of late systolic pressure peak and thus promote central vascular systolic blood pressure in the elderly (Malm et al. 2020). Further, the elevation of arterial stiffness promotes the afterload and end-systolic wall stress and subsequently may contribute to the progression of left ventricular hypertrophy (Table 2.1).

Increased impedance to left ventricular ejection and high systolic arterial pressure results in interstitial fibrosis and left ventricular hypertrophy (Mancusi et al. 2017). Aging reduced the myocardial relaxation rate. The left ventricle becomes stiffer and takes longer to relax and fill in diastole, and thereby increasing time of atrial contraction that contribute to normal left ventricular end-diastolic volume (Nichols 2005). When the pulse wave reaches the iliac bifurcation, it is reflected and transmitted back to the aorta. Likewise, the backward transmission wave is also accelerated (Weisfeldt 1998).

Aging is linked to an increased in sinoatrial node conduction time and a decrease in the intrinsic heart rate (Moghtadaei et al. 2016). There is a 40–50% decreased in the total number of nuclei and cells in the myocardium in individuals between 20 and 90 years old (Olivetti et al. 1991), suggesting that an age-related drop out of cells with compensatory hypertrophy of the remaining cells. Further, left ventricular

Table 2.1 Cardiovascular changes related to the aging process and their clinical responses

Cardiovascular structure and function	Outcomes	Clinical responses
Diastolic function	↓ Early diastolic filling	↓ E velocity
	↑ Late diastolic filling	Prolong E deceleration time
	↓ Myocardial diastolic velocities	↑ A velocity
Systolic function	Preserved	–
Cellular changes	↓ Sarcoplasmic reticulum Ca^{2+} ATPase protein level	Prolong of myocardial relaxation
	↓ Reuptake of Ca^{2+} into the sarcoplasmic reticulum	↑ Isovolumetric relaxation time
Myocardium	Loss of myocytes	–
	↑ Thickness left ventricular wall ratio to chamber size	
Arterial wall	↑ Thickness	↑ Systolic blood pressure
	↓ Compliance	↑ Pulse wave velocity
		Widening of pulse pressure

Source: Oxenham and Sharpe (2003)

cell hypertrophy also impairs left ventricular ejection (Milani et al. 2011). Strikingly, the central arterial stiffness is increased with age (Hughes et al. 2014). In the context of left ventricular function load, increased stiffness produces greater impedance to the left ventricular ejection (Weisfeldt 1998; Bell et al. 2017). Aging may stiffen the central aorta, and thereby result in the left ventricle ejecting the same amount of blood into the aorta (Weisfeldt 1998). This phenomenon may accelerate the velocity of blood movement to the arterial system. Acceleration in pulse wave velocity is then extended to the whole arterial tree (Weisfeldt 1998; Avramovski et al. 2018). The rate of transmission backward and forward is steady in individuals aged 20 years old and the systole is completed when the reflected wave returns to the heart (Weisfeldt 1998). The previous study has shown an effect in promoting the aortic diastolic pressure when the aortic valve is shut off (Weisfeldt 1998; Pagoulatou and Stergiopulos 2017). Indeed, it does not elevate the cardiac work and therefore regulates the aortic blood pressure during diastole. In individuals aged 40 years old, there is a small effect on blood pressure during systole, despite the reflected wave is returned well before the aortic valve is closed (Weisfeldt 1998). Likewise, the reflected wave in elderly people (80 years old) is also returned well before the aortic valve is shut off. This increases the arterial blood pressure and systolic left ventricular and thereby elevates the burden of the left ventricle in ejecting the blood (Weisfeldt 1998). Indeed, the reflected wave exerts an additional effect by reducing the diastolic aortic pressure to support the coronary flow. Reduced entire circulatory system response to β-adrenergic activation is one of the predominant changes in the cardiovascular system with age (Strait and Lakatta 2012). However, no alteration was found in response to α-stimulation. In particular, there is only a selective reduction of β-sympathetic in response with age (Weisfeldt 1998).

Compared to the young adults, elderly had a relatively constant or even higher circulating epinephrine and norepinephrine level (Fleg et al. 1985). Reduced cardiac response in the elderly is more likely due to the increased of activation, and thereby leading to desensitization as observed in heart failure (Fleg and Strait 2012). The age-related changes are mediated via a few mechanisms such as reduced intracellular calcium mobilization from the intracellular calcium stores of the cardiac muscle cells and decreased sympathetic response at the receptor levels (Weisfeldt 1998).

2.5 Changes in Renal System

The renal mass is reduced with age (Özcan et al. 2018), implied the decrease of nephrons (Denic et al. 2017). Increased age can also alter the intra-renal vascular activity, comprising of hyalinization of the vascular tuft, and thereby leading to the decreased blood flow in the afferent arterioles in the cortex (Weinstein and Anderson 2010). However, increased age did not show any changes in the medullary vasculature (Ljungqvist and Laggergren 1962). Indeed, the glomerular filtration rate and plasma flow were decreased with age (Abdulkader et al. 2017). Intriguingly, reduced glomerular filtration rate did not concomitant promote the creatinine plasma levels,

indicating that creatinine is not a reliable indicator of glomerular filtration rate in elderly individuals (Mangoni and Jackson 2004).

Under the physiological state, the acid-base balance is maintained. However, a decreased response to stress could be due to an inability to cope with the acid loads, and thereby leading to the defective renal tubular in secretion of ammonium ions (Batlle et al. 2001). In addition, the ability to concentrate the urine is decreased during water deprivation (Sands 2012). Such finding is more likely due to a reduced number of nephrons to counteract with elevation perfusion of juxtamedullary glomeruli or increased solute load to produce medullary washout (Denic et al. 2016). The previous study has stated that decreased thirst was observed in elderly individuals during water deprivation (Phillips et al. 1984), although the considerable increases in plasma osmolality. This finding could be due to the increased activity of the renin-angiotensin-aldosterone axis and decreased sensation of mouth dryness (Phillips et al. 1984; O'Neill and McLean 1992).

2.6 Changes in Gastrointestinal System

The predominant changes occurred during aging are the secretion of pepsin and hydrochloric acid, which are reduced under the basal state. This alteration could be due to the changes in the neural and hormonal regulatory system and the enzymes secreting cells (Blechman and Gelb 1999). Indeed, the gastric emptying in young individuals is similar to that of the elderly (Gainsborough et al. 1993). Webster and Leeming (1975) and Husebye and Engedal (1992) did not find any changes in motility and digestion. Nonetheless, the absorption of iron, calcium, and sugars is reduced with increased age. In the pancreas, an alteration of the pancreatic secretion is observed with increased age (Laugier and Sarles 1984). Of all major enzymes, trypsin and lipase are markedly reduced with advancing age (Meyer and Necheles 1940). Whereas some amylase is remain unchanged (Meyer and Necheles 1940). Similarly, the stimulation of secretin-activated bicarbonate and pancreatic juice is also remained constant (Rosenberg et al. 1966). In the context of the liver changes, increased age is related to a progressive decreased in liver blood flow and liver volume (Koff et al. 1973). The enzymatic functions and hepatic structure is altered moderately (Mangoni and Jackson 2004). Several studies reported by Koff et al. (1973) and Kampmann et al. (1975) evaluated the liver function on healthy elderly individuals. The data demonstrated that the metabolism and protein synthesis was not shown any significant changes in elderly between aged 50–69 and 70–89 years old (Koff et al. 1973; Kampmann et al. 1975; Fu and Sreekumaran Nair 1998).

2.7 Changes in Neuroendocrine Response

Aging is accompanied by changes in the neuroendocrine response to physical or psychosocial stress (Heffner 2011). An alteration of the hypothalamic-pituitary-adrenal (HPA) axis is increased with age (Harris and Saltzman 2013). Hypersecretion of glucocorticoids and overexpression of HPA can cause the dendritic atrophy in neurons of the hippocampus, and thereby leading to memory and learning impairment (Myers et al. 2014). Loss or damage of hippocampal neurons impairs glucocorticoid secretion and the feedback suppression of the HPA axis and further destroys the consequence caused by increased glucocorticoid levels (Sapolsky 1987). The positive feedback on hippocampal neuronal loss is also known as the glucocorticoid cascade hypothesis (Sapolski et al. 1985). In this regard, glucocorticoids may sensitize hippocampal neurons to functional impairment and cell death (Horchar and Wohleb 2019). Under the chronic stress state, it was insufficient modulating of HPA axis activity in response to the challenge of sustained glucocorticoid concentrations. This finding could be attributed to the impaired feedback mediation of the HPA axis activity (Gust et al. 2000).

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Chapter 3
Age-Related Oxidative Stress-Induced Redox Imbalance

3.1 Aging and Oxidative Stress

Aging is a biological process characterized by physiological, progressive, and time-dependent declines concomitantly with increased incidence of age-related diseases (Morrison and Newell 2012; Tan et al. 2018a). Several theories have been proposed to describe the underlying molecular mechanism of aging and the causality (Dice 1993). The widely accepted theory is the "oxidative stress hypothesis" (Ghezzi et al. 2017) that modified and advanced the free radical theory of aging (Harman 1956). Based on the oxidative stress hypothesis, oxidative damage is not only shown by the uncontrolled generation of ROS as described in the original free radical theory, other oxidants such as reactive lipid species and RNS are also contributed to this phenomenon. Notably, the oxidative stress hypothesis suggested the essential role of antioxidant defenses as a critical component of the overall redox balance of the organism, which was not regarded in the original theory of free radical (Sohal and Allen 1990; Sohal et al. 2002).

ROS production is an inevitable consequence of life occurred in an aerobic environment (Taverne et al. 2018). In general, ROS are characterized by an increase of chemical reactivity that includes both non-radical and free radicals species (Arman et al. 2019). Under a healthy state, there is a balance between the activities of non-enzymatic and enzymatic antioxidant systems that decreased or scavenge the ROS levels (Lobo et al. 2010). Redox imbalance is caused by a reduction in antioxidant reserve and increased ROS generation. Subsequently, this process may produce oxidative stress (Songbo et al. 2019).

Inappropriate modulating of the immune system and changing the redox status during aging may result in systemic inflammation (Weyand and Goronzy 2016). This process increased the stimulation of inflammatory mediators through oxidative stress to trigger redox imbalance (Charlotte 2019). In particular, the age-related redox imbalance could be attributed to the induction of the incessantly generate of

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reactive species such as reactive lipid aldehydes, peroxynitrite (ONOO−), superoxide (O_2^-), reactive nitric oxide (NO), H_2O_2, and hydroxyl radical (•OH), and the net effect of low antioxidative defense systems (Tan et al. 2018a). Indeed, unresolved chronic inflammation during aging may act as a pathophysiologic link that shifts the normal functional changes to age-related metabolic disorders (Natarajan et al. 2020). Oxidative stress is reinforced by several reactive species, for instance, singlet oxygen, H_2O_2, O_2^-, other radicals as well as non-radicals, which are produced continuously in the body due to the aerobic metabolism, and thus potentially changing the basic structural components, for instance, lipids, proteins, and nucleic acids and cellular activities (Krumova and Cosa 2016). The biological sources of reactive species varied based on the cellular activities that linked to the plasma membrane-related NADPH oxidase, cyclooxygenase (COX), and lipoxygenase; NADH dehydrogenase, ubiquinone, and mitochondrial electron transport system; microsomal electron transport, cytochrome b_5, and cytochrome P_{450}; oxidases and flavoproteins in peroxisome; and xanthine oxidase (XO) in the cytosol (Bodamyali et al. 2000).

Oxidative stress is regarded as an imbalance between anti- and prooxidant species and thereby leading to the cellular and molecular damage (Miletić et al. 2018). Mitochondria are primary organelles that generate energy via oxidative phosphorylation to produce adenosine triphosphate (ATP), a molecule that is pivotal for cells (Nolfi-Donegan et al. 2020). Nearly 90% of total oxygen (O_2) consumed by electron transport chain (ETC) is taken up by the cells (Wallace 2013). Under these circumstances, ROS are produced as by-products for the partial four-electron reduction of O_2 to generate a water molecule, a final electron acceptor during the ATP generation process (Zhao et al. 2019). During the normal physiological phenomena, approximately 0.1–0.5% of inhaled O_2 is shifted to O_2^- (Servais et al. 2009). Under a normal healthy state, the oxidation and production of ROS are occurred in a controlled condition (Tan et al. 2018a). On the other hand, the generation of ROS is stimulated under disease conditions or high-stress states (Pickering 2021). Indeed, the ROS produced from aerobic respiration can increase the oxidative damage in macromolecules, such as proteins, DNA, and lipids, and thereby resulted in cell deaths (Caliri et al. 2021), and influence the healthspan of a variety of crucial organ systems (Bornstein et al. 2020).

The interaction between inflammation and oxidative stress is tightly linked to the biosynthetic pathway of prostaglandins (PGs) that generates reactive species (Marqués et al. 2020). PGs are arachidonic acid-derived lipid metabolites that shown a potent proinflammatory and potentially pathogenic activity (Ricciotti and FitzGerald 2011). Production of reactive species from PGs metabolism aggravates inflammatory conditions and enhances tissue damage (Ricciotti and FitzGerald 2011). COX is another key enzyme that modulates PG synthetic pathway which converts arachidonic acid to prostaglandin H_2 (PGH_2) (Park et al. 2006). The reactive species generated by the PG synthesis pathway further intensify the overall reactive species pool under pathological and normal conditions, especially during aging (Tan et al. 2018a).

3.2 Redox Imbalance in Diabetes

Diabetes is the outcome of dysregulation of glucose metabolism, which is due to the stimulation of protein kinase C, activation of the poly ADP ribose polymerase (PARP) and polyol pathway, and increased protein glycation (Brownlee 2001, 2005; Luo et al. 2016; Zheng et al. 2016, 2017). These hyperglycemia activation pathways may lead to ROS production, which can trigger cell death, mitochondrial dysfunction, and oxidative stress (Robertson 2004; Kassab and Piwowar 2012).

Glucose is one of the pivotal sources of NADH. Excessive in this source can result in NAD^+ deficiency and NADH production, and thereby leading to the NAD^+/NADH redox imbalance (Wu et al. 2016). Redox imbalance between NAD^+ and NADH is the main contributor to oxidative stress and ROS production (Wu et al. 2016; Boesten et al. 2015). The predominant source of redox imbalance is believed to be activated from the stimulation of the PARP and polyol pathway (Masutani et al. 1999; Pieper et al. 1999; Tang et al. 2012; Boesten et al. 2015). In general, the reaction of the polyol pathway involves two enzymes, namely sorbitol dehydrogenase and aldose reductase (Ng et al. 1998). The polyol pathway shifts the NADPH to NADH when it converts to fructose from glucose by modulating the two-reaction mechanism (Kador and Kinoshita 1985), and thereby leading to the NADH overproduction (Yabe-Nishimura 1998; Hodgkinson et al. 2001). Another pathway is PARP that utilized NAD^+ as its substrate (Pacher and Szabo 2005). This enzyme is overexpressed by hyperglycemia triggered by DNA oxidative damage, which results in a potential depletion of NAD^+ (Szabo 2005; Obrosova et al. 2005). Subsequently, these two activated pathways, which are NAD^+/NADH redox imbalance with increased NADH expression and reduced NAD^+ levels, and thereby leading to reductive stress that may progress to oxidative stress (Yan 2014).

3.3 Redox Imbalance in Neurodegenerative Disease

Substantial evidence revealed that a positive association between neuroinflammation and oxidative damage in the neurodegenerative process (Kwon and Koh 2020; Tsukahara et al. 2020; Simpson and Oliver 2020). Neuroinflammation plays a crucial role in a common neurodegenerative disease (Song et al. 2020), which is accompanied by an elevation of $O_2^{\bullet-}$ and NO with the production of H_2O_2 (Brown 2007). The previous study has demonstrated that the brain tissues in patients with Alzheimer's disease had high oxidative stress markers, for instance, glycoxidation, protein oxidative damage, and lipid peroxidation (Barbagallo et al. 2015). The intraneuronal levels of glutathione (GSH) were markedly reduced in the cortex and hippocampus in Alzheimer's disease patients (Aquilano et al. 2014; Barbagallo et al. 2015). Therefore, the losses of ROS balance produced a chronic oxidative environment, which may trigger diminish of antioxidant activity and expression, and thereby increased the risk of developing neurodegenerative disease (García-Sánchez

et al. 2020). An alteration of redox homeostasis increases the peroxidation of fatty acids, modulates the protein unfolding, insulin resistance, and oxidation of cholesterol, and activates the advanced glycosylation products formation (McGrath et al. 2001; Uttara et al. 2009; Elfrink et al. 2012; Talbot et al. 2012; Gamba et al. 2015; Kuhla et al. 2015). Further, brains from patients with Alzheimer's disease show increased levels of 8-hydroxyguanosine (8-OHG) and heme oxygenase-1 (HO-1) compared with that of the control (Moreira et al. 2010). Although the cause of redox imbalance in Alzheimer's disease pathogenesis requires further elucidation, most of the experimental studies suggest that changes of redox transition metal balance such as copper and iron could play a vital role in neurodegeneration (Lovell et al. 1998; Molina et al. 1998; Hane and Leonenko 2014). Intriguingly, the brain of patients with Alzheimer's disease had high levels of copper and iron. The previous study revealed that the concentrations of iron, copper, and zinc in senile plaques cores and rims were significantly increased in patients with Alzheimer's disease (Lovell et al. 1998). Indeed, the activities of ceruloplasmin and ferritin are crucial for the mediation of metal homeostasis, which is altered in Alzheimer's disease (Torsdottir et al. 2011). Crouch et al. (2007) further revealed that several biometals are markedly reduced in the Alzheimer's disease brain, which may increase the development of senile plaques. In support of this, the brain from Alzheimer's disease patients and cortical neurons derived from Alzheimer's disease transgenic mice showed reduced levels of intracellular copper (Schrag et al. 2011). An alteration of these levels may partially contribute to Alzheimer's disease pathogenesis. In this regard, dysregulation of biometal homeostasis in Alzheimer's disease may provide a useful approach to restore neuronal functions (Barthelson et al. 2020).

3.4 Redox Imbalance in Cancer

Redox homeostasis is regulated by the net physiologic balance between oxidizing and reducing equivalents within subcellular components, including antioxidant enzymes and ROS (Hussain et al. 2003). RNS/ROS are thought to be involved in the mediation of redox-regulated signaling pathways and DNA damage (Tan et al. 2018b). For instance, ABL/BCR oncogenes trigger ROS and thereby leading to the modulation of nuclear factor erythroid 2-related factor 2 (Nrf2), a primary regulator of cellular redox homeostasis (Irwin et al. 2013).

Posttranslational modifications involved deletion/addition of low-molecular-weight metabolites to macromolecules or the redox-sensing Cys residues, triggered by redox imbalance and/or ROS (Cuello and Eaton 2019). Most of the intracellular protein possesses cysteine residues, which is placed in the activity center of the proteins (Liu et al. 2017). ROS can reversibly oxidize the active thiol group of cysteine residues into protein S-glutathione disulfide, intra/intermolecular disulfide bridge, or sulfenic acid (Wang et al. 2008). Posttranslational modifications controlled by redox reaction, accompanied by the intramolecular protein disulfide bonds between the Cys residues, comprising of two paired sulfhydryl (–SH) groups,

in which the reaction may reverse by reduction (Klomsiri et al. 2011). In general, oxygen is needed for cellular metabolism and produced ROS (Lee et al. 2013). Indeed, the physiological levels between antioxidants and oxidants are required to modulate the cellular process (Rahal et al. 2014). An alteration of these levels may lead to the progression of cancers (Harris and DeNicola 2020). Elevation of oxidants levels in a certain period may oxidize the intramolecular spaced –SH groups to disulfides, which is potentially influence the protein function (Wani et al. 2014). For instance, TRX is an antioxidant protein that provides a reducing equivalent to protein expression involved in cancer such as ribonucleotide reductase (Mohammadi et al. 2019). TRX may undergo reversible redox reactions such as Cys73, Cys69, and Cys62 located outside the active site, or other alterations such as Cys35 and Cys32 located within the active site (Lee et al. 2013).

The previous study has demonstrated that moderate ROS levels as signaling messengers, which could induce invasion and survival in cancer cells (Wang et al. 2020). Redox protein may inhibit the excessive ROS that acts as a tumor promoter (Chen et al. 2016). In particular, redox modification of proteins involved in colorectal cancer is mediated by several transcriptional factors and signaling pathways (Yang et al. 2013). In this regard, targeting redox-sensitive signaling pathways may provide great promise in the treatment of cancer including colorectal cancer.

3.5 Redox Imbalance in Cardiovascular Disease

Redox signaling has been identified as a predominant regulator in numerous disorders such as fibrosis, cardiac hypertrophy, angiogenesis, atherosclerosis, and vascular smooth muscle proliferation (Tavakoli and Asmis 2012; Sag et al. 2014; Prieto-Bermejo and Hernández-Hernández 2017; Durgin and Straub 2018; Veith et al. 2019). ROS may trigger acute stimulations in cellular functions through a covalent alteration of the target molecule (Rea et al. 2018). For instance, several critical proteins are involved in myocardial excitation-contraction coupling, including contractile proteins, sarcoplasmic reticulum calcium release channels, and sarcolemmal ion channels; all these may undergo redox-sensitive modulations in specific activity (Eisner et al. 2017). Further, ROS have also exerted a crucial acute effect on cellular energetics (Pizzino et al. 2017). An alteration of cell phenotype may lead to the mediation of intracellular signaling pathways, for instance, redox-sensitive transcriptional activity such as activator protein-1 (AP-1), hypoxia-inducible factors (HIF-1), and NF-κB levels and subsequently modify the protein and gene expression (Tan et al. 2015; Komatsu et al. 2018; Kobayashi et al. 2021). During endothelial cell stimulation, a broad spectrum of redox-sensitive genes mediated several signaling pathways including platelet-derived growth factor (PDGF), plasminogen activator inhibitor-I (PAI-1), monocyte chemoattractant protein-1 (MCP-1), and vascular cell adhesion molecule-1 (VCAM-1) (Sprague and Khalil 2009; Suganya et al. 2016; Gregg et al. 2018; Puy et al. 2019).

XO-derived ROS is implicated in the development and progression of ischemia-reperfusion (Zhou et al. 2018). Once XO is released into the blood circulation and bound to the luminal surface of endothelial cells, XO exhibits its crucial effects even in the tissues that are not usually expressed (Abooali et al. 2014). In this regard, XO appears to play a crucial role in endothelial dysfunction in certain circumstances (Dopp et al. 2011).

In addition to the different sources mentioned above, most of the experiment studies indicate that modulating NADPH oxidases could play a critical role in CVD (Touyz et al. 2019). NADPH oxidases are essential for the microbicidal activity of neutrophils, and this enzyme is extensively found in non-phagocytic tissues (Zeng et al. 2019). NADPH oxidase has been identified to contribute to the development of cardiac hypertrophy, endothelial dysfunction, atherosclerosis, and hypertension (Langbein et al. 2016; Touyz et al. 2019; Poznyak et al. 2020; Zhao et al. 2020). However, different NADPH oxidase isoforms may have distinct activity and function (Delaney et al. 2016; Fulton and Barman 2016). Overall, maintaining a precise redox balance status is important in the mediation of the physiological acid-base buffer system in the body for optimal homeostatic cellular activities. Indeed, an alteration in redox balance would provide a great impact on the cellular signaling pathways and transcriptional activity as the majority of the reactions and activation are dependent on the oxidation/reduction processes (Locato et al. 2018).

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Chapter 4
Chronic Inflammation and Aging (Inflammaging)

Aging is an inherent mode of action present in all living cells (Campisi et al. 2019). Indeed, organ functions decrease with age. Despite the interactions between the age-related diseases and the aging process require further elucidation, most of the studies revealed that aging is implicated in the development of many age-related diseases (Franceschi et al. 2018; Tan et al. 2018a; Krisko and Radman 2019). One of the most common aspects of the inflammation hypothesis of aging is that age-related diseases undergo several pathways related to the inflammatory process, which may lead to the progression and development of a variety of age-related diseases (DeBalsi et al. 2017). For instance, many age-related diseases including arthritis, osteoporosis, dementia, CVD, cancer, metabolic syndrome, diabetes have been recognized as inflammatory disorders (Tan et al. 2015; Franceschi et al. 2018; Tan and Norhaizan 2021) (Fig. 4.1).

Mitochondrial and free radical theories are the two most common theories related to aging. These theories described that a vicious cycle is produced within the mitochondria, while the ROS is markedly generated and thus promotes the damage potential (Romano et al. 2010). Oxidative stress is existing in all living beings at the system, tissue, cellular, molecular, and genetic levels. This is often manifested as a progressive increase or accumulation of detrimental changes in tissues and cells with advancing age (Knupp and Miura 2018). It has been demonstrated that ROS levels increased with age and usually accumulates in major organ systems such as skeletal muscle, brain, heart, and liver (Olgar et al. 2018; Zhou et al. 2018; Hunt et al. 2019; Stefanatos and Sanz 2018) either due to reduced detoxification or increased production. In this regard, aging is considered as a progressive reduction in the biological function of the tissues and thereby increased the vulnerability to the diseases (Kregel and Zhang 2007). The widely accepted theory, namely "oxidative stress hypothesis", describes that increases in ROS resulted in pathological conditions and observable signs related to aging as well as functional alterations, and ultimately death (Hagen 2003). Despite ETC damage and mitochondrial DNA

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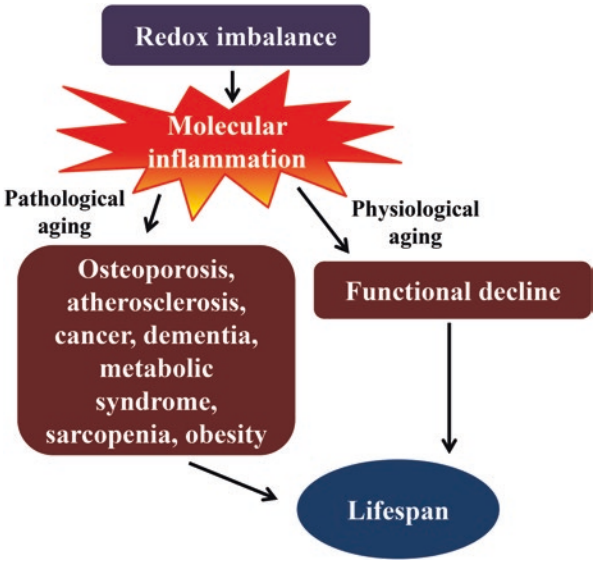

Fig. 4.1 The effects of inflammation in pathophysiological process

damage that may responsible for aging, the stimulation of redox-sensitive transcriptional factors or mediation of cellular signal response to stress by age-related oxidative stress upregulate the proinflammatory gene expression, and thereby enhances the ROS levels (Kregel and Zhang 2007).

4.1 Sources of Chronic Inflammation during Aging

Chronic, low-grade inflammation is thought to be a predominant contributor to a broad spectrum of natural processes and age-related pathologies in aging tissues, for instance, musculoskeletal and nervous systems (Libby and Kobold 2019; Cervo et al. 2020; Lin et al. 2020). In general, some tissues in the elderly are chronically inflamed (Gnani et al. 2019; Ziegler et al. 2019). Inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6) has been recognized as one of the contributor to diminish the anabolic signaling cascade such as erythropoietin and insulin signaling pathway, and thereby leading to an increased risk of developing sarcopenia (Beyer et al. 2012). Figure 4.2 summarizes the sources of chronic inflammation in aging.

Aging promotes the production of COX-derived reactive species and enhances the release of inducible nitric oxide synthase (iNOS), COX-2, TNF-α, IL-6, and IL-1β (Wojdasiewicz et al. 2014; Begg et al. 2020). Other proinflammatory proteins, for instance, P-, E-selectin, intercellular cell adhesion molecule-1 (ICAM-1), and VCAM-1 are also upregulated during the aging process (Zou et al. 2006). The

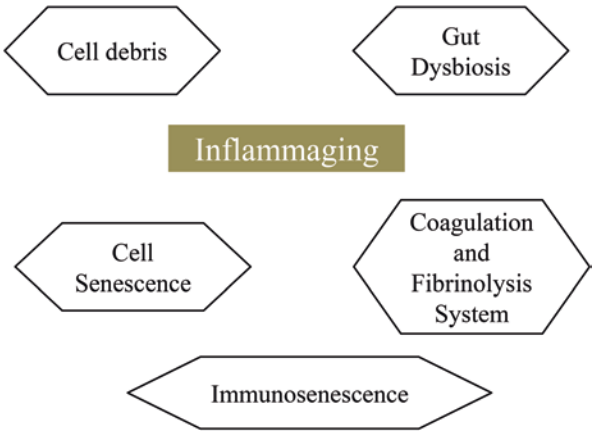

Fig. 4.2 Sources of chronic inflammation in aging

nuclear factor-kappa B (*NF-κB*) transcriptional activity is regarded as the master regulator of the inflammatory process and can be stimulated by oxidative stimuli (Park and Hong 2016; Liu et al. 2017). The stimulation of *NF-κB*-dependent genes is a key transcriptional factor for the systemic inflammatory process (Jakkampudi et al. 2016). During activation, proinflammatory genes encode proinflammatory proteins, for instance, chemokines, growth factors, and cytokines (Drago et al. 2015). The NF-κB activity is mediated by upstream signaling, for instance, mitogen-activated protein kinase (MAPK) and IκB kinase (IKK). The IκB subunits of NF-κB/IκB are phosphorylated by activated IKK complexes and thus stimulating the degradation of IκB, which subsequently lead to the activation of NF-κB. IKK activity is activated by NF-κB during aging (Tilstra et al. 2011), and subsequently promotes the activation of p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) activities that control *NF-κB*-dependent gene expression during an inflammatory response (Jnawali et al. 2014). A previous study revealed that aging promotes p38 MAPK, JNK, and ERK signaling pathways with an increase in ROS production (Ito et al. 2010).

Under normal circumstances, stimulation of NF-κB in response to oxidative stimuli is short-lived, and the reaction is halted with resolution. Nonetheless, when the input signal is not well-maintained during aging, chronic proinflammatory conditions may create a conducive environment for many chronic diseases (Rea et al. 2018). Several NF-κB-induced proteins such as COX-2, IL-6, and TNF-α are potent NF-κB activators that form an auto-activating loop (Oeckinghaus and Ghosh 2009). Substantial studies evaluated the changes of redox-sensitive transcriptional factors such as NF-κB in rodent models (Hansen et al. 2002; Kim et al. 2002; George et al. 2009). The study revealed that old rodents have consistently expressed high NF-κB activities in a variety of tissues, for instance, brain, kidney, liver, and heart compared to the young rodents (Korhonen et al. 1997; Radák et al. 2004; Ungvari et al. 2007; Lim et al. 2012). Data from the human study have also demonstrated that

circulating levels of proinflammatory cytokines such as IL-1ra, IL-6, and TNF-α are increased during aging (Bruunsgaard 2006). In addition, aging is also linked to the high inflammatory cell counts (monocytes and neutrophils) and increased levels of C-reactive protein (CRP) (Ritzel et al. 2018; Wong and Wagner 2018; Álvarez-Sánchez et al. 2020). High IL-6 plasma levels were shown a greater likelihood of morbidity, disability, and mortality in the elderly (Puzianowska-Kuznicka et al. 2016). High levels of CRP, IL-1β, and IL-6 are linked to many diseases in the elderly (Ng et al. 2018; Poole and Steptoe 2020). Plasma levels of TNF-α are positively linked to the high levels of CRP and IL-6, implied that an interrelated stimulation of inflammatory cascade (Oe et al. 2015).

Numerous studies have evaluated the relationship between insulin resistance and obesity, but there is no definitive resolution to date. A previous study showed that inflammation could be a possible underlying link between these metabolic ailments (Fiordelisi et al. 2019; Greten and Grivennikov 2019; Diedisheim et al. 2020). Excessive caloric consumption increased adiposity and thus leads to macrophage infiltration into adipose tissues that promote local chronic inflammation which potentiates insulin resistance (Poli et al. 2017; Tan et al. 2018b). Overexpression of *Mcp1* promotes insulin resistance, inflammation, and macrophage infiltration (Kanda et al. 2006; Patsouris et al. 2014; Gogh et al. 2016). Furthermore, knockout of *Mcp1* and its receptor (*Ccr2*) impairs migration of macrophages, and thus increases insulin sensitivity and reduces inflammation (Tamura et al. 2008; Sawyer et al. 2014).

4.1.1 Immunoglobulin or Cell Debris Production

Immunoglobulin or debris accumulation caused by an inappropriate cell elimination system in aging, which induces innate immune activity stimulation and thereby leading to inflammation (Sanada et al. 2018). In particular, glycosylation is the most often posttranslational modification of protein (Carnino et al. 2020). The protein-linked sugar chain plays a crucial role in the "fine-tuning" of molecules and cells (Ohtsubo and Marth 2006; Dall'Olio et al. 2013). High-throughput studies of the N-glycome, a sugar chain N-linked to asparagine, demonstrated a potential biomarker for natural aging, for instance, N-glycans devoid of galactose residues on the branch, in human studies (Parekh et al. 1988; Vanhooren et al. 2007; Ruhaak et al. 2011). This agalactosylated biantennary structure primarily decorates Asn297 of the Fc portion of IgG (IgG-G0) and is present in patients with inflammatory/autoimmune diseases or progeria syndromes (Dall'Olio et al. 2013). Accelerated aging syndromes or progerias are partially recapitulated normal aging (Dreesen and Stewart 2011). Progerias are predominantly triggered by defects in DNA repair systems or an alteration of the nuclear envelope (Burla et al. 2018). Indeed, IgG-G0 shows a proinflammatory effect via a few mechanisms including formation of autoantibody aggregates, binding to Fcγ receptors, and lectin pathway of complement

(Gudelj et al. 2018). Further, the age-related production of IgG-G0 can stimulate the immune system and hence result in inflammaging (Barrientos et al. 2020). By contrast, mitochondrial dysfunction has also drawn attention among scientists (Manolis et al. 2021). Mitochondria-derived damage-associated molecular patterns (DAMPs) such as cell-free circulating mitochondrial DNA have been extensively studied due to the involvement in chronic diseases and aging (Zhang et al. 2010; Dall'Olio et al. 2013). Through their bacterial ancestry, these molecules may promote the inflammatory response via interaction with receptors similar to those involved in pathogen-related response (Sanada et al. 2018).

4.1.2 The Microbiota and Gut Mucosa in Elderly

The ability of gut mucosa to sequester bacteria deteriorates with age (Shoemark and Allen 2015). Periodontal disease has been reported to cause chronic low-grade inflammation (Loos and Van Dyke 2020). The study found that the diversity of gut microbiota is reduced in older people (Claesson et al. 2011; Kinross and Nicholson 2012). In particular, the anti-inflammatory microbiota, for example, *F. prausnitzii*, *Bifidobacterium* spp., and *Clostridium* cluster XIVa, are reduced in the elderly (Toward et al. 2012). A study by Okada et al. (2009) further supported that the *Bifidobacterium* species is negatively linked to the serum IL-1β and TNF-α levels. By contrast, pathogenic and inflammatory microbiota, such as *Enterobacter* spp., *Enterococcus* spp., *Staphylococcus* spp., and *Streptococcus* spp., are increased with age (Toward et al. 2012). Alteration in gut microbiota diversity may increase the susceptibility to infectious agents by pathobionts colonization (Mosca et al. 2016).

4.1.3 Cell Senescence

Cellular senescence is an irreversible cell cycle arrest mediated by a few mechanisms such as inflammatory cytokines, mitogen stimuli, genotoxic stress, and telomere shortening, which can lead to the stimulation of the cyclin-dependent kinase inhibitor p16 and/or p53 tumor suppressor (de Magalhães and Passos 2018).

Senescence is a cellular response to damage and stress (Franceschi and Campisi 2014). It was evident that the number of senescent cells is increased with age, in which these organs secrete many inflammatory cytokines and produce low-grade inflammation. Senescent cells are linked to age-related diseases or aging through the secretion of proinflammatory cytokines that alter the function of normal cells or the tissue microenvironment (Baker et al. 2011). The phenotype of senescent cells is known as senescence-associated secretory phenotype (SASP), which is suggested as the primary origin of inflammaging in age-related diseases and aging (Sanada et al. 2009; Tchkonia et al. 2013; He and Sharpless 2017). The previous study showed that the elimination of senescent cells in prematurely aged mice ameliorates

the progression of age-related diseases (Coppé et al. 2010). Such findings indicate that the mediation of proinflammatory pathways linked to the acquisition of SASP, reprogramming of senescent cells, and elimination of senescent cells could be used as a potential anti-aging approach for extending healthspan and ameliorating the metabolic ailments (van Deursen 2014).

4.1.4 Immunosenescence

Immunosenescence is characterized by the chronic inflammatory response, due to the age-related dysregulation of an innate immune system (Shaw et al. 2013). Immunosenescence impairs wound healing, reduces the response to vaccinations, and increases the susceptibility to malignancy (Aw et al. 2007; Gruver et al. 2007). Aging modifies the immune system and thus contributes to inflammaging (Fulop et al. 2018). Indeed, the immunosenescence process can be accelerated by chronic inflammatory disease (Barbé-Tuana et al. 2020). The mechanisms underlying the persistent aging-associated basal inflammation are not fully understood, but it is hypothesized that the changes in functions and numbers of innate immune cells contribute to these phenomena. Most of the studies so far indicated that unusual downstream signaling pathway of pattern recognition receptors (PRRs) stimulation, activation of PRRs by endogenous ligands related to cellular damage, and changes in the PRRs levels may lead to the induction of chronic cytokine secretion (Hung and Suzuki 2017; Zhu et al. 2019). In this regard, dysregulation of immunological imprinting modulated by innate immunity as well as cell senescence may contribute to chronic low-grade inflammation. In addition, adaptive immunity declines with age; while innate immunity showed minute changes in mild hyperactivity (Santoro et al. 2018). However, the innate immune response might activate when adaptive immunosenescence progresses. Collectively, the age-related changes could be attributed to the intrinsic changes in immune cells and lifelong exposure to pathogens and antigens (Stephenson et al. 2018).

4.1.5 Coagulation and Fibrinolysis System

Activation coagulation and fibrinolysis system in the elderly increased inflammation by modulating the protease-activated receptor (PAR) (Chu 2010; Hess and Grant 2011; Sanada et al. 2016), and thereby lead to an increased risk for lung fibrosis and atherosclerosis (Biagi et al. 2011). Coagulation is considered as part of the inflammation system. The inflammatory process is linked to the potentially aggravating phenomenon of obesity (Tan et al. 2018b). Age-related obesity is predominantly due to the increased adiposity, especially visceral fat deposits, during aging via redistribution of fat deposits with age (Villarroya et al. 2018). Indeed, most of the proinflammatory cytokines are generated by resident macrophages and

adipocytes in adipose tissues, and thereby leading to systemic inflammation (Makki et al. 2013). Elevation of proinflammatory status is more likely to increase the susceptibility of several age-related diseases (Ackermann et al. 2020; Tu et al. 2020; Tahir et al. 2021). For instance, osteopenia and sarcopenia are characterized as the normal aging processes, which are good examples of the involvement of inflammation in the normal aging process to pathogenesis (Fig. 4.1).

Research evidence indicates that plasma concentrations of coagulation factor IX, VIII, VII, and V were increased in healthy subjects in conjunction with the physiological processes of aging (Chu 2011; Favaloro et al. 2014). The fibrinogen levels (coagulation factor I), a predominant risk factor for thrombotic disorders, are increased with age (Gligorijević et al. 2018). In particular, the coagulation factor X is overexpressed in human atherosclerotic plaques, such as inflammatory cells, smooth muscle cells, and endothelial cells (Sanada et al. 2017). Based on the evidence, increased plasma levels and local coagulation factors during physiological aging may increase the risk of CVD progression in the elderly. The previous study showed that the direct coagulation factor rivaroxaban, Xa inhibitor, decreased the risk of the composite endpoint of death from stroke, myocardial infarction, and CVD in patients with acute coronary syndrome (Mega et al. 2012). Despite the molecular mechanisms underlying the coagulation factor and reduced risk of CVD require further elucidation, most of the experimental studies indicate that stimulation of coagulation cascade following fibrinogen activation may elevate the thrombosis (Palta et al. 2014). Further, increased levels of thrombin and coagulation factor Xa may improve the inflammatory response via modulation of PAR-1/2 signaling (Spronk et al. 2014). Notably, PAR-1/2 signaling triggered by fibrinolytic factor plasmin and coagulation factor Xa (FXa) was shown to elevate the insulin-like growth factor binding protein-5 (IGFBP-5) levels (Kamio et al. 2008; Carmo et al. 2014; Sanada et al. 2016, 2017). A study by Kojima et al. (2012) found that IGFBP-5 mediates IL-6 expression to trigger ROS generation, and thereby leading to the DNA damage and senescence of fibroblast cells. Further, IGFBP-5 also stimulates a fibrotic phenotype by stimulating nuclear early growth response-1 (EGR-1) translocation and MAPK signaling that interacts with IGFBP-5 and upregulates inflammatory and fibrotic transcriptional activity (Yasuoka et al. 2009). In addition, activation of FXa in endothelial progenitor cells, endothelial cells, and smooth muscle cells promote cellular senescence by modulating the EGR-1-IGFBP-5-p53 signaling pathway (Sanada et al. 2016). This finding implies that cell senescence, hypercoagulability, and inflammaging may share a common pathway mediated by IGFBP-5 signaling. Intriguingly, some research has emerged to suggest that IGFBP-5- and FXa-positive areas were distributed in the human atherosclerotic plaques (Sanada et al. 2017). Collectively, locally produced coagulation factor Xa in atherosclerotic plaques may promote cellular senescence with SASP and trigger IGFBP-5 levels (Sparkenbaugh et al. 2014). Because aging is a complex mechanisms results from the epigenetic, genetic, and environmental factors, further studies focused on interventions that selectively damage senescent cells, for instance, “senolytic therapies” in the aging host may enhance the therapeutic approach (Roos et al. 2016; Farr et al. 2017; Lehmann et al. 2017; Collins et al. 2018).

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Chapter 5
Implications of Inflammation in Aging and Age-Related Diseases

Research evidence indicates that low-grade chronic systemic inflammation plays a crucial role in mediating the aging process and age-related diseases, for instance, osteoporosis, diabetes, cancer, atherosclerosis, neurodegenerative disease, and metabolic syndrome (Tan et al. 2018a, b), which is also known as "inflammatory diseases" (McGeer and McGeer 1999). Despite the precise molecular inflammatory process involved in each disease may vary from other diseases, the fundamental mode of actions of the proinflammatory cytokines and inflammatory mediators are similar (Kany et al. 2019; Rea et al. 2018). The role of chronic inflammation in age-related diseases will be described in the following section.

5.1 Obesity

Metabolic syndrome was originally known as Syndrome X, refers to a cluster of clinical factors, such as dyslipidemia with low high-density lipoprotein (HDL) levels and increased triglycerides (TG), hypertension, high blood glucose, hyperinsulinemia, and insulin resistance (Huang 2009; Bonomini et al. 2015). Nonetheless, reduced insulin sensitivity is linked to abdominal obesity, which is the predominant feature of the syndrome (Galderisi et al. 2019).

The prevalence of obesity has doubled from 1980 to 2008 worldwide. Nearly 50% of women and men in the WHO European Region were overweight in 2008, in which 23% of women and 20% of men were obese (World Health Organization 2017). Approximately 1.5 billion people are overweight or obese worldwide. Individuals who are obese or overweight are at risk of developing coronary heart disease, CVD, type 2 diabetes, nonalcoholic fatty liver disease, and inflammatory disturbances (Wang et al. 2011; Matsuda and Shimomura 2013). The rates of obesity have increased in both sexes and all ages irrespective of socioeconomic status, ethnicity, or geographical locality. Women and elderly people were shown to have a

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greater likelihood of obesity (Chooi et al. 2019). Obesity is linked to the high levels of 4-hydroxynonenal (4-HNE) adducts in skeletal muscle (Russell et al. 2003) and protein carbonyls in subcutaneous adipose tissues (Frohnert et al. 2011).

Under normal circumstances, the oxidation of fatty acids or glucose produces ATP via mitochondrial respiration, and thus results in the production of superoxide (Brownlee 2001). Fatty acid oxidation and glycolysis generate $FADH_2$ and NADH, which allow the electrons that fuel ATP and ETC production (Murphy 2009). $FADH_2$ and NADH donate their electrons to complexes II and I of the ETC, respectively. These complexes transfer electrons to ubiquinone, and thereby passed through the electrons to complex III, cytochrome c, and complex IV, and ultimately to molecular oxygen (Zhao et al. 2019a). The produced electrons are used to shuttle protons across the mitochondrial membrane to generate membrane voltage potential that drives mitochondrial respiration (Alberts et al. 2002). Superoxide can be generated when the electrons from coenzyme Q are received by molecular oxygen as they are shuttled from complexes I and II to complex III (Brownlee 2001). Excessive high-carbohydrate or high-fat diet may produce more substrates to enter into mitochondrial respiration. Subsequently, the number of electrons donated to the ETC may increase. Once the membrane potential reaches the threshold voltage, excess electrons may back up at complex III, with a subsequent donation to molecular oxygen, and thus produce high levels of superoxide (Brownlee 2001). Data from *in vitro* study showed that free fatty acids promote ROS production, suggesting that high fatty acids in obesity may provide an additional source of excess ETC substrates by increasing fatty acids oxidation (Furukawa et al. 2004). Obesity or increased caloric intake is linked to the activation of mitochondrial superoxide production. Feeding a high-fat diet significantly increased H_2O_2 emission from mitochondria isolated from skeletal muscle (Jain et al. 2014). The data further revealed that obese or high-fat diet animals promote ROS production in mitochondria of adipose tissue (Masschelin et al. 2020), liver (Vial et al. 2011), and kidney (Chang et al. 2019).

Another prominent contributor that promotes a prooxidant environment in obesity is through the mediation of proinflammatory response (Rodríguez-Cerdeira et al. 2019). Inflammation can lead to oxidative stress in *in vivo* model when there is a large increase in free radical production by immune cells (Pizzino et al. 2017). Obesity is linked to the changes of T-cell subsets related to adipose tissues (Misumi et al. 2019) and the activation of infiltration of macrophages into the adipose tissue (Surmi and Hasty 2008). These processes increase production of some proinflammatory cytokines by preadipocytes, mature adipocytes, and immune cells (Asghar and Sheikh 2017). Elevation of oxidative stress is related to chronic inflammation (Wiegman et al. 2015); other sources may also further enhance the production of proinflammatory cytokines in a "vicious cycle" (di Penta et al. 2013). ROS promotes the expression of proinflammatory monocyte chemotactic protein-1 (MCP-1) and cytokine IL-6 (Elmarakby and Sullivan 2012). In adipose tissue, this process further enhances the macrophage infiltration and thereby leading to the proinflammatory environment (Lee and Lam 2019). ROS can also induce NF-κB signaling pathway that activates and IL-6 and TNF-α (Yoshida et al. 1999; Kamata et al. 2005; Zhang et al. 2020). Furthermore, oxidative stress may promote cellular senescence,

particularly adipocyte senescence, partly via the cellular oxidation damage (Minamino et al. 2009; MacKellar et al. 2010). Adipocyte senescence may increase the generation of proinflammatory cytokines and recruit macrophages (Minamino et al. 2009; Lafontan 2014).

Adipose tissues are divided into two classes, namely brown adipose tissue (BAT) and white adipose tissue (WAT) (Kaisanlahti and Glumoff 2019). WAT is one of the predominant adipose tissues found in the organisms, which is a site for energy storage. BAT is mainly used for non-shivering thermogenesis, primarily in human neonates and small mammals (Fantuzzi 2005). Among all the cell types found in WAT, adipocytes are one of the abundant cells. The previous study has revealed that adipose tissue is characterized by an elevation infiltration of macrophages, suggesting the presence of inflammation in adipose tissues (Suganami and Ogawa 2010; Sharma et al. 2020). The macrophage infiltration may lead to a dysregulation in the adipose tissue endocrine system and stimulate the production of the inflammatory cytokines, and subsequently result in insulin resistance and endothelial dysfunction (Chait and den Hartigh 2020). Intriguingly, the inflammatory response in obesity is induced by adipose tissues (Pan et al. 2019). Adipocytes constitutively increased TNF-α levels, in which the adipocytes are markedly elevated with obesity (Poret et al. 2018; Tan and Norhaizan 2019). TNF-α activates the cellular kinase complex, which in turn promotes the NF-κB. Subsequently, this transcription factor mediates the production of proinflammatory cytokines, such as IL-6 and IL-1β (Kern et al. 2019).

The previous study has revealed that increased oxidative stress in obesity can reduce antioxidant defense system and increase superoxide production by NADPH oxidase (Olusi 2002; Furukawa et al. 2004; Serpillon et al. 2009; Marseglia et al. 2015). NADPH oxidase is mainly used by neutrophils to produce superoxide to kill fungi and invading bacteria (Gazendam et al. 2016; Belambri et al. 2018). It is stimulated by advanced glycation end products (AGEs), which are increased after high glucose diet consumption (Goldin et al. 2006; El-Bassossy et al. 2018). Interestingly, obesity is inversely associated with catalase, glutathione peroxidase 1 (GPx1), and SOD in the adipose tissues, but not in the liver or skeletal muscle (Furukawa et al. 2004). It remains unknown why the reduction of antioxidant enzymes is only observed in adipose tissues. It could be due to the high oxidative stress in this tissue that caused an inhibition of the antioxidant enzyme (Furukawa et al. 2004). This phenomenon suggests that the general increase in oxidative stress related to obesity may be due to the alteration in fat (Walle et al. 2017). Taken together, systemic oxidative stress-related high-fat diet and obesity may promote inflammation and metabolic dysfunction.

5.2 Neurodegenerative Diseases

Neurodegenerative diseases are characterized by progressive deterioration of neural cells and thus lead to compromised cognitive or motor function (Dugger and Dickson 2017; Liu et al. 2017a). There are several neurodegenerative diseases

including Huntington's disease, Parkinson's disease, Alzheimer's disease, spinocerebellar ataxia, and amyotrophic lateral sclerosis (Albers and Beal 2000; Silvade et al. 2000; Matilla-Duenas et al. 2014; Alzheimer's Association 2016). These diseases represent one of the greatest health threats, particularly among the elderly (Albers and Beal 2000; Hamer and Chida 2009). Dementia is a progressive or chronic syndrome, in which there is declined in their ability to conduct daily activities (World Health Organization 2020a). It affects behavior, thinking, memory, as well as orientation and judgment. Despite dementia is primarily affected the elderly, it is not an exclusive part for aging. Dementia accounts for nearly 50 million people worldwide (World Health Organization 2020a). In particular, Alzheimer's disease is the most common form of dementia and contributes to 60–70% of cases (World Health Organization 2020a). ROS are chemically reactive molecules that have been implicated in the pathogenesis of neurodegenerative diseases (Collin 2019). Research evidence suggested that ROS may play a crucial role in neurodegenerative disorders (Ballance et al. 2019). Patients with neurodegenerative diseases were shown high amounts of oxidative stress (Cenini et al. 2019). Despite ROS may not be an essential factor for neurodegenerative diseases, they are more likely to aggravate disease progression via interaction with mitochondria and oxidative damage (Dias et al. 2013). Notably, neuron cells are susceptible to oxidative damage due to the low antioxidant defense, high rates of oxygen consumption, and increased levels of polyunsaturated fatty acid in membranes (Rego and Oliveira 2003). The redox imbalance can lead to abnormal mitochondrial function and neural inflammation (Rego and Oliveira 2003; Mosley et al. 2006). The pathogenesis of several neurodegenerative diseases including Parkinson's disease and Alzheimer's disease are linked to the accumulation of misfolded proteins (Lim 2019). The aggregation of these proteins can induce an inflammatory response in the brain, and thus markedly release ROS (Wyss-Coray and Mucke 2002; Zuo et al. 2015). Mitochondrial dysfunction is accompanied by aberrant ROS generation, which is closely related to neurodegenerative diseases (Albers and Beal 2000; Lin and Beal 2006).

Alzheimer's disease represents the most common prevalent neurodegenerative condition (Magalingam et al. 2018). The Alzheimer's disease population is expected to increase to 65.69 million people by 2030 (Alzheimer's disease international 2009). The pathophysiology of Alzheimer's disease is primarily linked to the accumulation of intracellular tau neurofibrillary tangles and extracellular deposition of amyloid-beta (Aβ) plaques (Querfurth and LaFerla 2010; Butterfield 2014). Aβ plaques can diminish calcium ions (Ca^{2+}) storage in the endoplasmic reticulum and thus leading to an overload of cytosolic Ca^{2+} (Corona et al. 2011). When cytosolic Ca^{2+} is upregulated, it can cause an accumulation of ROS inside the cells and reduce endogenous GSH levels (Ferreiro et al. 2008). In particular, ROS-induced oxidative stress is a key factor in the pathogenesis of Alzheimer's disease. This finding implies that overexpression of ROS is considered critical in the deposition and accumulation of Aβ in Alzheimer's disease (Bonda et al. 2010). Mitochondrial dysfunction can cause an alteration of Ca^{2+} homeostasis, excitotoxicity, reduction of ATP, and misregulation of ROS (Gleichmann and Mattson 2011). All these modifications have been implicated in the development of Alzheimer's disease (Huang et al.

2016). Overproduction of oxidative stress in Alzheimer's disease patients could be attributed to the overactivation of N-methyl-D-aspartate-type glutamate receptors (NMDARs). Stimulation of NMDAR causes an excessive influx of Ca^{2+} by enhancing cell permeability and thus producing neurotoxic amounts of ROS/RNS (Nakamura and Lipton 2010, 2011). ROS plays a crucial role in modulating the JNK/stress-activated protein kinase signaling pathway (Benhar et al. 2002). The stimulation of these pathways triggered the Aβ-induced cell death and hyperphosphorylation of tau proteins (Patten et al. 2010). Furthermore, Aβ proteins can initiate the free radical formation through stimulation of NADPH oxidase (Shelat et al. 2008). Aβ-induced ROS accumulation alters cellular signaling pathways and initiates tau hyperphosphorylation through stimulation of p38 MAPK. Giraldo et al. (2014) and Bulat and Widmann (2009) found that dysfunction of hyperphosphorylated tau proteins can lead to the formation of intracellular neurofibrillary tangles. It has been reported that Aβ plays a crucial role in modulating cellular apoptotic cascades (Agostinho et al. 2008). In particular, Aβ can enhance calcineurin activity, and thereby induces Bcl-2-related death promoter. Ultimately, these lead to cytochrome c release from mitochondria (Awasthi et al. 2005). It may also link to the caspases, which in turn trigger neuron apoptosis (Awasthi et al. 2005).

The study has shown that environmental stress, inflammation, and aging can trigger oxidative stress that may contribute to the increased of Aβ production (Hamilton and Holscher 2012; Aseervatham et al. 2013). Elderly people are prone to oxidative stress, hence partially explaining the susceptibility of Alzheimer's disease among aging populations (Stadtman 2001; Hamilton and Holscher 2012). Inflammation promotes cellular toxicity, enhances ROS levels, and increases the amount of cytokines; all these may aggravate Alzheimer's disease progression (Blaser et al. 2016; Varvel et al. 2016; Italiani et al. 2018). In addition, Aβ accumulation leads to microglial activation (Hemonnot et al. 2019). It has been reported that prolonged stimulation of microglia may result in the release of proinflammatory cytokines, as well as initiating the proinflammatory cascade, and thereby resulting in neuronal loss and damage (Wang et al. 2015).

Oxidative stress can also be triggered by environmental factors such as radiation, chemicals, and pollutants (Nizzari et al. 2012; Aseervatham et al. 2013). For instance, excess iron deposits lead to the formation of ROS (Nizzari et al. 2012). Aβ interacts with metal ions and produces free radicals (Butterfield and Boyd-Kimball 2005; Nizzari et al. 2012). Notably, Cu^{2+}/Zn^{2+} -bound Aβ was shown a structure similar to SOD with antioxidant activity (Curtain et al. 2001). In this regard, supplementation of Zn^{2+} and Cu^{2+} could be served as a potential approach to reduce metal-catalyzed Aβ deposition and Aβ-induced ROS production (Curtain et al. 2001). Collectively, the molecular mechanisms that implicate the development of neurodegenerative diseases are complex and involved a few mechanisms. In particular, mitochondria dysfunction is linked to the oxidative stress in neurodegenerative diseases.

5.3 Atherosclerosis

CVD has become the leading cause of death worldwide, accounting for nearly 17.9 million lives annually, an estimated 31% of all deaths globally (World Health Organization 2020b). CVD is a cluster of disorders of the blood vessels and heart including rheumatic heart disease, cerebrovascular disease, coronary heart disease, and other conditions (World Health Organization 2020b). About 85% of all CVD are due to strokes and heart attacks, with one-third of this death occurred prematurely in individuals below 70 years old (World Health Organization 2020b). The major contributor to CVD is atherosclerosis, which is a multifactorial and progressive process that affects the large arteries characterized by the accumulation of fibrous particles and lipids in the walls. Inflammation has been demonstrated in all phases of the atherosclerotic process, from the initial steps of leukocyte recruitment to the rupture of a vulnerable plaque (Pant et al. 2014).

The initial stage of atherosclerosis has been implicated by the adherence or attraction of monocytes to the vascular endothelium as well as their migration into the vessel wall (Čejková et al. 2016). The adhesion molecules such as VCAM-1, ICAM-1, and selectins promotes the adhesion of leukocytes to the vascular endothelium (Pierangeli et al. 2001) and thus triggered by inflammatory factors, for instance, CRP, TNF-α, and interleukin-1 (IL-1) (Guo et al. 2018). Indeed, VCAM-1 binds to certain leukocytes was found in nascent atheroma. Both endothelial cells and macrophages generate ICAM-1 in response to inflammatory cytokines such as interferon-γ, TNF-α, and IL-1 (Ren et al. 2010; Paulsen et al. 2015; Wiesolek et al. 2020). The accumulation of macrophages and their uptake of oxidized-low density lipoprotein (ox-LDL) may result in the production of foam cells and thus promote fatty streaks (Moore et al. 2013).

The development of lesions is characterized by the migration of smooth muscle cells into the subendothelial space from the medial layer of the artery wall (Lusis 2000; Milutinović et al. 2020). Smooth muscle cells grow and migrate with the facilitation of several cytokines and growth factors produced by endothelial and inflammatory cells (Louis and Zahradka 2010). Nonetheless, the smooth muscle cell is a source of inflammatory mediators, for instance, monocyte chemoattractant protein-1 (MCP-1) (Lim and Park 2014). Mice lack of MCP-1 expression or its chemokine receptor, CCR2 was shown to develop fewer atherosclerotic lesions (Gosling et al. 1999; Wezel et al. 2015). Similar to the increase of chemoattractant proteins and adhesion molecules, initiators of the atherosclerotic cascade (ox-LDL) were found to promote the production of growth factors including macrophage colony-stimulating factor (M-CSF) (Wu et al. 2017).

The growth of smooth muscle cells further recruits the inflammatory cells and the synthesis of extracellular matrix proteins and thus leading to the formation of the atheroma, a mature atherosclerotic plaque comprised of fibrous cap separating the pro-thrombotic lipid pool from luminal blood flow (Newby and Zaltsman 1999; Lim and Park 2014; Basatemur et al. 2019). The stimulation of smooth muscle cells and inflammatory cells (T lymphocytes and macrophages) is linked to the release of

mediators such as growth factors, cytokines, and adhesion molecules (Ramel et al. 2019). IL-6 has been reported to increase plasma levels of CRP, plasminogen activator inhibitor type 1, and fibrinogen, and thereby enhance and amplify both procoagulant and inflammatory responses (Yamaguchi et al. 1998; Fischer et al. 2006; Cesari et al. 2010). This proinflammatory mediator has been suggested to be involved in the modulation of atherosclerosis pathogenesis (Moriya 2019).

They are several enzyme systems that can generate ROS in the vascular wall. Among the ROS-producing enzymes, four of them seem to play a crucial role, namely, a dysfunctional endothelial NO synthase, enzymes of the mitochondrial respiratory chain, XO, and NADPH oxidase (Landmesser et al. 2002; George and Struthers 2009; Faria et al. 2018; Daiber et al. 2019; Ding et al. 2019; Mazat et al. 2020). Notably, NADPH oxidase can induce eNOS uncoupling as well as XO activation (Landmesser et al. 2007).

5.3.1 NADPH Oxidases

NADPH oxidases are key sources of ROS in the vasculature, which generates superoxide from molecular oxygen by using NADPH as the electron donor (Yousefian et al. 2019). These oxidases are multi-subunit enzyme complexes that interact with one of few homologs of the membrane-bound Nox catalytic subunit (Bedard and Krause 2007; Drummond et al. 2011). The activity of Nox4 depends on its association with p22phox. Indeed, p22phox is not only essential for Nox2 and Nox1 activity in vascular cells, other Nox catalytic subunit such as Rac1, p67phox (or NOXA1), and p47phox (or NOXO1) also plays a crucial role in this phenomenon (Brandes and Kreuzer 2005).

Nox4 (Ellmark et al. 2005) and Nox1 (Lassegue et al. 2001) are found in vascular smooth muscle cells, while Nox4 (Ago et al. 2004; Xu et al. 2008) and Nox2 are expressed predominantly in endothelial cells. Atherosclerosis is linked to the upregulation of NADPH oxidase subunits (p67phox, p47phox, p22phox, and Nox2) in the coronary artery (Guzik et al. 2006).

Despite data from animal studies of global p47phox (Hsich et al. 2000) and Nox2 (Kirk et al. 2000) knockout mice demonstrated that no difference in atherosclerosis of the aortic sinus, few studies stated that global knockout of p47phox leads to a moderate decline in aortic atherosclerosis for both high-fat and chow fed animals (Barry-Lane et al. 2001). This finding implies that global Nox2 phosphorylation results in a decline in aortic atherosclerotic burden (Judkins et al. 2010).

The cell-specific effects of Nox2 were evaluated. An animal study showed that endothelium-specific overexpressing Nox2 enhanced the macrophage recruitment in early lesions, elevated the endothelial levels of VCAM-1, and increased vascular superoxide production in ApoE-KO mice. Nevertheless, neither the native nor the angiotensin II-driven atherosclerosis is influenced by endothelial Nox2 overexpression (Douglas et al. 2012). This finding implied that despite the stimulation of endothelial Nox2 alone is sufficient for the initiation of atherosclerosis, Nox2 in other

cell types could be an indispensable contribution to the development of atherosclerosis. Notably, the plaque core of atherosclerotic human arteries was shown the highest Nox2 expression, the Nox2 in macrophage is also abundant. Therefore, as long as the macrophage function is not changed and the lipid composition does not alter, the elevation of endothelial-derived ROS formation alone may not lead to atherosclerotic plaque progression (Haendeler et al. 2012).

5.3.2 Xanthine Oxidase

Similar to NADPH oxidases, XO has been demonstrated to be another key source of superoxide in human coronary artery disease (Guzik et al. 2006). XO was found in endothelial cells and the activity and expression of endothelial XO are increased in response to angiotensin II treatment (Landmesser et al. 2007). Furthermore, XO can be released from the circulation XO and the liver adheres to endothelial cells by interacting with the endothelial glycosaminoglycans (White et al. 1996). XO transfers the electrons to molecular oxygen and thereby generating H_2O_2 and superoxide. The activity of both plasma XO (White et al. 1996) and endothelial XO (Ohara et al. 1993) is elevated in human atherosclerotic plaque and atherosclerosis (Patetsios et al. 2001; Guzik et al. 2006), implied that XO-derived superoxide promotes atherosclerosis. Data from *in vivo* study showed that XO inhibitors improve the endothelium-dependent, NO-modulated vasodilation in aorta rings of hypercholesterolemic animals (White et al. 1996). In another study, XO inhibitor tungsten prevents endothelial dysfunction, alleviates the vascular superoxide anion formation, and decreases the development of atherosclerosis in the aorta (Schroder et al. 2006).

5.3.3 Mitochondria

Atherosclerosis is developed by inflammation and a mutually enhancing circuit of ROS (Marchio et al. 2019). In addition to the different sources of ROS including uncoupled eNOS, XO, and NADPH oxidases, the mitochondrial respiratory ETC is of vitally important to CVD, heart function, and atherogenesis (Madamanchi and Runge 2007; Madungwe et al. 2016; Chistiakov et al. 2018). It has been exemplified by the cardiac loss of mitochondrial Mn-SOD (SOD2), and causes perinatal lethality due to the congestive heart failure or cardiac myopathy (Nojiri et al. 2006). Furthermore, it has been demonstrated that S-nitrosation of the mitochondrial complex I, which is the site where electrons enter the ETC. This site is critically involved in the oxidative burst during reperfusion/ischemia damage (Shiva 2010). Given the systemic uptake of an antioxidant such as vitamins failed to show any benefit of atheroprotection in clinical studies (Sesso et al. 2012), and thus the mediation of local antioxidant processes is a critical option. Due to the vital role of mitochondria, some of the new compounds were recently developed by targeting antioxidative

components to the mitochondria to produce direct, efficient, and local ROS scavenging substances (Battogtokh et al. 2018; Goleva et al. 2019; Zhao et al. 2019b). Mitochondria-targeted antioxidants have great potential against detrimental impacts caused by ROS production. The ability of mitochondria-targeted antioxidants confer greater protection against oxidative damage, and this is primarily attributed to the ability to cross the phospholipid bilayer of mitochondria and thereby eliminating ROS (Oyewole and Birch-Machin 2015). In particular, MitoQ is one of the promising candidates, which is a mitochondria-targeted Q10 moiety that alleviates mitochondrial ROS production. In principle, a broad spectrum of antioxidants could be targeted to mitochondria through the conjugation of triphenylphosphonium (TPP) moiety (Smith and Murphy 2011). Indeed, ubiquinol (MitoQ) is the best-characterized antioxidant targeted to mitochondria through conjugation to the TPP cation (Smith and Murphy 2011). In an animal study, MitoQ decreased metabolic syndromes (hyperglycemia, hypercholesterolemia, and adiposity) by modulating oxidative DNA damage as well as macrophage infiltration into the plaques (Bond et al. 2019). The role of MitoQ in relation to atherosclerosis will be described in the ubiquinone section.

The "free radical theory" or "oxidative response to injury" has proposed that increased formation of radicals such as oxidative stress, is one of the predominant underlying modes of action that responsible for atherosclerosis (Volobueva et al. 2019). These data implied that the importance of mitochondria in atherosclerosis, which may involve ROS. Nonetheless, the elevation of ROS production is not necessarily the only link that responsible for atherosclerosis (Li et al. 2014). The previous study showed that increased mitochondrial DNA damage, which is observed in both hematopoietic and vascular cells as well as in early lesions that promotes vascular smooth muscle cells apoptosis, hyperlipidemia, atherogenesis, and release of IL-1β and TNF-α; all of these processes occur in the absence of increased ROS levels (Yu et al. 2013). mtDNA damage was also associated with plaque vulnerability (Yu et al. 2013).

5.3.4 Dysfunctional, "Uncoupled" Endothelial NO Synthase

Endothelial nitric oxide synthase (eNOS) generates NO under physiological circumstances, which represents a crucial element in the vasoprotective function of the endothelium (Suvorava et al. 2015). Under pathological conditions linked to oxidative stress, eNOS may become dysfunctional (Daiber et al. 2019). Oxidative stress leads to endothelial dysfunction, mainly due to the rapid oxidative inactivation of NO with an accumulation of superoxide (Daiber and Chlopicki 2020). In a subsequent stage, the oxidative stress renders eNOS uncoupled, in which it is no longer generates NO, but produces superoxide (Förstermann et al. 2017). In particular, phosphorylation of (6R-)5,6,7,8-tetrahydrobiopterin (BH_4), a crucial cofactor for the eNOS enzyme, is likely to be the primary cause for endothelial dysfunction and eNOS uncoupling (Förstermann and Sessa 2012). Peroxynitrite is another direct

reaction product of superoxide and NO, which is capable of oxidizing BH_4 and thus resulting in BH_4 deficiency (Forstermann and Munzel 2006; Li and Forstermann 2013). ApoE-KO mice demonstrate an eNOS uncoupling and increased oxidative phosphorylation of BH_4 in CVD (Alp et al. 2004; Wohlfart et al. 2008; Xia et al. 2010). Data from the human study showed that eNOS uncoupling was shown in patients with endothelial dysfunction due to diabetes mellitus (Heitzer et al. 2000) or hypercholesterolemia (Stroes et al. 1997).

It has been reported that eNOS-derived H_2O_2 is essential in both flow- (Drouin and Thorin 2009) and acetylcholine-induced (Drouin et al. 2007) vasodilation of cerebral arteries isolated from healthy young mice. The catalase-sensitive acetylcholine-induced dilation could be restored by eNOS cofactor BH_4 (Drouin et al. 2007). Nonetheless, it remains obscure whether the physiological role of eNOS-derived H_2O_2 is a ubiquitous pathway in some vasoactive stimuli in some specified vascular beds or the vasculature (Chen et al. 2018). Despite endothelial cells in the vasculature share several basic characteristics, they differ between species in function and structure as well as vascular beds (Yokoyama and Hirata 2007). Taken together, decreased antioxidant defense mechanisms and extramitochondrial and mitochondrial sources of ROS have occurred in the myocardium of animals and humans (Ilkun and Boudina 2013).

5.4 Cancer

Cancer is the second leading cause of death worldwide, accounting for nearly 9.6 million deaths (or one in six deaths) in 2018 (World Health Organization 2020c). Breast, colorectal, lung, cervical, and thyroid cancers are the most common types of cancer in women, while lung, prostate, colorectal, stomach, and liver cancers are the most common among men (World Health Organization 2020c). Indeed, 30–50% of cancers could be prevented (World Health Organization 2020c).

The incidence of cancers increases steeply with age. A study has found that a single cell lineage must occur before malignant tissues are formed (Quinn et al. 2021). A study reported by Peto et al. (1977) stated that cancer is not associated with aging. Nonetheless, aging has been suggested as a time-dependent process, and probably the summation of innumerable different events. In this regard, the time-dependent emergence of cancer may relate to other age-related conditions (Le et al. 2019).

ROS is a hallmark of many types of cancer. ROS and its functions with respect to cancer progression and initiation in cancer cells are prime concerns in cancer research (Tan et al. 2014). Inflammatory cells produce most of the ROS (Aminjan et al. 2019). The stimulation of the redox metabolism of the inflammatory cells creates a highly oxidative environment within an organ of aerobic organisms (Di Marzo et al. 2018). The oxygen biochemistry via the stimulation of neutrophils, macrophages, and plasma membrane NADPH oxidase, and thus release the hydroxyl radicals, H_2O_2, and superoxide anion (Nguyen et al. 2017). Furthermore, inflammation

reacts via the formation of RNS and ROS, and leads to oxidative damage in the cellular components (Mittal et al. 2014; Di Meo et al. 2016). Many proinflammatory mediators such as prostaglandins, chemokines, and cytokines turn on the angiogenesis switches primarily controlled by vascular endothelial growth factors (VEGF) (Fu et al. 2020). Cancer-related inflammation is also associated with the immune suppression that allows cancer cells to evade detection by the immune system (Grabowski et al. 2021). Inflammation is a crucial component for tumor progression (Chakraborty et al. 2020). In particular, several cancers may arise from sites of inflammation, chronic irritation, and infection (Piemonte et al. 2018; Siegfried et al. 2020; Eyvazi et al. 2020). It has been demonstrated that the tumor microenvironment, which is primarily orchestrated by inflammatory cells, is an indispensable player in the promotion of migration, survival, proliferation as well as neoplastic process (Guo and Deng 2018). Pathological angiogenesis is a hallmark of inflammatory diseases, ischemic, and cancer (Aguilar-Cazares et al. 2019; Johnson et al. 2019). Chronic inflammation is linked to angiogenesis, a process that promotes the proliferation of cancer cells. Angiogenesis is essential for the expansion of tumor mass, tumor cells, fibroblasts, platelets, and macrophages, which is a major source of angiogenic factors (Huong et al. 2019; Ireland and Mielgo 2018; Wang et al. 2019; Teleanu et al. 2020). The inflammation in the tumor microenvironment is characterized by leukocyte infiltration, ranging from composition, distribution, and size, like lymphocytes, eosinophils, neutrophils, natural killer (NK) cells, dendritic cells, mast cells, and tumor-associated macrophages (TAM) (Eiró and Vizoso 2012; Comen et al. 2018). These cells generate a wide range of cytotoxic mediators, for instance, RNS and ROS, cysteine and serine proteases, interferons (IFNs), interleukins (IL-8, IL-6, and IL-1), matrix metalloproteinase (MMP), and enzymes such as phospholipase A2 (PLA2), lipooxygenase-5 (LOX-5), and cyclooxygenase-2 (COX-2) (Tan et al. 2018a, b; Andreou et al. 2020). The AP-1 may cause basal gene expression in biological systems. ROS can stimulate AP-1 via several biological mechanisms. Activation of AP-1 promotes cell growth by inhibiting p21waf protein levels and increasing growth stimulatory gene expression such as cyclin D1 (de los Fayos Alonso et al. 2018). It has been demonstrated that NF-κB and AP-1, inducible by tumor promoters of oxidative stimuli, show activation in response to tumor promoters or differential protein levels in JB6 cells (Hsu et al. 2000). Several growth factors such as fibroblast growth factor 2 or insulin-like growth factor I produce ROS in PANC-1 and MIA PaCa-2 cells, which are human pancreatic adenocarcinoma cells that promote cell proliferation (Vaquero et al. 2004). Suppressing ROS production with NADPH oxidase (Nox4) antisense or antioxidants may promote apoptosis in PANC-1 and PaCa-2 cells (Acharya et al. 2010). This finding implies that this biological mechanism may mediate the pancreatic cancer resistance for treatment and thus may represent a potential therapeutic target. It has been demonstrated that GSH antioxidant defense system and oxidative pentose pathway (OPP) play a crucial role in the regulation of colon and gastrointestinal cancer cell proliferation and apoptosis (Acharya et al. 2010). The OPP provides NADPH for the synthesis of GSH and mediates intracellular redox status, which is responsible for the inactivation of intracellular ROS that leads to cell injury and induces apoptosis

(Wang et al. 2018). Depletion of GSH enhances the sensitivity of cells toward ROS. Therefore, suppression of OPP and/or GSH defense system may increase the sensitivity of colon and gastric cancer cells to anticancer therapy (Matthews et al. 2006). The previous study has demonstrated that the enzymatic product of thymidine phosphorylase (TP) produced ROS within cancer cells that facilitate maintaining the proliferation of colon cancer cells (Allavena et al. 2008).

The MAPK signaling pathway is stimulated by a broad spectrum of receptors involved in differentiation and proliferation including ion channels, integrins, and receptor tyrosine kinases (RTKs). This signaling pathway is stimulated in more than 50% of acute lymphocytic leukemia and acute myelogenous leukemia and is often stimulated in the prostate, breast, and other cancers (McCubrey et al. 2008; Mebratu and Tesfaigzi 2009). Under optimal circumstances, transiently increased ROS levels confer a growth advantage to tumor cells (Acharya et al. 2010). Nevertheless, treatment of cancer cells with anticancer agents trigger ROS levels and thus leading to potentiating of apoptosis. In this regard, ROS mediates the ability of stress kinases to activate cell death or cell proliferation, and this depends on the signal duration and signal intensity (Gechev et al. 2006). Proline oxidase (POX) is considered as a "housekeeping enzyme", which triggers apoptosis via extrinsic and intrinsic pathways. These signalings are involved in the regulation of the ERK/MEK pathway and mediation of nuclear factor of activated T cells (NFAT) signaling in colon cancer cells (Salaroglio et al. 2019). As a nutritional factor, POX may mediate apoptosis signals triggered by p52 or other anticancer agents and thus promote apoptosis under stress conditions (Surh 2008).

5.5 Diabetes

Insulin resistance is a condition that plays a prominent role in the development and progression of vascular complications in diabetes including type 2 diabetes (Wu et al. 2020a). Insulin resistance refers to failed or impaired cell response to insulin receptor-activated signaling in insulin-sensitive tissues, for instance, brain (Talbot et al. 2012; Bomfim et al. 2012), adipose, skeletal muscle, and liver (Newsholme et al. 2014). Reduced glucose uptake by these tissues concomitantly with the increase in hepatic glucose output leading to the increased plasma glucose levels (Kubota et al. 2011). The subsequent changes in glucose homeostasis increased the burden on pancreatic β-cells to secrete and produce more insulin to restore normal blood carbohydrate levels. Despite this compensatory process may attenuate glucose levels in prediabetes, exposure of β-cells to excess lipids and blood glucose as well as persistent insulin resistance increase β-cells dysfunction, failure, and lastly death, culminating in overt diabetes (Eizirik et al. 2020).

Insulin elicits its anabolic metabolism through association with the transmembrane insulin receptor (IR) in target tissues. The interaction of insulin stimulates related downstream signaling cascades such as protein kinase B (Akt) and phosphatidylinositol 3-kinase (PI3K), recruits and phosphorylates insulin receptor substrate

(IRS) proteins, and triggers autophosphorylation of the receptor (White et al. 1988; White 2003). Akt is a crucial regulator for GLUT-4 vesicle translocation to the plasma membrane, which is important for the intracellular uptake of free glucose in insulin-sensitive tissues (Taniguchi et al. 2006; Henriksen et al. 2011).

Insulin resistance occurs when there is interference in the insulin signaling cascade due to the structural or mutation alterations in the insulin signaling pathways. Serine-related hyperphosphorylation of insulin receptor substrate (IRS) and mutation has been associated with the development of insulin resistance. This finding could be due to the decreased interaction with PI3K (Saini 2010). An animal study has shown that homozygous interruption of IRS1 level in mice results in mild insulin resistance (Araki et al. 1994), while phosphorylation of IRS2 levels in rodents led to severe insulin resistance (Kubota et al. 2000).

Apart from that, structural alteration through hyperphosphorylation of serine at residues Ser^{632}, Ser^{612}, Ser^{307}, and Ser^{602} in IRS1 has been suggested to be a crucial mechanistic element that responsible for the elevation of insulin resistance in rodent models (Saini 2010). Increased expression of signaling proteins, for instance, JNK1 and TNF-α, could be derived from the adipose expansion and can trigger serine hyperphosphorylation of IRS1 (Hotamisligil et al. 1996; Stuart et al. 2014), especially at residue Ser^{636}. Nonetheless, it remains unknown whether the combination of residues or individual residues must be hyperphosphorylated to enhance insulin-resistant phenotype.

Insulin resistance in type 2 diabetes has been characterized by hyperinsulinemia, dyslipidemia, and hyperglycemia (American Diabetes Association 2010; Czech 2017; Ormazabal et al. 2018). Oxidative stress plays a crucial role in the development of type 2 diabetes (Molehin et al. 2020). RNS and ROS, for instance, peroxynitrite ($ONOO^-$), nitric oxide (NO), hydroxyl radical ($OH^\bullet$), H_2O_2, and superoxide anion ($O_2^{\bullet -}$) are key physiologic and metabolic processes. Impairment of mitochondrial function may decrease ATP production capacity, and thereby detrimental to the β-cell glucose-stimulated insulin secretion (GSIS) (Cerf 2013).

With respect to the progression of type 2 diabetes and insulin resistance, overnutrition leads to the production of RNS and ROS, and thereby promotes oxidative stress in organs, tissues, and cells. Ultimately, NO and oxygen based free radicals destroy protein, DNA, and cell membrane structures, as well as mediating the transcriptional activity via redox chemistry, such as NF-κB, and thus leading to cell apoptosis and chronic inflammation (Newsholme et al. 2009). Despite every single cell is potentially destroyed by oxidative stress, the decreased capacity of peroxidase-based antioxidant defense may expose the β-cells to damage and thus leading to the development of type 2 diabetes. Increased cytosolic Ca^{2+} levels, AGEs, inflammation, and mitochondrial dysfunction can enhance redox dysregulation and oxidative stress in type 2 diabetes (Rosales-Corral et al. 2015).

Decreased capacity in scavenging of free radicals is the main avenue for ROS production (Poprac et al. 2017). GSH is a free radical scavenger that is produced when there is a reduction in glutathione disulphide (GSSG) by glutathione reductase (Kurutas 2016). Besides reducing enzymes, NADPH is a crucial cofactor for glutathione reductase activity (Jain and Micinski 2013). The metabolic pathways

that are mediated the hyperglycemia or overnutrition utilized NADPH, and thereby decreasing the cell capacity to produce GSH. For example, during polyol pathway flux, glucose is reduced by aldose reductase to sorbitol. Subsequently, sorbitol is converted into fructose by sorbitol dehydrogenase (Zhou et al. 2006). Despite aldose reductase has a low affinity to glucose, their activities are increased under hyperglycemic circumstances and thereby more NADPH is consumed (Rosales-Corral et al. 2015). Reduced amounts of GSH can lead to type 2 diabetes and this condition could be attributed to the deficiency in essential amino acids that are required to synthesize GSH or the impairment of protein turnover (De Luca et al. 2001). This finding is in line with the previous study who reported that reduced GSSG expression in Alzheimer's disease patients are linked to the decline of cognitive function (McCaddon et al. 2003; Cristalli et al. 2012). Suppression of the polyol pathway has been demonstrated to normalize sorbitol in the brain in the presence of hyperglycemia (Malone et al. 2008), implied that impaired cognitive function linked to hyperglycemia may be ameliorated by preventing the breakdown of sorbitol. Collectively, inflammation plays a pivotal role in insulin resistance and type 2 diabetes. Excessive consumption of saturated fats and carbohydrates affects insulin secretion. Intracellular signaling pathways in type 2 diabetes such as active inflammatory process, oxidative stress, and aberrant redox regulation may detrimental insulin secretion and its signaling.

5.6 Osteoporosis

Osteoporosis has been characterized by microarchitectural deterioration and low bone mass of bone tissues, and thus increased fracture risk and enlarged bone fragility (Sözen et al. 2017). Fractures caused by either disease-induced skeletal fragility (Hernlund et al. 2013) or traumatic injury (Mathew and Hanson 2009) leading a significant global health burden (Odén et al. 2015). It is due to the changed in balance between activities of osteoclasts and osteoblasts (Kim et al. 2020). These specialized cells are responsible for bone resorption and formation (Kim et al. 2018). The negative balance between osteoclastic and osteoblastic activity may lead to osteoporosis (Demontiero et al. 2012). The activity of bone cells can be affected by several cellular and nutritional factors, such as free radicals, growth factors, cytokines, endocrines, nutrients, and supply of oxygen (Abdollahi et al. 2005). The differentiation of osteoclasts and osteoblasts are believed to contribute to the pathogenesis of osteoporosis (Li et al. 2020; Wu et al. 2020b).

Osteoblasts are derived from osteoprogenitors that reside in the bone marrow. Osteoblasts are present throughout the lifespan, in which the highest activity was demonstrated during embryonic skeletal growth and formation (Boskey and Coleman 2010). In an adult organism, osteoblast is stimulated when the bone matrix has been depleted or when there is a need to regenerate a defect (Rutkovskiy et al. 2016). Osteoblasts secrete several matrix protein expressions, such as alkaline phosphatase (ALP), osteocalcin (OC), and collagen type 1 alpha 1 (Col1α1) (Rutkovskiy

et al. 2016). It's worth taking notes that osteoblasts are not fast responders, in which the osteoblast takes 4 months to mature until the synthesis of bone matrix by the cells is detected (Canalis 2008). Osteoblasts are post-mitotic cells, but they are not terminally differentiated (Rutkovskiy et al. 2016). The osteoblasts that encircled with bone matrix may subsequently differentiate into osteocytes, which are interconnected stellar cells that modulate the turnover of bone matters (Florencio-Silva et al. 2015). When the mature osteoblast cells are reduced, new osteoblasts are differentiated from mesenchymal progenitor cells (Long 2012).

Despite research studies revealed that several signaling pathways and transcriptional factors may be involved in osteoblast differentiation, the molecular mechanism that diminishes the osteoblastic differentiation in osteoporosis are remained obscure (Carina et al. 2020). Oxidative stress has been described as a disruption balance of ROS and antioxidant defense levels (Birben et al. 2012). Oxidative stress is involved in the mediation of cadmium-induced osteoblast apoptosis (Branca et al. 2020). Increased production of intracellular ROS, including hydroxyl radicals, H_2O_2, and superoxide anions may subsequently result in the oxidation of proteins, DNA, and lipids (Schieber and Chandel 2014). The previous study showed that oxidative stress contributes to several age-related diseases including osteoporosis and that antioxidants can alleviate the damaging effect of oxidative stress (Zhu et al. 2018). Cadmium is a toxic heavy metal released from agricultural and industrial activities into water and soil, in which it can be accumulated in and absorbed by aquatic organisms and plants destined for the food supply (Agency for Toxic Substances and Disease Registry 2012). Indeed, diet is the key source of cadmium exposure to most individuals (Kim et al. 2019). Cadmium can trigger oxidative stress via suppression of antioxidant enzyme activity or depletion of the antioxidant GSH (Unsal et al. 2020). Bone is recognized as one of the target organs for cadmium toxicity (Chen et al. 2019). Exposure to cadmium has been recognized as a risk factor for osteoporosis (Buha et al. 2019). A study found that high levels of cumulative intake of cadmium are linked to an increased rate of fractures and osteoporosis in women (Chen et al. 2019). Data from *in vivo* study revealed that environmental cadmium disrupts bone mineralization in male rats (Buha et al. 2019). Hydrogen peroxide can induce oxidative stress in osteoblastic cells (MC3T3-E1), and thereby promotes apoptosis and suppresses osteoblast differentiation (Bai et al. 2004; Arai et al. 2007).

A study found that treatment osteoblast with H_2O_2 downregulated the expression of Runt-related transcription factor 2 (RUNX2) (Arai et al. 2007). The runt-associated transcriptional activity, for instance, RUNX2 is a crucial mediator of osteoblast phenotype that is involved in the osteoblast function and differentiation by regulating bone sialoprotein, osteopontin, and osteocalcin (Ducy et al. 1997). The primary role of RUNX2 in osteoblast differentiation was described by Komori et al. (1997). The data from the human study further revealed that patients with mutations in RUNX2 have been linked to the skeletal disorder of cleidocranial dysplasia (Komori 2002).

In addition, RUNX2 protects against osteoporosis in postmenopausal women by modulating bone mineral density (Vaughan et al. 2004). Declining of estrogen in

women after menopause leads to derangement of osteoblasts and osteoclasts, with an elevation of bone turnover rate and a phenomenon in which resorption exceeds formation (Ji and Yu 2015). This metabolic change underlies the onset of postmenopausal osteoporosis, a progressive disease characterized by low bone mass density (White et al. 2010; Faienza et al. 2013). The molecular mechanisms underlying the deficiency of estrogen in postmenopausal osteoporosis are complex and multifaceted (Cervellati et al. 2014). Several studies from animal and *in vitro* have demonstrated that estrogen removal alters the ROS and the antioxidant defense capacity (Li et al. 2017), and subsequently resulting in an accumulation of these oxidant species. Ultimately, these lead to stimulation of resorption activity and osteoclast formation (Hodge et al. 2011). In support of this, research evidence suggests that a relationship between oxidative stress and postmenopausal osteoporosis onset, implied that a potential role of reactive species in uncoupling bone turnover (Bonaccorsi et al. 2018).

ROS, for instance, H_2O_2 and superoxide have been identified as regulatory factors that are involved in osteoclastic bone resorption (Agidigbi and Kim 2019). Superoxide produced from osteoclasts leads to bone degradation (Darden et al. 1996). Key et al. (1990, 1994) exploring the impact of superoxide on osteoclasts. The data showed that the accumulation of superoxide may lead to osteoclastic bone resorption. Similarly, suppression of osteoclastic superoxide production caused a decrease in bone resorption (Ries et al. 1992; Darden et al. 1996). Nicotinamide adenine dinucleotide phosphate, a reduced form (NADPH)-oxidase is the enzyme involved in the generation of ROS by osteoclasts (Wegner and Haudenschild 2020). A study found that interferon-γ, a stimulator of NADPH oxidase activity, enhanced the defective osteoclastic function in osteoporotic in calvaria cultured from animals or microphthalmic mice (Rodriguiz et al. 1993). The enzymatic production of superoxide by XO and xanthine was increased concomitantly with bone resorption in mouse calvarial organ cultures (Fraser et al. 1996). Some studies suggest that H_2O_2 may promote bone resorption by stimulating osteoclast formation in marrow cultures (Bax et al. 1992; Baek et al. 2010). Despite the study has reported a positive association between H_2O_2 and osteoclast formation, not all data showed such a link. Garrett et al. (1990) showed that H_2O_2 level does not promote bone resorption. Furthermore, calvarial bone treated with H_2O_2 significantly increased the osteoclast numbers, implied that H_2O_2 may improve mature osteoclasts and activate the osteoclast formation (Fraser et al. 1996).

The nuclear factor-kappa B (NF-κB) transcriptional factor has been demonstrated as a crucial factor for inflammation, which can be activated by oxidative stimuli (Liu et al. 2017b). In general, the activation of NF-κB-dependent gene expression is a key culprit involved in the systemic inflammatory process (Lin et al. 2017). In the context of osteoporosis, the major role of NF-κB was demonstrated by the phenotype of NF-κB knockout mice, which is primarily due to the impairment of osteoclastic and osteoclastogenesis function (Herrington et al. 2016). The molecular mechanisms underlying the increased of oxidative stress and bone loss are not fully understood, but it is hypothesized that NF-κB (Zhang et al. 2011), augmented by TNF-α (de Araújo et al. 2019), and increased oxidative stress production (Xu

et al. 2020) contribute to these phenomena. In addition, oxidative stress also destroys fibronectin (Abdollahi et al. 2005). Fibronectin is the key component in the extracellular matrix of bone (Abdollahi et al. 2005). The glycoprotein serves as a substratum of the osteoblast that is involved in several cellular activities, for instance, differentiation, cell shape, migration, proliferation, and adhesion (Miller et al. 2020). Because the metabolic turnover of fibronectin is slightly slower than that of some cellular components; it will be influenced by several nonenzymatic modifications, such as the production of free radicals during the aging process. ROS can lead to the partial modification and degradation of fibronectin molecules (Eble and de Rezende 2014). Subsequently, the damaged fibronectin molecule may lose its function in bone nodule formation.

Cytokines are crucial regulators for bone cell activity (Zhou et al. 2019). Among all the cytokines, interleukin (IL-1) is one of the most potent stimulators for bone resorption through suppression of collagen synthesis and elevation of osteoclasts number (Weitzmann 2013). IL-6 appears to be a potent osteotropic factor that may play a crucial role in disease characterized by promoting osteoclast fusion and increasing bone resorption (Hienz et al. 2015). TNF-α improves bone resorption by enhancing the activity of mature cells and activating the development of osteoclast progenitors (Hienz et al. 2015). A study found that oxidative stress not only a powerful stimulant for proinflammatory cytokines in the pancreas (Yu and Kim 2014), inflammatory bowel disease (Tian et al. 2017), and heart (Voigt et al. 2013); in fact, it has also been reported to increase cytokine levels in bone, suggesting that oxidative stress may induce osteoporosis (Bonaccorsi et al. 2018).

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Chapter 6
Antioxidant and Age-Related Diseases

6.1 Antioxidant

Antioxidant refers to any components that at low concentration compared to an oxidizable substrate (Kurutas 2016). Antioxidants have an ability to prevent or delay the oxidation of the substrate (Santos-Sánchez et al. 2019). The previous study has demonstrated that antioxidants reduce the malignant transformation, decrease DNA mutations, and reduce oxidative stress, as well as prevent cell damage (Poljsak et al. 2013). In support of this, several epidemiological studies have shown that antioxidant was inversely associated with numerous age-related diseases including diabetes (Mancini et al. 2018), cardiovascular disease (CVD), and cancer (Aune et al. 2018). Nonetheless, at the sustained free radical circumstances, the defense systems capacity towards ROS could be overwhelmed and thereby resulting in disease occurrence (Godic et al. 2014).

The first types of antioxidant defense systems developed against oxidative damage are those that capture and block radicals that are generated and those that prevent ROS occurrence (Cheeseman and Slater 1993). In general, the repair intervention system is comprised of repairing oxidized lipids by acyltransferases, peroxidases, or phospholipases (Hitchon and El-Gabalawy 2004), removing oxidized proteins by proteolytic systems, and repairing oxidatively damaged nucleic acids by specific enzymes (Poljsak et al. 2013). It has been suggested that damage of repair systems could result in more age-related diseases and aging than moderate changes of the antioxidant defense's potential against ROS (Gems and Doonan 2009; Perez et al. 2009; Jang and Remmen 2009).

The study reported by Dröge (2002) has revealed that a shift in the balance between antioxidant and prooxidant is favorably of prooxidants under physiological circumstances, and therefore producing oxidative stress, that is requiring the intervention of endogenous antioxidant systems of the organism. Under this phenomenon, oxidative stress is increasing with age when the repair systems and endogenous

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antioxidants cannot counteract effectively. Subsequently, several interventions inhibiting or limiting these aggressive factors are directed to reduce these diseases. Nonetheless, the utilization of synthetic antioxidants in age-related diseases including cancer is still subject to controversy (Cheeseman and Slater 1993; Halliwell and Gutteridge 1999; Godic et al. 2014).

The redox homeostasis of the cells is maintained by a complex endogenous antioxidant defense system including endogenous antioxidant enzymes, for instance, low molecular weight scavengers (lipoic acid, coenzyme Q, and uric acid), proteins (albumin, ceruloplasmin, transferrin, and ferritin), non-enzymatic compounds (glutathione), and complex endogenous antioxidant enzymes (glutathione peroxidase (GPx), catalase, and SOD) (Poljsak et al. 2013). The previous study revealed that exogenous antioxidants present in vegetables and fruits could counterpart the endogenous antioxidative defense activity (Pisoschi and Pop 2015). Antioxidants such as anthocyanidins, flavonoids, phenolics (hydroxycinnamic and cinnamic acid derivatives, hydroxybenzoic and benzoic acids), carotenoids, and vitamins E and C, are regarded as the predominant exogenous antioxidants (Xu et al. 2017; Lourenço et al. 2019; Neha et al. 2019). Many studies reported by Tan et al. (2018a) have demonstrated that age-related diseases and oxidative stress can be modulated by diet-rich antioxidants. In support of this, the recent study showed that diets rich in legumes, nuts, vegetables, fruits, and whole grains are inversely related to CVD risk (Hemler and Hu 2019). Several epidemiological studies, for instance, Nurses' Health Study (NHS) (Stampfer et al. 1993), European paradox study (Bellizzi et al. 1994), Harvard Health Professionals Follow-Up Study (HPFS) (Rimm et al. 1993), and World Health Organization (WHO)/Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study (Gey and Puska 1989) have demonstrated that antioxidant was inversely related to age-related diseases. This finding could be attributed to the unique complex of bioactive compounds, which can protect against oxidative stress that can lead to inflammation (Tan et al. 2015a, b; Tan and Norhaizan 2017). In this regard, the antioxidant capacity in natural products has drawn great deals of interest among scientists in industry and academia to prevent age-related diseases.

6.2 Natural Antioxidants

Natural antioxidants, for instance, carotenoids, phenolic compounds, and vitamins are predominantly present in vegetables and fruits (Septembre-Malaterre et al. 2018). Natural antioxidants present in low levels within cells, in which they can effectively decrease free radicals to protect against age-related diseases (Tan et al. 2018a; Tan and Norhaizan 2019a). Because food tissues are (or were) living, and thus they are under constant oxidative stress from prooxidants, ROS, and free radicals produced both endogenously (transition metals and H_2O_2) and exogenously (light and heat). In this regard, most of the tissues have developed antioxidant systems to control secondary breakdown products, oxidation intermediates, lipid

oxidation catalysts, and free radicals (Nimse and Pal 2015). These antioxidant components including tocopherols, carotenoids, phenolic acids, and flavonoids can act as reductants, scavenge free radicals, and suppress Fe^{3+}/ascorbic acid-induced oxidation (Lü et al. 2010).

Natural antioxidants possess the ability to suppress oxidation of breakdown products, lipid peroxidation, and oxidative stress (Yadav et al. 2016). It can function either synergistically or individually to remove free radicals produced during oxidative metabolism to mediate the balance between antioxidants and oxidants (AlBasher et al. 2020). Nevertheless, when there is an excessive production of reactive nitrogen and oxygen species (RNS and ROS, collectively known as RONS), it may breakdown in the delicate physiological balance and thereby results in oxidative stress (Sies and Jones 2020). Subsequently, this oxidative stress may contribute to several chronic diseases such as diabetes, cancer, and CVD (Liguori et al. 2018; Tan et al. 2018b; Hayes et al. 2020).

Plant polyphenols are the components holding one or more phenolic rings derived from the secondary metabolism of plants (Lin et al. 2016). Polyphenols are present in many drinks and foods of plant origin including chocolate, wine, beer, tea, coffee, fruits, and vegetables (Fukushima et al. 2014). Phenolic compounds are not only being present in many foods naturally (Table 6.1), they can also be extracted from their respective source and thereby added into the foods to provide antioxidant and coloring effects (Soto-Vaca et al. 2012; Caporaso et al. 2018). Previous studies have illustrated the effectiveness of phenolic compounds in the prevention of lipid oxidation (Socrier et al. 2019). Plant extracts high in polyphenolic components were shown to be a safe additive because they can easily reserve from natural sources and hinder lipid oxidation effectively (Difonzo et al. 2018). In recent decades, plant polyphenols extracts have been increasingly utilized in the food industry to retard lipid oxidation and prolong their shelf-life (Zhang et al. 2021). Nonetheless, the plant extracts derived from different plants may exhibit considerable variations in their antioxidant activity (Hung 2016). This could be due to several factors, for instance, soil type, light, temperature, climate, growing season, growing environment, genotype, or variety, which may alter both phenolic or antioxidant components and antioxidant activity in the plants (Shamloo et al. 2017; Kabtni et al. 2020). Several studies have reported that the quantity of bioactive compounds and their activities could be affected by species variation, environmental, and genetic (Alfaro et al. 2013; Pohl et al. 2019; Ruiz-López et al. 2019; Zalazar et al. 2019; Przybylska-Balcerek et al. 2020). A study reported by Alfaro et al. (2013) has revealed that genotype and growing season had a significant effect on dry matter, antioxidant activity, and polyphenol components of murtilla fruits from three genotypes. Herbs and spices are usually added to food for their medicinal mixtures and improved their flavor (El-Sayed and Youssef 2019). Herbs and spices possess high amounts of phenolic compounds that have strong H-donating activity (Ulewicz-Magulska and Wesolowski 2019). Several of these herbs and spices contain high values of oxygen radical absorbance capacity (ORAC) (Table 6.2). The previous study demonstrated that plant-derived components (rosmaridiphenol, rosmariquinone, rosmanol, and carnosol) show a better antioxidant activity compared

Table 6.1 Phenolic antioxidants from selected natural sources

Category	Natural sources	Phenolic compounds	References
Fruits	Apple peel	Chlorogenic acid, epicatechin, phloridzin, catechin, hyperoside, and quercitrin	Mihailović et al. (2018)
	Apple pulp	Chlorogenic acid, epicatechin, phloridzin	Mihailović et al. (2018)
	Strawberry	Anthocyanidins, flavanols, flavonols, phenolic acids, hydroxybenzoic acids, hydroxycinnamic acids	Miller et al. (2019)
	Citrus	Luteolin, kaempferol, quercetin, apigenin, diosmetin, chrysoeriol, isorhamnetin, vicenin 2, lucenin 2, vitexin, isovitexin, isoquercitrin, diosmin, rutin, scoparin, neodiosmin, eriodyctiol, hesperetin, naringenin, hesperidin, naringin	Brito et al. (2014)
	Mango	Chlorogenic acid, gallic acid, vanillic acid, protocatechuic acid	Palafox-Carlos et al. (2012)
	Black currants	Anthocyanins, hydroxycinnamic acid, flavonols, delphinidin-3-*O*-glucoside, delphinidin-3-*O*-rutinoside, myricetin-3-*O*-glucoside	Zheng et al. (2012)
	Sweet cherry	Anthocyanins, flavonols, chlorogenic acids, hydroxycinnamic acid, flavan-3-ols	Martini et al. (2017)
	Persimmon	Gallic acid, (+)-catechin, quercetin, luteolin, kaempferol	Fu et al. (2016)
	Guava	Gallic acid, (+)-catechin, (−)-epicatechin, quercetin, luteolin, kaempferol	Fu et al. (2016)
	Sweetsop	Gallic acid, (+)-catechin, chlorogenic acid, ferulic acid, quercetin, luteolin	Fu et al. (2016)
	Pineapple	Epicatechin and felinic acid	Jianwen and Chenghai (2006)
	Plum	Cyanidin 3-rutinoside, flavonols (rutin and quercetin 3-glucoside)	Slimestad et al. (2009)
	Blueberry	Gallic acid, p-coumaric acid, ferulic acid, ellagic acid, catechin, myricetin, quercetin, kaempferol	Sellappan et al. (2002)
	Apricot	Gallic acid, procatechin (acid), 4-aminobenzoic acid, chlorogenic acid, catechin, caffeic acid, epicatechin, vanillin, p-coumaric acid, rutin, ferulic acid, salicylic acid, resveratrol, quercetin	Sochor et al. (2010)
	Kiwi	Protocatechuic acid, chlorogenic acid, caffeic acid, rutin, p-hydroxybenzoic acid, quercetin	Wang et al. (2018d)

(continued)

Table 6.1 (continued)

Category	Natural sources	Phenolic compounds	References
Vegetables	Broccoli	Flavonoids and hydroxycinnamoyl acid derivatives	Vallejo et al. (2004)
	Leafy vegetables	Salicylic acid, vanillic acid, gallic acid, caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, m-coumaric acid, isoquercetin, rutin	Khanam et al. (2012)
	Carrot	3′-caffeoylquinic acid, 5′-caffeoylquinic acid, caffeic acid, cis-5′-caffeoylquinic acid, 4′p-coumaroylquinic acid, hydroxycinnamic derivative, 3′4′-dicafferoylquinic acid, 3′5′-dicafferoylquinic acid	Zhang and Hamauzu (2004)
	Chinese cabbage	Flavonols (quercetin and kaempferol), phenolic acids (sinapic, ferulic, p-coumaric, and caffeic acids), cyanidin	Lee et al. (2018a)
	Curly kale	Quercetin-3-sinapoyl-diglucoside-7-diglucoside, kaempferol-3-sinapoyl-diglucoside-7-diglucoside, quercetin, kaempferol, p-coumaric, ferulic, sinapic, and caffeic acid, hydroxycinnamic acids, flavonoid, quercetin-3-disinapoyl-triglucoside-7-diglucoside	Olsen et al. (2009)
	Iceberg lettuce	Caffeic acid, chlorogenic acid, phaseolic acid, chicoric acid, isochlorogenic acid, luteolin-7-O-glucuronide, quercetin-3-O-glucuronide, quercetin-3-O-galactoside, quercetin-3-O-glucoside, quercetin-3-O-(6″-malonyl)-glucoside, syringin	Mai and Glomb (2013)
	Potato	Chlorogenic, caffeic, coumaric, protocatechuic, vanillic, ferulic, syringic, *p*-coumaric, sinapic, gallic acids	Akyol et al. (2016)
	Artichoke	Apigenin 7-O-glucoside, chlorogenic acid	Alarcón-Flores et al. (2014)
	Spinach	Ferulic acid	Alarcón-Flores et al. (2014)
	Tomato	4-caffeoylquinic acid, 5-caffeoylquinic acid, dicaffeoylquinic acids I and II, tricaffeoylquinic acid, quercetin trisaccharide, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-rutinoside, naringenin, naringenin chalcone	Ribas-Agustí et al. (2012)

(continued)

Table 6.1 (continued)

Category	Natural sources	Phenolic compounds	References
Cereals and legumes	Soybean	Gallic acid, pyrogallol, homogentisic acid, chlorogenic acid, catechin, vanillic acid, caffeic acid, syringic acid, ρ-coumaric acid, rutin, ferulic acid, naringin, hesperidin, *o*-coumaric acid, myricetin, quercetin, *trans*-cinnamic acid, naringenin, kaempferol, hesperetin, biochanin A	Kim et al. (2006)
	Oat	Avenanthramides A, avenanthramides C, caffeic acid, quercetin-3,4′-O-di-beta-glucopyranoside derivative, 6-hydroxykaempferol 3,5,7,4′-tetramethyl ether 6-rhamnoside	Rao et al. (2019)
	Wheat grain	p-hydroxybenzoic acid, vanillic acid, syringic acid, p-coumaric acid, ferulic acid, four ferulic acid derivatives, apigenin	Hernández et al. (2011)
Herbs and spices	Basil	Rosmarinic, chicoric, caffeic, caftaric acid	Kwee and Niemeyer (2011)
	Garlic	Caffeic acid, quercetin	Alarcón-Flores et al. (2014)
	Ginger	Pyrogallol, p-hydroxybenzoic acid, ferulic acid, vanillin, p-coumaric acid, gallic acid, caffeic acid	Tohma et al. (2017)
	Mint	Rosmarinic acid, neoponcirin, narirutin, chlorogenic acid, biochanin A, caffeic acid, apigenin, hesperetin, naringenin	Tang et al. (2016)
	Onion	Isorhamnetin, kaempferol, luteolin, quercetin	Leighton et al. (1992); Miean and Mohamed (2001); Lanzotti (2006)
	White pepper	Decaffeoylacteoside, forsythoside D, vanillin, norbergenin, N-trans coumaroyltaramine, protocatechuic aldehyde, tribulusamide A, moupinamide, 1,5-bis(4-hydroxy-3 methoxyphenyl)-1,4 pentadien-3-one, moracin H, cishinokiresinol, moracin O, kukoamine A, moupinamide, 6-gingerol, moracin C, 2-octylphenol, octahydrocurcumin, 2,6-di-tert-butyl-4-hydroxy toluene, 6-gingerol	Olalere et al. (2019)
	Black pepper	Forsythoside D, decaffeoylacteoside, vanillin, norbergenin, N-trans Coumaroyltaramine, moupinamide, tribulusamide A, cishinokiresinol, moupinamide, 1,5-bis(4-hydroxy-3 methoxyphenyl)-1,4 pentadiene-3-one, N-dihydro- caffeoyltyramine, moracin C, 2-octylphenol, octahydrocurcumin, kukoamine A, 2,6-di-tert-butyl-4-hydroxytoluene, 6-gingerol	Olalere et al. (2019)

to butylated hydroxyanisole (BHA) (Richheimer et al. 1996; Carvalho et al. 2005). In a study by Cheng et al. (2019) focusing on various flaxseed phenolic extracts on the oxidative and physical stability of flaxseed oil-in-water nanoemulsions, flaxseed lignan extract and secoisolariciresinol were shown to inhibit lipid oxidation in nanoemulsion, suggesting that both flaxseed lignan extract and secoisolariciresinol are good plant-based antioxidants for improving the stability of flaxseed oil nanoemulsions. A further study reported by de Florio Almeida et al. (2017) showed that the antioxidant effect of lyophilized bee pollen extract was effective in retarding lipid oxidation in pork sausage.

In addition, the plant extracts have also been demonstrated their anticancer ability. For example, sapodilla leaf extracts have been demonstrated their abilities to inhibit different cancer cells including human hepatocellular carcinoma (HepG2) (Tan et al. 2018c), human cervical cancer (HeLa) (Tan et al. 2018d), and human colorectal cancer (HT-29) cells (Tan and Norhaizan 2019b). This favorable effect is more likely due to the presence of phenolic compounds including gallic acid, p-coumaric acid, ferulic acid, caffeic acid, and vanillic acid (Tan et al. 2018c, d; Tan and Norhaizan 2019b). The anticancer ability of sapodilla leaf extracts is modulated via a few mechanisms including apoptosis, cell cycle arrest, and caspase-dependent pathway (Tan et al. 2018c, d; Tan and Norhaizan 2019b).

6.3 Mechanism of Action of Antioxidants

Antioxidants can act at successive stages of the oxidative radical process, namely initiation, propagation, and chain termination (Kurutas 2016). The detailed explanations of the steps, which are part of the radical sequences is particularly centered on the propagation and initiation, implied that lipid oxidation in cell membranes can be activated by exogenous chemical and physical factors, including endogenous enzyme systems (cytochrome P450, uncoupled nitric oxide synthase, XO, and NADPH oxidase), ionization radiation, UV-light, smoking, air pollution, as well as the ETC in mitochondria (Yin et al. 2011).

The previous study has revealed that propagation step peroxidation initiates when oxygen reacts with carbon-centered radicals, occurring near or at the diffusion-controlled rate. The propagation, occurring at most oxidations following a radical mechanism, and usually at a slow rate, is represented by the transfer of a hydrogen atom to the chain carrying peroxyl radical (Pisoschi and Pop 2015). Peroxyl free radicals can react to carbon-carbon double bonds. In particular, the conjugated dienes may subject to peroxyl addition. Furthermore, the intramolecular radical substitution on peroxide and radical cyclization reactions may occur, resulting in cyclic peroxides, while the polyunsaturated lipids involve in the peroxidation process (Yin et al. 2011).

In addition, antioxidants can react by quenching singlet oxygen ($^1O_2$) or breaking the chain of a radical sequence, scavenging chain initiating radicals such as peroxyl $ROO^{\bullet}$, alkoxyl $RO^{\bullet}$, or hydroxyl $OH^{\bullet}$, trapping aggressive ROS including H_2O_2 or

Table 6.2 ORAC amounts of selected herbs and spices

Herbs and spices	Total ORAC (μm TE/100 g)
Basil (fresh)	4805
Oregano (fresh)	13,970
Sage (fresh)	32,004
Thyme (fresh)	27,426
Basil (dried)	61,063
Thyme (dried)	157,380
Cinnamon (ground)	131,420
Clove (ground)	290,283
Ginger (ground)	39,041
Nutmeg (ground)	69,640
Turmeric (ground)	127,068
Sage (ground)	119,929
Oregano (dried)	175,295
Rosemary (dried)	165,280
Black pepper	34,053

Source: USDA (2010)
ORAC oxygen radical absorbance capacity, *TE* trolox equivalent

superoxide anion radical, removing prooxidative metal ions, and depleting molecular oxygen (Nimse and Pal 2015).

The primary antioxidants are the chain-breaking antioxidants that can scavenge radical species; while secondary antioxidants are UV radiation absorbers or oxidative enzyme inhibitors, metal chelators, peroxide decomposers, and singlet oxygen quenchers (Simitzis 2018). In general, secondary antioxidants may show synergistic effects in combination with primary antioxidants via different mechanisms. The mechanisms include (1) quenching molecular oxygen; (2) chelating pro-oxidative transition metal cations; (3) regenerating primary antioxidants through hydrogen donation; and (4) stabilizing primary antioxidants by creating an acidic environment (Tan et al. 2018a).

Antioxidant controls the autoxidation by suppressing the generation of free radicals or by disrupting the propagation of free radicals through several mechanisms (Gholamian-Dehkordi et al. 2017). This compound facilitates in breaking the autoxidative chain reaction, preventing the formation of peroxides, scavenging the species that initiate the peroxidation, and quenching $\bullet O_2^-$ (Gaschler and Stockwell 2017). Among the mechanism of action, interruption of the free radical chain reaction is the most effective antioxidant (Nimse and Pal 2015). It contains aromatic or phenolic rings that allow antioxidants to donate H• to the free radicals formed during oxidation. Subsequently, the radical intermediate is stabilized by the resonance delocalization of the electron within the aromatic ring (Wojtunik-Kulesza et al. 2016). Notably, both natural botanicals (phenolics (flavonoids)) and synthetic antioxidants (propyl gallate, butylated hydroxytoluene (BHT), and BHA) function in

this manner (Brewer 2011). The botanicals extracts exert antioxidant activity and usually quench free radical oxygen with phenolic compounds (Xu et al. 2017).

Antioxidants play a prominent role in the termination of oxidative chain reactions by removing the free radical intermediates (Gholamian-Dehkordi et al. 2017). Chain-breaking antioxidant varies in their antioxidative effectiveness based on the physical location within the food (aqueous phase, emulsion interfaces, and proximity to membrane phospholipids) and chemical characteristics (Jacobsen et al. 2019). The chemical potential of the solubility in oil and an antioxidant affect its accessibility to peroxy radicals particularly in the amphiphilic character, emulsion, micellar system, and in the membrane, which is required for the effectiveness in the system (Watanabe et al. 2010).

The effectiveness of antioxidants is linked to the antioxidant solubility, the ease with which the antioxidant is destroyed or lost (heat susceptibility and volatility), oxidation-reduction potential, rate constant, and activation energy (Brewer 2011). Furthermore, chain and inhibitor propagation reactions are both exothermic (Lazarovici et al. 2004). When the R:H and A:H bond dissociation energy is increased, the antioxidant efficiency decreases, and the activation increases (Brewer 2011). However, when the bond energy decrease, the antioxidant efficiency increases (Brewer 2011).

The presence of bivalent transition metal ions, particularly Fe^{2+}, can catalyze oxidative processes and thereby resulted in the formation of hydroxyl radicals, as well as can decompose hydroperoxides through Fenton reactions. Through these reactions, chelating metals can effectively decrease oxidation (Goddard et al. 2012). For example, food such as red meat containing significant levels of these transition metals and thus is susceptible to metal-catalyzed reactions (Domínguez et al. 2019).

A study reported by Fang et al. (2018) revealed that cellular redox status is critical for mitochondrial function and ROS-mediated signaling. The reduction of intracellular GSH levels markedly induces mitochondrial membrane depolarization and triggers mitochondrial ROS production (Lohan et al. 2018). Activation of the Nrf2/antioxidant response element (ARE) pathway is crucial for the mediation of the intracellular GSH in response to stress and antioxidant defense enzyme (Liu et al. 2018). *N*-acetylcysteine restores ARE-related gene expression and reverses GSH depletion to basal levels (Limón-Pacheco et al. 2007). Indeed, appropriate intracellular amounts of ROS are crucial for the physiological redox signaling by regulating and activating endogenous defenses to protect cells from oxidative, electrophilic, and nitrosative stress (Moldogazieva et al. 2018). Administration of exogenous antioxidants reduces exercise-triggered improvements in insulin sensitivity and antioxidant transcriptional activity (Ji et al. 2006), implied the crucial of ROS-triggered endogenous antioxidant enzymes in restoring physiological redox balance. It has been suggested that Nrf2 can protect oxidative stress in aging (de Oliveira et al. 2018). The development of age-related diseases has been associated with the reduction of Nrf2 activity (Cuadrado et al. 2018).

6.4 Reversal of Age-Related Changes by Antioxidants

Coronary heart disease has become one of the leading causes of disability and death worldwide. The predominant underlying cause of the disease is atherosclerosis, which occurs in the large or medium-size arteries, and thereby resulted in necrosis or cell death and loss of vascular functions (Geovanini and Libby 2018). Inflammation and oxidative stress are prominent factors responsible for injury and endothelial dysfunction (Incalza et al. 2018). The vascular cells are vital sites for oxidative stress and ROS production (Sena et al. 2018). Many naturally occurring antioxidants are being evaluated for their potential to enhance vascular integrity and regenerate vascular cells by restoring the cellular functions of diseased vessels (Shafi et al. 2019). Indeed, natural antioxidants regulate oxidative stress in different types of vascular cells including progenitor, stem, and endothelial cells (Kumar et al. 2009; Shaban et al. 2017; Pereira et al. 2017; Abdel-Daim et al. 2018; Su et al. 2018). The data from *in vitro* and animal studies revealed that antioxidants mediate oxidative stress via a few mechanisms including modulation of proinflammatory vascular adhesion molecules (E-selectin, ICAM-1, and VCAM-1), NF-κB, and MAPK signaling pathways (Li et al. 2014a). Nonetheless, the studies examined natural antioxidants, for example, polyphenols and vitamins (E, D, and C), and the regeneration potential of vascular cells are remained obscure (Tan et al. 2018a). Natural antioxidants are being investigated for their potential to improve the reendothelialization process by enhancing rapid endothelial cell growth and stimulating adhesion molecules (Shafi et al. 2019) (Fig. 6.1). The previous study has revealed the new approach involving several vitamins on direct reprogramming of progenitor or stem cells into endothelial cells (Cimmino et al. 2018). A study by Rodrigo et al. (2007) and Wong et al. (2014) further supported that vitamins E, D, and C improved the reendothelialization process and thereby leading to vascular repair following vascular injury. This process is more likely due to the cell proliferation and growth (Ulrich-Merzenich et al. 2007), which enhanced the vascular endothelial cells functions (Rodrigo et al. 2007; Mazidi et al. 2017; Jamali et al. 2018). Table 6.3 summarizes the effect of natural antioxidants on the vasculature. Although antioxidant pharmacological properties were demonstrated in various studies, there is still a lack of clinical evidence on the specific molecular targets and benefits of dietary antioxidants on health (Dalle-Donne et al. 2006). It has been suggested that diets containing natural antioxidants may provide vascular regenerating properties (Huang 2018). Collectively, dietary antioxidants may play an essential role in preventing vascular disorders.

In addition to the effect observed in vascular disease, dietary intake of plant-based foods, for example, whole grains, vegetables, and fruits are related to the positive health effects (Kim et al. 2019). Numerous epidemiological and case-control studies have revealed that consumption of phytochemical-rich foods was negatively associated with the incidence of the prostate (Hoang et al. 2018), pancreas (Morrison et al. 2021), lung (Cohen et al. 2019), colon (Lee et al. 2018b), and breast (Sharif et al. 2021) cancers. The phytochemical-rich diets prevent cancers via

a few mechanisms including modulation of carcinogen detoxification/activation, cell differentiation, DNA repair, cell cycle, and apoptosis by tumor-suppressor genes and xenobiotic-metabolizing enzymes (Tan et al. 2018b) (Fig. 6.1). In this regard, alleviating the oxidative stress-related tumorigenesis is one of a mode of action to explain this anticancer potential (Chikara et al. 2018). Indeed, oxidative stress contributes to all stages of tumorigenesis either through an indirect mechanism by mediating the cell signaling transduction or directly caused in the DNA damage (Tan et al. 2018b). Hence, decreasing oxidative stress may play a pivotal role in chemoprevention. Diet rich in phytochemicals has emerged as a promising chemopreventive potential towards different types of cancers (Tan et al. 2018b) due to its less or without significant undesirable effects on healthy tissues (Tan et al. 2018a). Some phytochemicals are not only exerting anticancer potential, but they are also demonstrated their anti-invasive, anti-migratory, and anti-proliferative properties on cancer cells, suggesting that a phytochemical-rich diet may act as adjuvant therapy in cancer (Tan and Norhaizan 2019c).

Dietary antioxidant not only reduces CVD and cancer but it also exerts a beneficial impact on glucose homeostasis and insulin sensitivity (Straub et al. 2019). The Rotterdam Study, a population-based cohort, has demonstrated an inverse relationship between total dietary antioxidant capacity and type 2 diabetes (van der Schaft et al. 2019). The study further revealed that high total dietary antioxidant capacity is negatively linked to the risk of prediabetes in men (van der Schaft et al. 2019). Notably, a study by van der Schaft et al. (2019) found a significant association between dietary antioxidant capacity and homeostasis model assessment of insulin resistance (HOMA-IR) or type 2 diabetes in both prediabetes and normoglycemia individuals. Chronic hyperglycemia and prolonged hyperinsulinemia, along with increased RNS and ROS levels, may result in the impairment of pancreatic β-cell

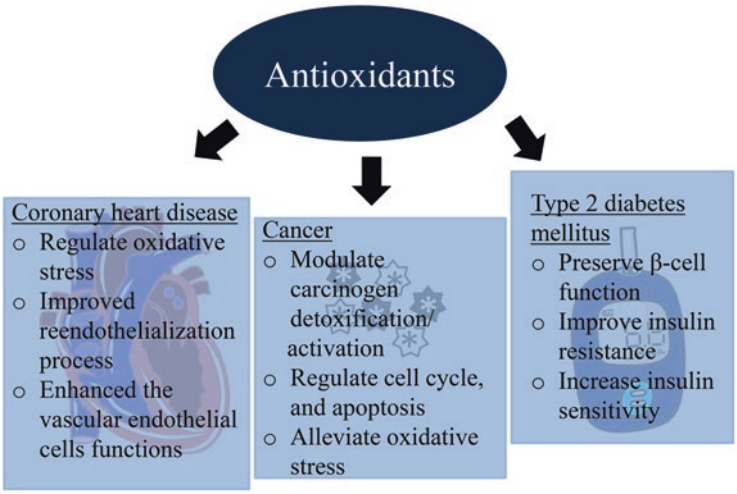

Fig. 6.1 Effect of antioxidants on coronary heart disease, cancer, and type 2 diabetes mellitus

Table 6.3 Effect of natural antioxidants on the vasculature

Antioxidants	Food rich in antioxidants	Findings	References
Flavonoids	Plants, berries, honey	Downregulate iNOS expression	Di Tomo et al. (2012); Zeng et al. (2017); Abdel-Daim et al. (2018); Mozos et al. (2018)
Trace elements	Dietary source from animal	Scavenge ROS, neovascularization	Shen et al. (2016); Zeng et al. (2017)
Polyphenols	Peaches, red wine, green tea, cocoa	↓ Blood cholesterol	Basu and Lucas (2007); Zhen et al. (2012); Cong et al. (2018)
		Reendothelialization	
		↓ Blood pressure	
		Suppresses ox-LDL	
		Regulates TLR4 pathway	
		↑ Antioxidant enzymes	
Lycopene, β-carotene, carotenoids	Yellow, green, red fruits and vegetables	↓ ox-LDL	Oak et al. (2003); Hibino et al. (2012); Boydens et al. (2015); Wang et al. (2018a)
		↓ Blood cholesterol	
		Preserve endothelial function	
		↓ iNOS	
		↑ NO	
		↓ TNF-α	
		↑ Antioxidant enzymes	
		Scavenge ROS	
Vitamin E (α-tocopherol)	Broccoli, spinach, nuts, vegetable oils	Preserve endothelial function	Martin-Nizard et al. (1998); Azzi (2007); Rodrigo et al. (2007); Lee et al. (2018a)
		↓ Blood cholesterol	
		Suppress ox-LDL	
		↑ Antioxidant enzymes	
Vitamin D	Beef liver, cheese, egg yolk, fish	Reendothelialization	Wong et al. (2014); Mazidi et al. (2017)
		Suppress NADPH oxidase	
		↑ Antioxidant enzymes	
Vitamin C	Kiwi, berries, pineapple, papaya, mango, citrus fruits	Preserve endothelial function	Ulrich-Merzenich et al. (2002, 2007, 2009); Heller et al. (2004); Rodrigo et al. (2007); Honarbakhsh and Schachter (2009); Cimmino et al. (2018)
		↓ NADPH oxidase	
		Scavenge ROS	
		↑ SOD	
		Reendothelialization	
		↓ Blood pressure	
		Suppress ox-LDL	
		Preserve endothelial function	

iNOS inducible nitric oxide synthase, *NADPH* nicotinamide adenine dinucleotide phosphate, *NO* nitric oxide, *ox-LDL* oxidized low-density lipoprotein, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *TLR4* toll-like receptor 4, *TNF-α* tumor necrosis factor-α

and subsequently contribute to the pathogenesis of type 2 diabetes (Prentki and Nolan 2006). Dietary antioxidants have been suggested to decrease the risk of type 2 diabetes by preserving the β-cell function (Prentki and Nolan 2006) (Fig. 6.1). Such finding indicates that a diet high in antioxidant capacity possesses protective effects against type 2 diabetes (Tan et al. 2018a). Despite the mechanism underlying dietary antioxidants' protective effect and type 2 diabetes requires further elucidation, most of the experimental studies hypothesized that the protective role is linked to both β-cell dysfunction and insulin resistance (van der Schaft et al. 2019). Individuals with type 2 diabetes have relatively high oxidative stress markers and reduced total antioxidant status compared to healthy individuals (Rani and Mythili 2014). Similarly, several findings have corroborated these data and found that high intakes of tea, vegetables, and fruits, which are known to be rich in antioxidant components, are inversely linked to type 2 diabetes (Maritim et al. 2003; Li et al. 2014b; Yang et al. 2014; Mancini et al. 2018). The preventive role of fruits and vegetables and tea toward type 2 diabetes is more likely due to the synergistic effect of the antioxidant components (Mancini et al. 2018). Compared to those who never consume alcohol, individuals who consume high alcoholic beverages are positively linked to diabetes (Carlsson et al. 2005). Whereas consumption of moderate alcohol is linked to a reduced risk of diabetes compared to none consumption individuals (Carlsson et al. 2005). Intriguingly, wine was found to be linked to the decreased risk of diabetes; while none of the associations was reported on spirits or beer and diabetes (Zenebe et al. 2001; Arranz et al. 2012). The favorable effect of wine could be attributed to the polyphenols and phenolic acids, which exert antioxidant activity that prevail over the deleterious effect of the alcohol itself (Howard et al. 2004; Hodge et al. 2006).

6.5 Natural Products as a Protective Agent against Age-Related Diseases

Substantial evidence has shown that oxidative stress and obesity-associated age-related diseases can be modulated by antioxidant-rich in natural products (Tan et al. 2018b). A unique complex of bioactive compounds can protect against oxidative stress (Tan et al. 2015a, b; Tan and Norhaizan 2019a). In this regard, the development and progression of these diseases could be prevented by changing dietary habits (Tan et al. 2018b).

6.5.1 *Fruits and Vegetables*

Fruits and vegetables contain an abundance of dietary fibers, vitamins, and minerals. High consumption of fruits and vegetables is inversely related to the incidence and mortality of obesity-associated diseases, for instance, cancer, type 2 diabetes, and CVD (Saad et al. 2017). This favorable effect has been accredited to antioxidant vitamins such as vitamin C, vitamin E, and β-carotene (Leenders et al. 2014). In general, hydrophilic antioxidants contributed to nearly 85% of total antioxidants in fruits and vegetables (Jędrejek et al. 2017). Vitamins C and E and β-carotene are crucial for the proper regulation of physiological function (Hecht et al. 2016). Vitamin E has been demonstrated to modulate oxidative-antioxidant balance, yet vitamin C can improve antioxidant protection (Williamson 2013). Bright-colored fruits and vegetables are rich in β-carotene (Rodriguez-Casado 2016). A previous study has found that β-carotene exerts ability in reducing low-density lipoprotein (LDL)-cholesterol oxidation and maintaining the immune system via the regulation of antioxidant enzymes (Rodriguez-Casado 2016). Furthermore, other dietary compounds, for instance, flavonoids have preventive effects against oxidative stress. Flavonoids possess several biological activities including antimicrobial action, antioxidant activity, anti-inflammatory activity, and antitumor effects (Priviero et al. 2017).

Anthocyanins are one of the flavonoids abundantly found in fruits and vegetables (Azevedo da Silva et al. 2014; Faria et al. 2014; de Oliveira et al. 2015; Zanotti et al. 2015). They are one of the most widespread natural pigments in the plant kingdom (Li et al. 2017a). It has been demonstrated that anthocyanins in blackcurrant, blackberry, and blueberry (0–20 μg/mL for 12 h) are potent inflammatory mediators in the alleviation of lipopolysaccharides (LPS)-induced (100 ng/mL for 3 h) NF-κB translocation to the nucleus and thus mediates inflammatory responses in RAW 264.7 macrophages (Lee et al. 2014). In this regard, this finding showed that blackcurrant, blackberry, and blueberry exert their anti-inflammatory effects in macrophages, possibly by inhibiting nuclear translocation of NF-κB independent of the Nrf2. Data from *in vivo* study using 24 adult male Wistar rats further revealed that anthocyanins-rich extract from Kamchatka honeysuckle berry (2 g/kg for 4 weeks) can alleviate the disturbances in glucose and lipid metabolism (Fig. 6.2), which are the fundamental risk factors for CVD and diabetes (Jurgoński et al. 2013) (Table 6.4). Additionally, many studies demonstrated that an anthocyanin-rich diet is related to weight loss. Anthocyanins (cyanidin 3-glucoside) (2 g/kg for 12 weeks) promote the secretion of adipocytokine (leptin and adiponectin) and uncoupling protein 2 (UCP2), stimulate adipocyte fatty acid-binding protein (aP2), upregulate lipoprotein lipase (LPL), and promote peroxisome proliferator-activated receptor gamma (PPAR-γ) expression in isolated rat adipocytes (Tsuda et al. 2004) (Table 6.4). In a human study, intakes of fruits and vegetables (≥500 g/day for 16 weeks) significantly decreased the sagittal abdominal diameter, body weight, and waist circumference (Fig. 6.2) in obese and overweight individuals aged 35–65 years (BMI >27 kg/m^2) (Järvi et al. 2016). Table 6.5 shows the effects of fruits and vegetables on human health.

Low intake of fruits and vegetables is a major risk factor for CVD (Seferidi et al. 2019). A study reported by Aune et al. (2017) revealed that nearly 1.3 million CVD deaths could have been prevented in 2013 worldwide when the intakes of fruits and vegetables were at 800 g/day (10 servings/day). The European Prospective Investigation into Cancer and Nutrition-Netherlands study involving 34,560 participants (26% men and 74% women) aged 20–69 years suggested that consumption of pure fruit juice up to 7 glasses/week but not ≥8 glasses were significantly reduced the risk of coronary heart disease (CHD) and CVD. The data further revealed the highest three quintiles of fruit consumption were significantly related to lower CVD incidence (Scheffers et al. 2019). Wood et al. (2017) further showed that encapsulated fruit and vegetable juice concentrate (6 capsules for 8 weeks/day) could reduce the systolic blood pressure, plasma TNF-α, LDL-cholesterol, and TC in overweight and obese adults aged ≥40 years (BMI ≥28 kg/m^2). The favorable effect could be attributed to the alteration of gene expression through several signaling pathways, for instance, NF-κB related genes and adenosine monophosphate-activated protein kinase (AMPK) (Wood et al. 2017). Collectively, fruits and vegetables protect against CVD by reducing oxidative stress, ameliorating ischemia/reperfusion injury, alleviating inflammation, suppressing thrombosis, regulating blood pressure, protecting vascular endothelial function, and modulating lipid metabolism (Buil-Cosiales et al. 2016; Zhao et al. 2017).

Emerging evidence has suggested that fruits and vegetables are related to a lower incidence of type 2 diabetes. Data from systematic review and meta-analysis of

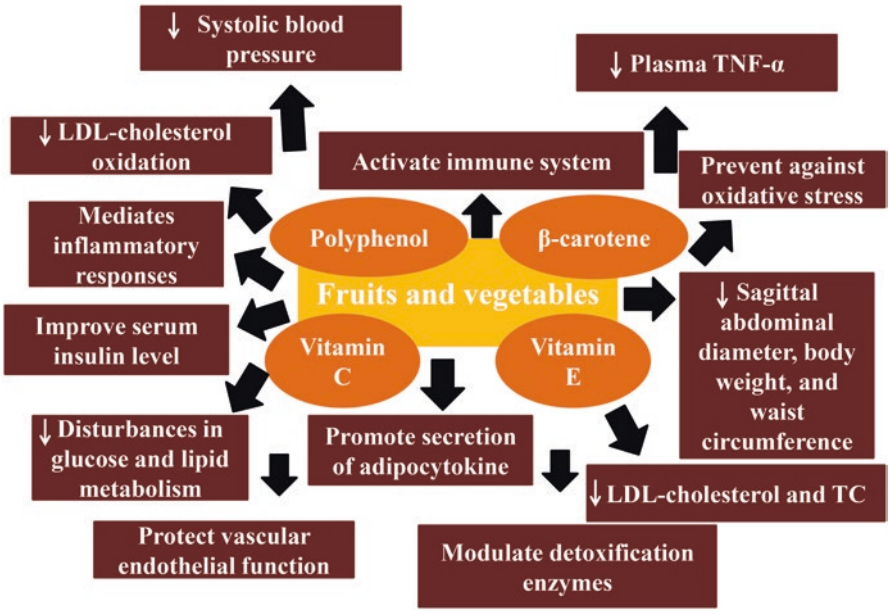

Fig. 6.2 Biological mechanism of fruits and vegetables in relation to several diseases. *LDL* low-density lipoprotein, *TC* total cholesterol, *TNF-α* tumor necrosis factor-α

Table 6.4 The effects of fruits and vegetables on age-related diseases in *in vitro* and *in vivo* studies

Age-related diseases	*In vitro* and *in vivo* models	Treatment	Findings	References
CVD and diabetes	Adult male Wistar rats	Anthocyanins-rich extract from Kamchatka honeysuckle berry (2 g/kg for 4 weeks)	↓ Glucose and lipid metabolism disturbances	Jurgoński et al. (2013)
Type 2 diabetes mellitus	Human intestinal Caco-2 cells	Berry extract (0.125% (w/v) for 16 h)	↓ SGLT1 and GLUT2 mRNA expression ↓ Facilitated glucose uptake	Alzaid et al. (2013)
Type 2 diabetes mellitus	Alloxan-induced diabetic rats (150 mg/kg body weight)	Water extract of garden strawberry (50 mg/kg body weight) for 45 days	Improve serum insulin level	Abdulazeez and Ponnusamy (2016)
Obesity	Isolated rat adipocytes	Cyanidin 3-glucoside (2 g/kg for 12 weeks)	↑ Secretion of adipocytokine (leptin and adiponectin) and UCP2, aP2, LPL, and PPAR-γ expression	Tsuda et al. (2004)

aP2 adipocyte fatty acid-binding protein, *CVD* cardiovascular disease, *GLUT2* glucose transporter 2, *LPL* lipoprotein lipase, *UCP2* uncoupling protein 2, *PPAR-γ* peroxisome proliferator-activated receptor gamma, *SGLT1* sodium-dependent glucose transporter 1

prospective cohort studies involving 194,019 participants and 13,013 type 2 diabetes mellitus cases showed that intakes of berries were associated with an 18% reduction of type 2 diabetes mellitus risk. The data further revealed that the risk of type 2 diabetes mellitus was reduced by 5% with a 17 g/day increment of berry fruits intake (Guo et al. 2016). Data from *in vitro* study revealed that berry extract (0.125% (w/v) for 16 h) significantly decreased the sodium-dependent glucose transporter 1 (SGLT1) and glucose transporter 2 (GLUT2) mRNA expression and reduced the facilitated glucose uptake in human intestinal Caco-2 cells (Alzaid et al. 2013) (Table 6.4). The concentrations of berry extract used are consistent with the amounts of polyphenols that are found in the intestinal lumen after consumption of polyphenol-rich fruits or beverages (Williamson 2013). Furthermore, the oral administration of water extract of garden strawberry (50 mg/kg body weight) for 45 days could improve serum insulin level in alloxan-induced diabetic rats (150 mg/kg body weight) (Abdulazeez and Ponnusamy 2016) (Table 6.4). This biological effect highlights the role of unique complexes of bioactive constituents in fruits and vegetables.

In addition to the effects mentioned above, fruit consumption is negatively associated with cancer risk. A human study involving 90,476 premenopausal women aged 27–44 years old from the Nurses' Health Study II in 1991 and 44,223 of women in 1998 revealed that high intakes of fruits (2.9 servings/day), particularly grapes, banana, and apple during adolescence and kale and oranges during early

Table 6.5 The effects of fruits and vegetables on human health

Metabolic ailments	Subjects	Treatment	Findings	References
Obesity	Obese and overweight individuals	≥500 g/day for 16 weeks	↓ Sagittal abdominal diameter, body weight, and waist circumference	Järvi et al. (2016)
CVD	Patients with coronary heart disease and stroke combined	800 g/day (10 servings/day)	↓ Risk of CVD	Aune et al. (2017)
CVD	Overweight and obese adults	Encapsulated fruit and vegetable juice concentrate (6 capsules for 8 weeks/day)	↓ Systolic blood pressure, plasma TNF-α, LDL-cholesterol, and TC	Wood et al. (2017)
CVD	Two cohort studies (34,560 participants, 26% men and 74% women aged 20–69 years)	Up to 7 glasses/week but not ≥8 glasses of pure fruit juice	↓ Risk of CHD and CVD	Scheffers et al. (2019)
Type 2 diabetes mellitus	5 prospective cohort studies (194,019 participants and 13,013 type 2 diabetes mellitus cases)	Berries	↓ by 5% with a 17 g/day increment	Guo et al. (2016)
Breast cancer	90,476 premenopausal women (aged 27–44 years old from the Nurses' Health Study II in 1991) and 44,223 of women in 1998	Fruits (2.9 servings/day), particularly grapes, banana, and apple during adolescence; kale and oranges during early adulthood	↓ 25% risk of breast cancer	Farvid et al. (2016)

CHD coronary heart disease, *CVD* cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TNF-α* tumor necrosis factor-α

adulthood was associated with a 25% lower risk of breast cancer (Farvid et al. 2016). Research evidence has suggested that phytochemicals in fruits and vegetables can have overlapping and complementary mechanisms of action, such as hormone metabolism, scavenging of oxidative agents, modulation of detoxification enzymes, activation of the immune system, and modulation of gene expression in apoptosis and cell proliferation (Waladkhani and Clemens 1998). The short-chain fatty acids are produced when the dietary fiber in fruits and vegetables undergo fermentation by gut microbiota. The short-chain fatty acids such as propionate (Yang et al. 2017), butyrate (Han et al. 2017), and acetate (Schug et al. 2016) may have protective effects against cancers. Collectively, bioactive compounds in fruits and vegetables might be a useful nutritional intervention for the attenuation of age-related diseases (Alissa and Ferns 2017). However, the bioactive components responsible for the effects that we stated above require further elucidation.

6.5.2 Whole Grains

Given the role of diet, long-term intake of staple food with functional properties as a daily dietary habit has gained more acceptability rather than drug treatment in a disease setting. Whole grains are rich in dietary fiber with some vitamins, minerals, and phytochemicals. Grains contain various bioactive compounds beneficial to human health besides their nutritional contents. Among these components, arabinoxylans are a significant source of fiber. The anti-inflammatory effect and antioxidant activities in polyphenols could be attributed to their chemical structures (Zhang and Tsao 2016). Similar to other secondary metabolites, polyphenols are the frontline defense of plants. They act as a predominant non-nutrient bioactive group in the human diet, primarily found in plants (Marilo et al. 2018). A highly conjugated system with several hydroxyl groups and aromatic characteristic make these polyphenols a good hydrogen atom and electron donor by neutralizing free radicals (Tsao 2010). These bioactive compounds may serve as a preventative strategy in combating oxidative stress by suppressing the proinflammatory signaling transductions (Tan et al. 2018b).

Whole grains have beneficial antioxidants and biochemical effects on oxidative stress-induced diseases (Table 6.6). Data from randomized, double-blind, controlled cross-over trial involving 14 middle-aged obese and diabetic adults (age = 38 ± 2 years; BMI = 34.0 ± 1.1 kg/m^2) revealed that intakes of whole grains (50 g per 1000 kcal) for 8 weeks reduced risk of diabetes by modulating peripheral insulin resistance and postprandial blood glucose (Malin et al. 2018). A human study conducted in healthy men (age = 21 ± 2 years; BMI = 21.4 ± 1.0 kg/m^2) revealed that plasma glucose response during oral glucose tolerance test (OGTT) after the intake of cooked barley kernels (86 g) was 29% smaller compared to those who consume 105 g white wheat bread (Priebe et al. 2010). The improvement in plasma glucose response is more likely due to the fermentation of soluble fiber in whole grains (Higgins 2012). The dietary fibers and phenolic are metabolized by the gut microbiota and converted into short-chain fatty acids (Fardet 2010) to facilitate gut permeability (Suzuki et al. 2008), immune homeostasis (Furusawa et al. 2013), lipid and glucose metabolism (Priebe et al. 2010), and gut hormone secretion (Wichmann et al. 2013). Figure 6.3 showed the mechanisms of whole grains involved in the modulation of age-related diseases.

Notably, data from a randomized cross-over trial involving 60 Danish adults at risk of developing metabolic syndrome revealed that intake of whole grains (179 ± 50 g/day) for two 8-week dietary intervention periods did not significantly alter glucose homeostasis. The study further demonstrated that consumption of whole grain decreased body weight, CRP, and IL-6 levels (Roager et al. 2019). This finding implies that whole grain can reduce systemic low-grade inflammation compared to a refined grain diet. In another study, Hajihashemi and Haghighatdoost (2019) evaluated the whole grain in relation to inflammatory markers and proinflammatory cytokine production. The data involving 13 randomized clinical trials with 466 participants demonstrated that whole grain consumption significantly

reduced the serum concentration of IL-6 and CRP but did not result in a significant decrease in serum concentration of TNF-α. Similarly, a systematic review and dose-response meta-analysis included 19 cohort studies involving 1,041,692 participants and 96,710 deaths in total suggested that intake of 28 g/day whole grain could reduce the total mortality by 9%, CVD mortality by 14%, and cancer mortality (3%) (Zhang et al. 2018). Hollænder et al. (2015) further demonstrated that intakes of whole grains (28–213 g/day for 6–8 weeks) reduced TC and LDL-cholesterol compared to those who never consume whole grains, suggesting the cardioprotective potential of whole grains intake. A similar dietary intake was also found to improve glucose homeostasis and postprandial levels (Hollænder et al. 2015; Marventano et al. 2017). By contrast, refined grain intakes (3 servings/day), particularly from white rice were found to increase the risk of type 2 diabetes mellitus (Aune et al. 2013a). Such findings imply that coarsely milled grains or whole kernels tend to have a lower glycemic index (GI) and contain a higher amount of phytochemicals and fibers with antioxidant and anti-inflammatory properties compared to refined grains.

Table 6.6 The effects of whole grains on human health

Metabolic ailments	Study conditions	Treatment	Findings	References
Type 2 diabetes mellitus	Cross-over design (Healthy men)	Cooked barley kernels (86 g)	↓ 29% of OGTT plasma glucose response compared to those who consume 105 g white wheat bread	Priebe et al. (2010)
Type 2 diabetes mellitus	16 cohort studies	Refined grain intakes (3 servings/day)	↑ Risk of type 2 diabetes mellitus	Aune et al. (2013a)
Type 2 diabetes mellitus	Randomized, double-blind, controlled cross-over trial (obese and diabetic adults)	(50 g per 1000 kcal) for 8 weeks	↓ Risk of diabetes	Malin et al. (2018)
Type 2 diabetes mellitus	Randomized cross-over trial (60 Danish adults at risk of developing metabolic syndrome)	179 ± 50 g/day for two 8-week dietary intervention periods	No effect on glucose homeostasis ↓ Body weight, CRP, and IL-6 levels	Roager et al. (2019)
CVD and cancer	19 cohort studies	28 g/day	↓ Total mortality by 9%, CVD mortality by 14%, and cancer mortality (3%)	Zhang et al. (2018)
CVD	24 randomized controlled studies	28–213 g/day for 6–8 weeks	↓ Total cholesterol, and LDL cholesterol	Hollænder et al. (2015)

CVD cardiovascular disease, *CRP* C-reactive protein, *IL-6* interleukin-6, *LDL* low-density lipoprotein, *OGTT* oral glucose tolerance test

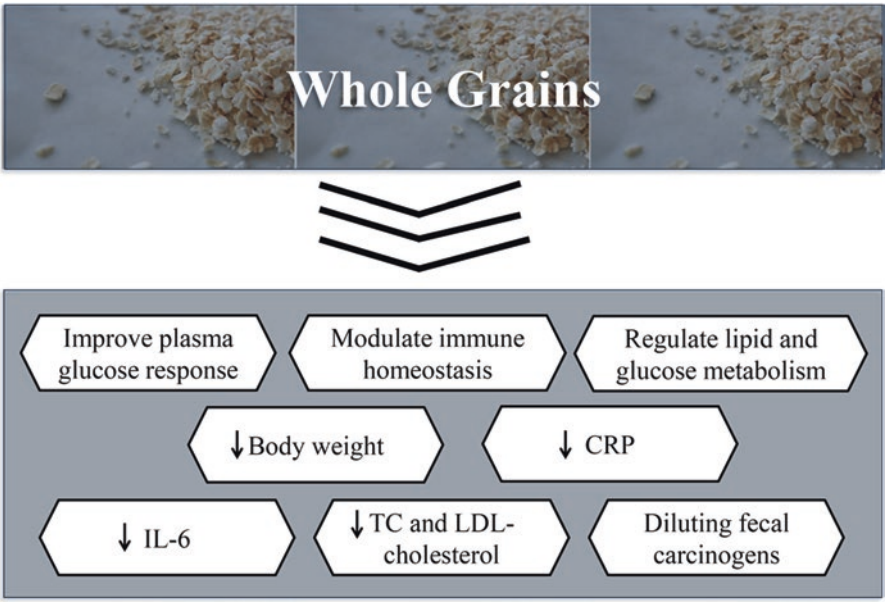

Fig. 6.3 The mechanisms of whole grains involved in the modulation of age-related diseases. *CRP* C-reactive protein, *IL-6* interleukin-6, *LDL* low-density lipoprotein, *TC* total cholesterol

The implications of dietary fibers in relation to age-related diseases have also been widely studied in a human study (Slavin 2013). Data from the meta-analysis and systematic review involving 4635 adults of 58 randomized controlled trials included a study from inception to February 28, 2018, and 185 prospective studies from inception to April 30, 2017 suggest a 15–30% decrease in colorectal cancer, type 2 diabetes, stroke incidence and mortality, and CHD when daily intake of dietary fiber was 25–29 g (Reynolds et al. 2019). Indeed, food containing fibers need to be chewed before passing via the stomach and small bowel, which may affect lipid absorption, insulin and glucose responses, and satiety (Grundy et al. 2016). The previous study suggested that the whole foods that require chewing can retain much of their physical structures in the gut, and are more likely to enhance satiety via different mechanisms, and ultimately modulate the lipid and carbohydrate metabolism and weight loss (Mattes and Dreher 2010; Tan et al. 2018b). In the large bowel, the fibers are almost completely broken down by the resident microflora in an anaerobic reaction known as fermentation (Hur and Lee 2015). In addition, the gut microbiota also plays a crucial role in human health, such as xenobiotics metabolism, vitamin synthesis, and gut immune system development. The microbiome digested carbohydrates and fibers and breakdown in the small bowel. The availability of fiber in the diet may enhance the metabolism of the gut microbiome and thus protect against colorectal cancer (Shanahan et al. 2017). Substantial evidence highlights that whole grain foods could reduce the risk of colorectal cancer by diluting fecal carcinogens, increasing stool bulk, reducing transit time, and hence

decreasing the interaction between carcinogens and the lining of the colorectum (Slavin 2013). What is apparent from studies on whole grains is that it could reduce oxidative stress and therefore prevent or at least delay oxidative stress-associated complications. However, further studies are required to explore the types of whole grains and the bioavailability of their bioactive compounds and metabolites in subjects with one or more risk factors for chronic diseases through long-term interventional studies.

6.5.3 Milk and Dairy Products

Milk has become an important dietary component in the diet for nearly 6 billion people (FAO 2012). Many dairy products have been produced and consumed worldwide including butter, kefir, yogurt, cheese, and cream. Therefore, the impact of dairy products and milk on human health is vitally important (Table 6.7 and Fig. 6.4). Randomized clinical trials involving 903 healthy adolescents showed that intake of milk and dairy products for at least 2 serving/day (1 serving = 125 g of yogurt, 200 mL of milk, or 28 g of cheese) can significantly reduce the body fat and promote weight loss (Abreu et al. 2012a, b). Of all the milk components, dairy protein is the most common nutrient found in milk and dairy products. Dairy protein has been suggested as a reducer for body weight and adipose mass (Vergnaud et al. 2008; Bendtsen et al. 2013) in both diabetic patients (Shahar et al. 2007) and overweight and obese individuals (Faghih et al. 2011; Josse et al. 2011; Sanders 2012; Abargouei et al. 2012). Whey protein appears to be substantially effective in weight control (Pal et al. 2010; Sousa et al. 2012) by increasing satiety and decreasing appetite (Sousa et al. 2012). In addition, whey protein can also suppress gastric (Pal et al. 2010) and promote glucagon-like peptide 1 (GLP-1) (Brubaker and Anini 2003; Hall et al. 2003) and glucose-dependent insulinotropic polypeptide (GIP) secretion (Samra et al. 2007), accompanied by the inhibition of ghrelin secretion (Bowen et al. 2006), and subsequently contribute synergistically to the weight control.

The bioactive components in milk theoretically exert chemopreventive activity. Data from cohort and case-control studies have demonstrated that consumption of milk fat-containing dairy products was inversely associated with breast (>3 servings/day of total dairy food) and colon (400 g/day of total dairy products and 200 g/day of milk intake) cancers (Dong et al. 2011; Pala et al. 2011; Zhang et al. 2011; Aune et al. 2012; Chagas et al. 2012). This protective effect can be ascribed to vitamin D, calcium, and conjugated linoleic acid (Norat and Riboli 2003; Średnicka-Tober et al. 2016). Calcium has been suggested to suppress cell growth, activate apoptosis and differentiation in the mammalian gland and gastrointestinal tract, interact with fatty acids and biliary salts in the intestine, and reduce noxious effects in the mucosa (Visioli and Strata 2014). However, Bermejo et al. (2019) showed that high consumption of whole milk increased the risk of bladder cancer. The calcium may bind to vitamin D and insulin-like growth factor-1 (IGF-1) and promote the risk of prostate cancer (Giovannucci 1998; Rodriguez et al. 2003). In this regard,

Table 6.7 The effects of milk and dairy products on human health

Metabolic ailments	Study conditions	Treatment	Findings	References
Obesity	Randomized clinical trials	At least 2 serving/day (1 serving = 125 g of yogurt, 200 mL of milk, or 28 g of cheese)	↓ Body fat and promote weight loss	Abreu et al. (2012a, b)
Cancer	Cohort and case-control studies	>3 servings/day of total dairy food	↓ Breast cancer	Dong et al. (2011); Pala et al. (2011); Zhang et al. (2011); Aune et al. (2012); Chagas et al. (2012)
		400 g/day of total dairy products and 200 g/day of milk intake	↓ Colon cancer	
Cancer	Meta-analysis of 32 prospective studies	Total dairy products (400 g/day), total milk (200 g/day), low-fat milk (200 g/day), cheese (50 g/day), and dietary calcium (400 mg/day)	↑ Risk of total prostate cancer	Mandair et al. (2014); Aune et al. (2015)
Cancer	Meta-analysis of 26 epidemiologic studies (8 cohort and 18 case-control)	High consumption of whole milk (~220 mL/day)	↑ Risk of bladder cancer	Bermejo et al. (2019)
Cancer	Meta-analysis of 26 epidemiologic studies (8 cohort and 18 case-control)	Medium consumption of total dairy products (~345 g/day), medium and high consumption of milk (medium = ~227 mL/day; high = ~336 mL/day) and fermented dairy products (medium = ~67 g/day; high = ~160 g/day)	↓ Risk of bladder cancer	Bermejo et al. (2019)
Type 2 diabetes mellitus	Randomized clinical trials (Type 2 diabetic subjects)	Whey protein (27.6 g) in the diet (breakfast = 102 g white wheat bread or lunch = 52.2 g instant potato powder and 50 g meatballs)	↓ 21% of blood glucose response	Frid et al. (2005)
Type 2 diabetes mellitus	Meta-analysis of 17 cohort studies	200 g low-fat dairy products/day, 400 g total dairy products/day, or 50 g cheese/day	↓ Risk of type 2 diabetes	Aune et al. (2013b)
Type 2 diabetes mellitus	Randomized double-blind placebo-controlled clinical trial (60 diabetic patients)	Probiotic fermented milk (kefir) (600 mL/day for 8 weeks)	↓ HbA1c level compared to control group	Ostadrahimi et al. (2015)

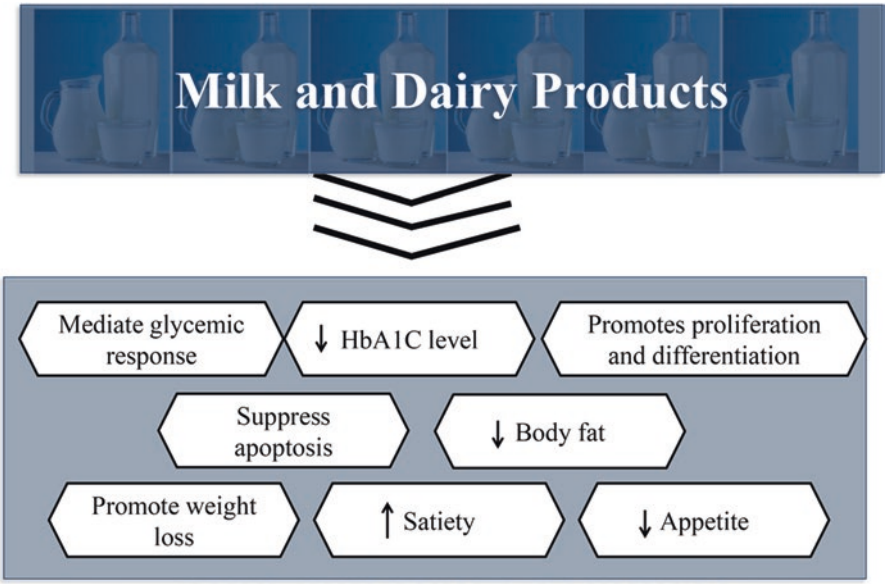

Fig. 6.4 The mechanisms of milk and dairy products involved in the modulation of age-related diseases

intakes of total dairy products (400 g/day), total milk (200 g/day), low-fat milk (200 g/day), cheese (50 g/day), and dietary calcium (400 mg/day) were associated with increased risk of total prostate cancer (Mandair et al. 2014; Aune et al. 2015). Although research evidence demonstrated that dairy intake was positively related to prostate cancer, not all data showed such a link. Huncharek et al. (2008) did not find an association between prostate cancer and dairy or milk intake.

Besides the bioactive components, relatively little attention has been paid to bioactive hormones. The extent and the nature of the role of IGF-1 in the development of numerous diseases are highlighted here. IGF-1 is increased proportionally with the presence of casein in milk. In particular, milk protein promotes postprandial hyperinsulinemia and shifts the growth hormone (GH)/IGF-1 axis, and subsequently leads to an irreversible increase of IGF-1 serum levels (Ludwig 2002). In addition, it has been demonstrated that more than 90% of this hormone is bound to IGF-binding protein 3 (IGFBP-3), the rest is bound to IGFBP-1, -2, -4, and -6. IGF-1 receptor (IGF-1R) involves in the regulation of many signal transductions. Because of their tyrosine kinase activity, IGF-1R can form a heterodimer with the insulin receptor. The IGF-1R-mediated signal transduction pathway mainly via the activation of Ras/Raf/MAP kinase signaling cascade concomitantly with the stimulation of PI3K signaling pathway, suggesting that these pathways may stimulate lipogenesis and cellular proliferation and suppress apoptosis. Since IGF-1 promotes proliferation and differentiation and suppresses apoptosis, implies that this hormone may influence the growth of tumors (Duan et al. 2010). In support of this, several studies demonstrated a positive correlation between high IGF-1 serum levels and the risk of

colorectal, prostate, esophageal, and breast cancers (Shiratsuchi et al. 2011; Walsh and Damjanovski 2011; Doyle et al. 2012; Cao et al. 2015). In short, consumption of milk and dairy products does not consistently increase the risk of cancers, the evidence in favor or against such effect remains too limited to draw a firm conclusion.

In addition to the effects mentioned above, data from a meta-analysis of 17 cohort studies have shown an inverse relationship between risk of type 2 diabetes and consumption of 200 g low-fat dairy products/day, 400 g total dairy products/day, or 50 g cheese/day (Aune et al. 2013b), but the underlying mechanisms in relation to these observations have yet to be elucidated (Visioli and Strata 2014). Notably, including whey protein (27.6 g) in the diet (breakfast = 102 g white wheat bread or lunch = 52.2 g instant potato powder and 50 g meatballs) can reduce 21% of blood glucose response in patients with type 2 diabetes, aged 27–69 years (Frid et al. 2005). This finding suggests that the addition of whey protein to meals rapidly absorbed and digested carbohydrates could promote the release of insulin and decrease postprandial blood glucose excursion after a lunch meal consisting of meatballs and mashed potatoes in type 2 diabetic subjects (Frid et al. 2005). Even though the fact in favor or against lactose used by diabetic patients is scant, the American Diabetes Association recommended the consumption of milk and dairy products. This is partially due to the milk has a relatively low GI and the dairy proteins which are mainly from casein, and thus mediate glycemic response through stimulation of certain plasma amino acids and incretins (Gunnerud et al. 2012). A randomized double-blind placebo-controlled clinical trial involving 60 diabetic patients aged 35–65 years revealed that intake of probiotic fermented milk (kefir) (600 mL/day for 8 weeks) significantly decreased the HbA1c level compared to the control group, suggesting that probiotic fermented milk can be useful as adjuvant therapy in the treatment of diabetes (Ostadrahimi et al. 2015). Although limited available evidence to draw a firm conclusion, previous studies suggest that milk and dairy products may be potential to some population segments. Collectively, further studies are warranted to evaluate the implication of specific types of dairy products in different populations on metabolic ailments and any gender-specific recommendations.

6.5.4 Olive and Fish Oils

Research evidence revealed the beneficial effects of dietary monounsaturated fatty acids (MUFA) in regulating body weight and cardiometabolic risk factors (Viitasalo et al. 2016). The main active components in olive are oleic acid (18:1 n-9), squalene, and phenolic compounds such as hydroxytyrosol, oleuropein, and tyrosol (Roselló-Soto et al. 2015). Both oleuropein and hydroxytyrosol have established bioactivity, primarily associated with their antioxidant properties. These compounds appear to play a role in several diseases in preclinical studies, especially in cardiovascular and metabolic disorders (Bulotta et al. 2014).

Adherence to the Mediterranean dietary pattern is related to a lower risk of obesity and metabolic ailments (Álvarez-Pérez et al. 2016). Olive phenolics act as

α-glucosidase and α-amylase inhibitors to hinder carbohydrate digestion and thus suppressing carbohydrate uptake and absorption (Collado-González et al. 2017) (Fig. 6.5). Both *in vitro* and *in vivo* studies have demonstrated that olive polyphenols can suppress pre-adipocyte differentiation, inhibit lipogenesis, promote lipolysis, and induce adiponectin secretion (Fig. 6.5), possibly mediated via inhibition of adipogenic gene expressions such as leptin, FAS, CCAAT-enhancer-binding proteins (C/EBPα), and PPAR-γ, and upregulation the genes related to the inhibition of adipogenesis like GATA2, GATA3, WNT3A, SFRP5, HES1, and SIRT (Higa et al. 2014; Shen et al. 2014; Stefanon and Colitti 2016).

Furthermore, intakes of olive oil can also reduce insulin resistance. Dysfunction of pancreatic β-cell is a major determinant for the development of type 2 diabetes, while endoplasmic reticulum (ER) stress plays a crucial role in the β-cell failure. The bioactive components in olive oil can attenuate ER stress-mediated apoptosis and unfolded protein response via inhibition of JNK phosphorylation (Lee et al. 2016).

In addition to the effects observed in olive oil, fish oil may also emerge as a key element for the modulation of age-related diseases. The main elements in fish oil are n-3 polyunsaturated fatty acids (PUFA) including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Fish oil supports various body functions and reduces several diseases such as diabetes, cancer, CVD, and other conditions, for instance, inflammation by downregulating CRP, TNF-α, and IL-6 expression (Ellulu et al. 2015).

Observational studies involving young male adults (18–25 years old) have demonstrated that daily fish oil supplements (up to 3 g omega-3 fatty acid for 12 weeks) can reduce serum TG effectively (Roke et al. 2015). Omega-3 fatty acids in fish oil are ligands for PPAR, which may induce changes in cardiometabolic markers (Binia et al. 2017). Patients with coronary artery disease supplemented with fish oil (≥1000 mg/day for at least 1 month) improved intermediate-density lipoprotein cholesterol, TG, and very-low-density lipoprotein (VLDL)-cholesterol (Franzese et al. 2015). Table 6.8 summarizes the effects of fish oil on age-related diseases in *in vivo* and human studies.

Omega-3 PUFAs are not only improved lipid profiles, they also having beneficial effects on type 2 diabetes. Several studies as reported by Kröger and Schulze (2014) have shown that long-chain n-3 PUFA from dietary fish intake can reduce the risk of type 2 diabetes. In this regard, a key mode of action to explain this relationship is via the reduction of 7α-hydroxylase, 3-hydroxy-3-methylglutaryl-CoA, and LDL-cholesterol (Scicchitano et al. 2014). Consistent with the study reported by Kröger and Schulze (2014), Gao et al. (2017) also found that diet enriched with fish oil (1–4 g/day for 4–24 weeks) enhanced insulin sensitivity among people with at least one symptom of metabolic disorders. The insulin-sensitizing effects of n-3 PUFA may be partially due to the anti-inflammatory properties which are mediated by G-protein coupled receptor GPR120 (Oh et al. 2014).

In addition to the effects mentioned above, fish oil has the potential to protect against cancers. Dietary administration of fish oil for 21 weeks at 15 mg/kg body weight of azoxymethane/2% dextran sodium sulfate (AOM/DSS)-induced rats can

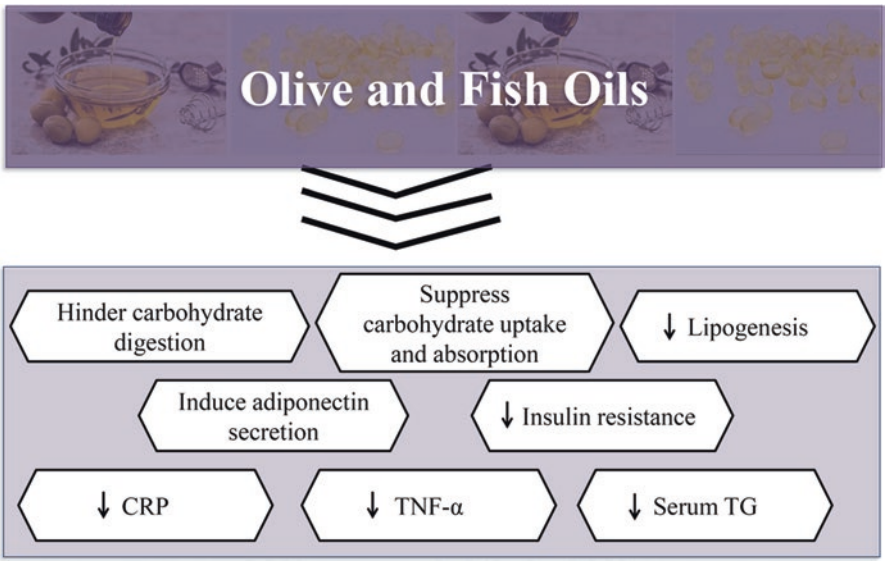

Fig. 6.5 The mechanisms of olive and fish oils involved in the modulation of age-related diseases. *CRP* C-reactive protein, *TG* triglycerides, *TNF-α* tumor necrosis factor-α

significantly reduce the mean colon tumor volume and tumor multiplicity (Djuric et al. 2017) (Table 6.8). Fish oil modulates cancer via several mechanisms including promotion of BAD-dependent apoptosis via PI3K/AKT survival pathway, suppression of raft-associated signal transduction, activation of Nrf2, and resolution of inflammation by D-resolvins (RvD2 and RvD1), protectin (PD1), and E-resolvins (RvE1 and RvE2) through lipoxygenase (LOX) and COX pathways (Aucoin et al. 2017). Collectively, the available research evidence suggests that MUFA and other main active components appear to be favorable for its beneficial effects, suggesting that including olive oil or fish oil in a diet may extend cardioprotective effects and reduce other metabolic disorders beyond those defined for a contemporary healthy dietary pattern. Further studies are warranted to elucidate whether the antioxidant or its PUFA content is responsible for its beneficial effects.

6.6 Dietary Antioxidants and Age-Related Diseases

6.6.1 Curcumin

Curcumin is a bioactive compound extracted from turmeric rhizome *Curcuma longa* L., is a perennial herbaceous plant of the ginger family (Zingiberaceae) (Priyadarsini 2014). It is widely utilized in India, China, and Southeast Asia for medicinal purposes and in food colorants (Kocaadam and Şanlier 2017). Curcumin usage dates

Table 6.8 The effects of fish oil on age-related diseases in *in vivo* and human studies

Metabolic ailments	*In vivo* models and human studies	Treatment	Findings	References
CVD	Young male adults	Fish oil supplements (up to 3 g omega-3 fatty acid for 12 weeks)	↓ Serum TG	Roke et al. (2015)
CVD	Patients with coronary artery disease	Fish oil (≥1000 mg/day for at least 1 month)	Improved intermediate-density lipoprotein cholesterol, TG, and VLDL-cholesterol	Franzese et al. (2015)
Type 2 diabetes mellitus	People with at least one symptom of metabolic disorders	Diet enriched with fish oil (1–4 g/day for 4–24 weeks)	Enhanced insulin sensitivity	Gao et al. (2017)
Colon cancer	AOM/DSS-induced rats	Fish oil for 21 weeks on 15 mg/kg body weight	↓ Mean colon tumor volume and tumor multiplicity	Djuric et al. (2017)

AOM azoxymethane, *CVD* cardiovascular disease, *DSS* dextran sodium sulfate, *TG* triglycerides, *VLDL* very-low-density lipoprotein

back more than 2500 years in Asia, particularly in traditional Indian Medicine (Ayurveda) (Gupta et al. 2013). It has been used for the treatment of numerous diseases including stress, depression, rheumatism, eye infections, skin diseases, burns, and wounds (Singh 2007; Hatcher et al. 2008; Qin et al. 2009). Several studies reported by Farooqui and Farooqui (2019) and Sharifi-Rad et al. (2020) evaluated the pharmacological and biological activity of curcumin, which having a polyphenol structure, in relation to several receptors, growth factors, transcription factors, enzymes, kinases, and cytokines. The data showed that curcumin has some hypoglycemic (Rivera-Mancía et al. 2018), hepatoprotective (Khan et al. 2019), renoprotective (Huang et al. 2020), immunomodulatory (Yang et al. 2020), antioxidant (Boroumand et al. 2018), anti-inflammatory (Zhang et al. 2015), and antimicrobial effects (Zhu et al. 2015).

The data from *in vitro* studies have demonstrated the anticancer potential of curcumin in reducing oxidative stress by mediating several signaling pathways (Wang et al. 2018b; Lin et al. 2019). Curcumin was shown its cytotoxicity against androgen-independent prostate cancer cell lines (PC-3 and DU-145) and androgen-dependent prostate cancer cell line (LNCaP) (Jordan et al. 2016). The animal model studies further revealed the chemopreventive potential of curcumin in chemical-induced animal models of the liver (Damiano et al. 2021), colon (Byun et al. 2015), and skin (Tsai et al. 2012) cancers. This favorable effect could be attributed to its antioxidant effect. Yet, the chemopreventive ability of curcumin is mediated via several mechanisms such as triggers heme oxygenase (HO) phase II enzymes and Nrf2/Keap signaling pathway (Fig. 6.6), the transcriptional regulator for detoxification of ROS

(Muhammad et al. 2018; Ashrafizadeh et al. 2020). However, a study reported by Huang et al. (1997) has shown that feeding mice with curcumin showed a little or no effect on 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast carcinogenesis and 4-(methylnitosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancer. The data further showed that poor circulating bioavailability of curcumin may contribute to the lack of the inhibition of breast and lung cancers (Huang et al. 1997).

The anticancer activity of curcumin was not only observed in both *in vivo* and *in vitro*, the efficacy of curcumin has also been demonstrated in clinical trials. Data from a phase II clinical study involving 44 colon cancer lesions patients showed that curcumin (4 g/day for 30 days) reduced 40% number of lesions (Carroll et al. 2011). In another clinical study involving 199 localized prostate cancer patients, with an average age of 74 years, who are given an oral capsule containing a mixture of turmeric (100 mg), broccoli (100 mg), pomegranate (100 mg), and green tea (100 mg) for 6 months showed a median increase in prostate-specific antigen (PSA) was 63.8% lower than the placebo group on primary active surveillance and those experiencing a PSA relapse after radiotherapy (Thomas et al. 2014). Indeed, several initial stage studies have shown a favorable response in the reduction of symptoms and adverse outcomes related to radiotherapy (Amir et al. 2018). A study that analyzed 50 patients with neck and head cancer undergoing radiotherapy found that cream containing turmeric (2 g) and sandal wood oil (2 mL) (5 times/day for 2 weeks) is effective in preventing radiodermatitis (Palatty et al. 2014). Indeed, phase I and II clinical trials have shown that curcumin is safe and exhibit some therapeutic effects in certain cancer (Cheng et al. 2001; Tan and Norhaizan 2019c). The data showed that consumption of curcumin (500–8000 mg/day for 3 months) may improve the histology of precancerous lesions in resected uterine cervical intraepithelial neoplasms, intestinal metaplasia, oral leucoplakia, and bladder cancer patients (Cheng et al. 2001). Likewise, patients with advanced pancreatic cancer who received 8 g curcumin reduced COX-2 and NF-κB expression (Dhillon et al. 2008). The implication of curcumin combination chemotherapy has also been evaluated in several clinical studies (Table 6.9). The phase I escalated clinical trial measured the tolerability and feasibility of combination curcumin and docetaxel in relation to metastatic or advanced breast cancer among 14 patients. The patients were given 500 mg/day of curcumin for 7 days and increased until dose-limiting toxicity. The study showed that combination therapy of curcumin (500 mg/day) with docetaxel (100 mg/m^2) show a promising biological response by decreasing carcinoembryonic antigen (CEA) tumor marker (Bayet-Robert et al. 2010). The data further revealed that the maximum concentration of curcumin that could be tolerated is 6000 mg/day for 7 consecutive days in every 3 weeks when combined with the standard dosage of docetaxel (Bayet-Robert et al. 2010). Another phase I clinical study involving 21 gemcitabine-resistant pancreatic cancer patients revealed that oral administration of 8 g/day curcumin and gemcitabine [(1000 mg/m^2 on day 1 and 8) and (60 mg/m^2 of S-1 orally for 14 consecutive days every 3 weeks)] was demonstrated no dose-limiting toxicities (Kanai et al. 2011). Such findings implied that administration of curcumin (8 g/day) orally is feasible and safe in pancreatic cancer patients (Kanai et al. 2011). The efficacy and safety of curcumin were further

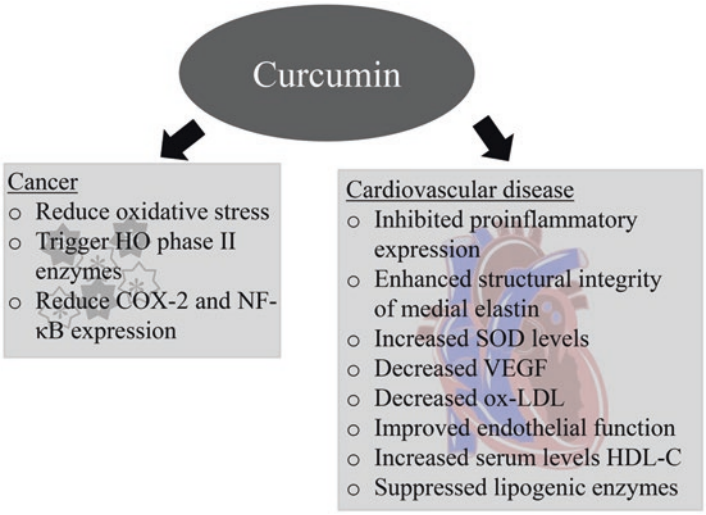

Fig. 6.6 Mechanisms of curcumin in the modulation of cancer and cardiovascular disease. *COX-2* cyclooxygenase-2, *HDL-C* high-density lipoprotein cholesterol, *HO* heme oxygenase, *NF-κB* nuclear factor-kappa B, *ox-LDL* oxidized low-density lipoprotein, *SOD* superoxide dismutase, *VEGF* vascular endothelial growth factors

evaluated in a phase II trial in metastatic and advanced pancreatic cancer patients. The study found that a combination of gemcitabine (10 mg/m^2) and curcumin (2000 mg/die continuously (4 capsules, each of 500 mg/day)) showed the overall survival and median progression-free survival were 10.2 and 8.4 months, respectively. This finding suggests that combination therapy of curcumin and gemcitabine is efficient and safe to translate a good response rate in first-line therapy of advanced pancreatic cancer (Pastorelli et al. 2018). While for colorectal liver metastases, James et al. (2015) found that administration of 5 μM curcumin could improve FOLFOX-based chemotherapy (5 μM 5-FU and 2 μM oxaliplatin) in colorectal liver metastasis patients. Collectively, the synergistic effects played by curcumin combination chemotherapeutic drugs on cancer worth further investigation in large clinical trials.

Curcumin is not only exerted anticancer effects (Adiwidjaja et al. 2017), existing research evidence has been demonstrated the benefit of curcumin in treating osteoporosis (Jiang et al. 2021), CVD (Pourbagher-Shahri et al. 2021), arthritis, liver problem (Nabavi et al. 2014), neurological disorders (Bagheri et al. 2020), diabetes (Shome et al. 2016), and chronic inflammatory disease (He et al. 2015), suggesting the numerous functional potential of curcumin. Specifically, substantial studies have shown that curcumin exerts preventive effects toward the diabetic and stroke cardiovascular complications, aortic aneurysm, atherosclerosis, myocardial infarction, drug-induced cardiotoxicity, heart failure, and cardiac hypertrophy (Aggarwal and Harikumar 2009; Campbell and Fleenor 2018; Farkhondeh and Samarghandian 2016; Karuppagounder et al. 2017). Aortic aneurysm, one of the cardiovascular

Table 6.9 Clinical studies conducted in curcumin combination chemotherapy

Subjects	Sample size	Treatment	Outcomes	References
Metastatic or advanced breast cancer patients	14	Curcumin (500 mg/day) and escalated until a dose-limiting toxicity + docetaxel (100 mg/m^2) for 7 days every 3 weeks	↓ CEA tumor marker	Bayet-Robert et al. (2010)
Gemcitabine-resistant pancreatic cancer patients	21	8 g/day curcumin and gemcitabine (1000 mg/m^2 on day 1 and 8) and (60 mg/m^2 of S-1 orally for 14 consecutive days every 3 weeks)	Median survival time was 161 days and 1-year survival rate was 19%	Kanai et al. (2011)
Chronic myeloid leukemia	50	Turmeric powder (5 g 3 times/day) + imatinib (400 mg twice/day) for 6 weeks	↓ Nitric oxide levels	Ghalaut et al. (2012)
Colorectal liver metastases	12	5 μM curcumin +5 μM 5-FU + 2 μM oxaliplatin	Curcumin enhance FOLFOX-based chemotherapy	James et al. (2015)
Metastatic and advanced pancreatic cancer patients	44	Gemcitabine (10 mg/m^2) and curcumin (2000 mg/die continuously (4 capsules, 500 mg/day each))	Overall survival and median progression-free survivals were 10.2 and 8.4 months, respectively	Pastorelli et al. (2018)
Metastatic colorectal cancer patients	28	FOLFOX +2 g oral curcumin/day	The addition of daily oral curcumin to FOLFOX chemotherapy was tolerable and safe	Howells et al. (2019)

CEA carcinoembryonic antigen, *FOLFOX* folinic acid/5-fluorouracil/oxaliplatin, *5-FU* 5-fluorouracil

phenomenon, can cause death in case of rupture (Chen et al. 2011). In the last few decades, several key elements have been suggested in the development of aortic aneurysms such as loss of smooth muscle cells, destructive connective tissue remodeling, and chronic inflammation in the aortic wall (Guo et al. 2006). A study reported by Parodi et al. (2006) showed that feeding curcumin (100 mg/kg/day for 14 days) inhibited proinflammatory expression, enhanced the structural integrity of medial elastin, and decreased the aortic diameter enlargement via suppression of AP-1 and NF-κB. The data from animal study further demonstrated that pretreatment of curcumin (100 mg/kg/day for 4 weeks) alleviated the stimulation of ERK signaling pathway, mediated the production of pro-inflammatory mediators and macrophage infiltration, decreased the development and progression of the aortic aneurysm, and elevated SOD levels in apoE-deficient (ApoE$^{-/-}$) mice induced with a subcutaneous infusion of angiotensin II (Ang II) (Hao et al. 2014). In line with this, Li et al. (2017b) also found that curcumin (100 mg/kg/day for 4 weeks) decreased the production of VEGF and neovascularization, and reduced the size of thoracic aortic

aneurysm in rats. Nonetheless, there was limited clinical trial evidence evaluated on the beneficial effects of curcumin on aortic aneurysms. In the context of atherosclerosis, emerging evidence has suggested that curcumin exerts hypolipidemic activity along with the anti-inflammatory and antioxidant effects, which may lead to the reduction of atherosclerosis (Panahi et al. 2018). The remarkable antioxidant activity of curcumin decreases the production of ox-LDL and lipid peroxidation, which in turn leading to the reduction of inflammatory response. Ultimately, these lead to the progression of atherosclerosis (Panahi et al. 2018). Endothelial dysfunction is demonstrated in patients with CVD such as atherosclerosis (Karimian et al. 2017). In this regard, endothelial cells are potential targets for curcumin to protect against atherosclerosis and enhance endothelial function (Santos-Parker et al. 2017). Pretreatment of curcumin (1, 0.5, and 0.1 μM) significantly decreased the adhesion of monocytes to activated human umbilical vein endothelial cells (HUVECs) via suppression of gene expression implicated in adhesion, for instance, *E*-selectin, ICAM-1, and VCAM-1, which were mediated by TNF-α stimulation (Coban et al. 2012). In another study using a TNF-α stimulation of the HUVECs model showed that pre-exposure of curcumin (0.5–1 μM) decreased monocyte adhesion and endothelial permeability in both flow and static circumstances (Monfoulet et al. 2017). Data from a randomized controlled double-blind prospective study involving 59 healthy adults revealed that curcumin oral supplementation (200 mg/day for 8 weeks) showed a concentration-mediated improvement in endothelial function, suggesting that it may reduce the risk of CVD in healthy adults (Oliver et al. 2016). Similarly, Akazawa et al. (2012) also found that postmenopausal women who received 150 mg/day theracurcumin for 8 weeks improved flow-mediated dilation (FMD). By contrast, it has been shown that postmenopausal and older women (mean 60 years old) have low baseline FMD (<3%), implied that increased risk of CVD (Akazawa et al. 2012). A 12-week randomized double-blind placebo-controlled study on 118 type 2 diabetes patients showed that curcuminoids (1000 mg/day + piperine 10 mg/day) increased serum levels of high-density lipoprotein cholesterol (HDL-C) and decreased lipoprotein(a) (Lp(a)), non-HDL-C, and TC (Panahi et al. 2017b). Importantly, Lp(a) is a plasma lipoprotein comprising of apolipoprotein(a) covalently interact to apolipoprotein B-100, which is linked to the increased risk of CVD, given the scarcity of pharmacological approach to decrease its activity (van der Valk et al. 2016; Panahi et al. 2017b). In this regard, curcuminoids may represent a plausible strategy to alleviate the complications related to the increased expression of Lp(a) in diabetes mellitus. Such finding indicates that curcuminoids supplementation may reduce the serum levels of atherogenic lipid indices in dyslipidemic patients with type 2 diabetes (Panahi et al. 2017b). While, a randomized clinical trial analyzed of 60 overweight and obese female adolescent revealed that curcumin supplementation (500 mg/day, containing 95% turmeric extract, for 10 weeks) can improve the lipid profiles such as HDL-C levels and TG/HDL-C ratio (Saraf-Bank et al. 2019). Curcumin is believed to have hypolipidemic activity by suppressing lipogenic enzymes and expression such as peroxisome proliferator-activated receptor-α, acetyl-CoA carboxylase, and sterol-regulatory element-binding protein-1, downregulating fatty acid synthase, and increasing

lipoprotein lipase and fatty acid β-oxidation (Sahebkar 2014; Panahi et al. 2016). Through modulating ATP-binding cassette subfamily G member 1 (ABCG1) expression, curcumin may increase serum HDL-C levels by stimulating HDL-dependent lipid efflux (Peschel et al. 2007).

Several studies have reported that curcumin supplementation exerts its benefit in decreasing insulin resistance and fasting glucose levels (Chuengsamarn et al. 2012; Na et al. 2013). A study reported by Saraf-Bank et al. (2019) revealed that consumption of curcumin (500 mg/day, containing 95% turmeric extract, for 10 weeks) can significantly increase insulin levels. It has been suggested that curcumin may improve pancreatic function and promote insulin secretion from pancreatic cells (Ghorbani et al. 2014) (Fig. 6.7). A similar dietary intake was also found to increase insulin secretion, possibly by stimulating the glucagon-like peptide-1 secretion (Kato et al. 2017). Nevertheless, some surveys failed to identify any significant decreasing effect on glycemic indices in non-diabetic patients (Tang et al. 2008; Panahi et al. 2016). One of the largest randomized double-blinded placebo-controlled trials with curcumin involving 240 pre-diabetic participants for 9-month period was that of Chuengsamarn et al. (2012). In this phenomenon, curcumin was used for preventive purposes in the pre-diabetic population. Notably, Chuengsamarn et al. (2012) did not identify an association between the curcumin-treated group (1500 mg of curcuminoids/day) and diabetes mellitus after 9 months of treatment. Curcumin has also been suggested to be beneficial in several parameters including improved insulin resistance, increased adiponectin levels, decreased C-peptide, insulin, and glucose concentration, and lowered waist circumference and body weight (Chuengsamarn et al. 2012). The previous study suggests that a protective role of curcumin on diabetes by lowering the circulating IL-6 levels (Usharani et al. 2008; Na et al. 2014). Increased inflammatory cytokine IL-6 levels have been identified as an independent predictor of type 2 diabetes in the European population (Spranger et al. 2003).

Diabetes nephropathy represents one of the severe microvascular complications (Sagoo and Gnudi 2020). Nearly 40% of diabetic patients develop diabetic nephropathy (Tervaert et al. 2010; Schernthaner 2011). The nephroprotective potential of curcumin has been evaluated in human studies. The study reported by Yang et al. (2015) showed that curcumin promotes renal function by modulating the urinary microalbumin and blood urea nitrogen (BUN). The nephroprotective effect is more likely due to the stimulation of the Nrf2 antioxidative system in the lymphocytes of type 2 diabetes mellitus patients treated with curcumin. This mechanism of action has also been demonstrated in animal models of diabetes (Kim et al. 2016). However, the findings in clinical trials are inconsistent to a certain degree. Jiménez-Osorio et al. (2016) did not identify any positive effect on Nrf2 and proteinuria in patients with nondiabetic or diabetic proteinuric chronic kidney disease who received curcumin (320 mg/day for 8 weeks). Similarly, Panahi et al. (2017a) also did not identify an association of curcuminoids and glycosylated hemoglobin or glucose levels in type 2 diabetes mellitus patients who received curcuminoids (1000 mg/day) mixed with piperine for 12 weeks. From the study reviewed, administration of curcumin increased SOD1 activity and total antioxidant capacity and decreased

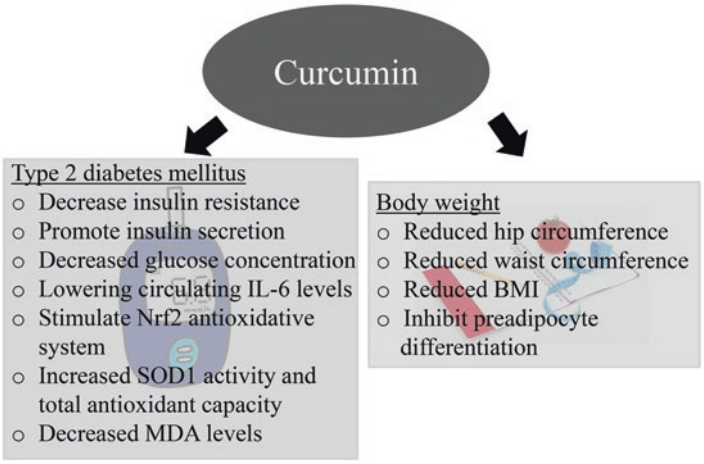

Fig. 6.7 Mechanisms of curcumin in the modulation of type 2 diabetes mellitus and body weight. *BMI* body mass index, *IL-6* interleukin-6, *MDA* malondialdehyde, *Nrf2* nuclear factor erythroid 2-related factor 2, *SOD1* superoxide dismutase 1

malondialdehyde (MDA) levels (Panahi et al. 2017a). Data from *in vitro* study has revealed that curcuminoids can suppress the activity of the cytochromes, for instance, CYP3A4, CYP2E1, CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP1B1, and CYP1A2, and upregulated the activity of CYP1A1 (Bahramsoltani et al. 2017). Furthermore, clinical studies have demonstrated that curcumin triggers CYP2A6 and suppresses CYP1A2 (Bahramsoltani et al. 2017). This finding suggests a potential pharmacological activity between conventional drugs and curcuminoids that are metabolized by them. For example, gliquidone, glipizide, gliclazide, glimepiride, glibenclamide, and tolbutamide are anti-diabetic drugs metabolized by CYP2C9; while, glibenclamide is metabolized by CYP3A4 (Holstein and Beil 2009). A study reported by Sakunthala Devi et al. (2015) found that curcumin improved the apparent volume of distribution, the mean residence time, and the half-life at the steady manner of glibenclamide, suggesting that such effects are likely due to the reduced metabolism of drugs modulated by the suppression of hepatic and intestinal CYP3A4 (Sakunthala Devi et al. 2015). The beneficial effect of a combination of curcumin and the antidiabetic drug has also been described by Rivera-Mancía et al. (2018). Notably, co-administration of curcumin may increase the bioavailability of glibenclamide (Neerati et al. 2014). The bioavailability of glibenclamide can be influenced by permeability glycoprotein (P-gp)-modulated efflux mechanism (Neerati et al. 2014). In another study, administration of curcumin and gliclazide showed a suppressive reduction in glucose levels for both diabetic and normal rats but no pharmacokinetic interaction was found in rabbits (Vatsavai and Kilari 2016).

In addition, clinical trials have also found that curcumin (500 mg/day, containing 95% turmeric extract, for 10 weeks) reduced hip circumference, waist circumference, and body mass index (BMI) (Saraf-Bank et al. 2019) (Fig. 6.7). A crucial underlying mode of action that has been proposed to explain an inverse association

between curcumin and BMI or body weight is by stimulating the metabolic rate (Ejaz et al. 2009) via suppression of adipocytic transcriptional activity including PPAR-γ, and thereby inhibition of preadipocyte differentiation (Ejaz et al. 2009; Zhao et al. 2011). Table 6.10 summarizes the clinical trials of curcumin on metabolic ailments.

Although the beneficial effects of curcumin were demonstrated *in vivo* and *in vitro*, several clinical trials and experimental studies have revealed that the systemic bioavailability of orally administered curcumin is low. In particular, curcumin shows a rapid elimination in the urine, bile, and feces and the serum concentration often does not reach >0.1% of the intake (Anand et al. 2007), which limits the therapeutic potential of curcumin/curcuminoids. Therefore, researchers have attempted to explore the pharmacological and biological activity of curcumin and overcome its drawbacks through an efficient delivery system including co-administration with piperine (Panahi et al. 2017a, b), nanoformulation, or nanoencapsulation (de Souza Ferreira and Bruschi 2019), and phytosomes (a lecithin formulation) (Appendino et al. 2011). A study reported by Steigerwalt et al. (2012) evaluated the lecithinized curcumin delivery system in relation to diabetic retinopathy and microangiopathy. The data showed that lecithinized curcumin (200 mg/day for 4 weeks) with original medication had positive microcirculatory effects on patients suffering from diabetic retinopathy and microangiopathy (Steigerwalt et al. 2012). Emerging curcumin nanoformulations have been developed in recent decades (Wong et al. 2019) (Table 6.11). The studies are mainly focused on shielding curcumin from hydrolysis inactivation as well as enhancing curcumin's solubility and bioavailability (Karthikeyan et al. 2020). A study reported by Sun et al. (2013) found that curcumin solid lipid nanoparticles showed the inhibition of cancer cell proliferation and extended cellular uptake with enhanced chemical stability and dispersibility of the drug. Curcumin solid lipid nanoparticles have demonstrated a high solubility and improved drug release compared to curcumin alone. Curcumin solid lipid nanoparticles significantly triggered the apoptosis in breast adenocarcinoma cells (MDA-MB-231), suggesting that this formulation is useful for cancer treatment (Bhatt et al. 2018). A recent study further demonstrated that a combination of curcumin solid lipid nanoparticles and doxorubicin is used to overcome Pgp-modulated chemoresistance in triple-negative breast cancer cells (Fathy Abd-Ellatef et al. 2020). P-gp is a protein that expels xenobiotics from the intracellular space (Choi 2005), in which the expression and activity are suppressed by curcuminoids in human cell cultures (Romiti et al. 1998; Anuchapreeda et al. 2002; Chearwae et al. 2004). This nanoformulation appears to be safe and effective due to the less toxicity and high biocompatibility (Fathy Abd-Ellatef et al. 2020). In the context of diabetes mellitus, the hypoglycemic effects of curcumin are contradictory along with all the studies, despite most of the studies suggest that curcumin exert a potential effect in many diseases (Nelson et al. 2017). This favorable effect could be attributed to the suppressive effect on glycogen synthase kinase-3β (GSK-3β) that regulates the upstream and downstream factors and pathophysiology of a wide variety of diseases, for instance, Alzheimer's disease, malaria, cancer, and diabetes mellitus (Bustanji et al. 2009; Saraswati et al. 2018). Nonetheless, Nelson et al. (2017) stated

Table 6.10 Clinical studies of curcumin on age-related diseases

Subjects	Sample size	Duration/Intervention	Outcomes	References
Resected uterine cervical intraepithelial neoplasms, intestinal metaplasia, oral leucoplakia, and bladder cancer patients	25	500–8000 mg/day for 3 months/curcumin	Improved histology of precancerous lesions	Cheng et al. (2001)
Advanced pancreatic cancer patients	25	8 g/day until disease progression, with restaging every 2 months/curcumin	↓ COX-2, NF-κB expression	Dhillon et al. (2008)
Colon cancer lesions patients	44	4 g/day for 30 days/ curcumin	↓ 40% number of lesions	Carroll et al. (2011)
Postmenopausal women	32	8 weeks/150 mg/day theracurcumin	Improved FMD	Akazawa et al. (2012)
Patients with neck and head cancer	50	5 times/day for 2 weeks/ sandal wood oil (2 mL) and turmeric (2 g) based cream	Prevent radiodermatitis	Palatty et al. (2014)
Localized prostate cancer patients	199	6 months/mixture of turmeric (100 mg), broccoli (100 mg), pomegranate (100 mg), and green tea (100 mg)	The median increase in PSA was 63.8% lower than the placebo group	Thomas et al. (2014)
Healthy adults	59	8 weeks/curcumin (200 mg/day for 8 weeks)	Improved endothelial function	Oliver et al. (2016)
Dyslipidemia in diabetic patients	118	12 weeks/curcuminoids (1000 mg/day + piperine 10 mg/day)	↑ HDL-C ↓ Lp(a), non-HDL-C, and TC	Panahi et al. (2017b)
Non-alcoholic fatty liver disease patients	228	8 weeks/≥1000 mg/day curcumin	↓ ALT and AST levels	Mansour-Ghanaei et al. (2019)
Overweight and obese female adolescent	60	10 weeks/500 mg/day, containing 95% turmeric extract	Improved lipid profiles (HDL-C levels and TG/ HDL-C ratio)	Saraf-Bank et al. (2019)
Overweight and obese female adolescent	60	10 weeks/500 mg/day, containing 95% turmeric extract	↑ insulin levels	Saraf-Bank et al. (2019)
Overweight and obese female adolescent	60	10 weeks/500 mg/day, containing 95% turmeric extract	↓ Hip circumference, waist circumference, and BMI	Saraf-Bank et al. (2019)
Mild-to-moderate UC	70	8 weeks/1500 mg/day curcumin	↓ Serum hs-CRP concentration and ESR levels No significant changes in the TNF-α levels	Sadeghi et al. (2020)

ALT Alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *COX-2* cyclooxygenase-2, *ESR* erythrocyte sedimentation rate, *FMD* flow-mediated dilation, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *Lp(a)* lipoprotein(a), *NF-κB* nuclear factor-kappa B, *PSA* prostate-specific antigen, *TC* total cholesterol, *TG* triglycerides, *TNF-α* tumor necrosis factor alpha, *UC* ulcerative colitis

Table 6.11 Summary of nanoformulations curcumin on age-related diseases *in vitro* and *in vivo* studies

Age-related diseases	Co-delivery system	Cell lines and animal models	Outcomes	References
Breast cancer	Solid lipid nanoparticles	MDA-MB-231 cells	↓ Cancer cell proliferation ↑ Apoptosis	Sun et al. (2013); Bhatt et al. (2018)
Liver cancer	Dendrosomal curcumin	HepG2 and Huh7 cells (18 μM for 24, 48, and 72 h)	↑ Apoptosis in a time-dependent manner	Montazeri et al. (2016)
Skin cancer	2-FA/CA/CUR@ CMC-CA NGs (13.1 μg/mL for 48 h)	MEL-39 cell lines	↑ Percentage of apoptotic cells	Priya et al. (2020)
CVD	CUR encapsulated by carboxymethyl chitosan nanoparticle-peptide (5 mg/kg body weight)	Rat (*Rattus norvegicus*) model	Produced regression of cardiac hypertrophy	Ray et al. (2016)
CVD	CurNisNp (10 and 21 mg/kg)	Guinea pigs	Prevented the increment in hypertrophy index	Nabofa et al. (2018)
CVD	CCNP (100, 150, and 200 mg/kg) for 15 days	Rats	Prevent CK-MB leakage from cardiomyocytes	Boarescu et al. (2019)
Neurodegenerative disease	Dendrosomal nanocurcumin	Male C57BL/6 mice (12.5 mg/kg/day) for 6 weeks	↓ Accumulation and activation of astrocytes and microglia in corpus callosum of cuprizone treated mice	Motavaf et al. (2020)
Neurodegenerative disease	CUR-HA-palmitate (CUR-loaded) nanoparticles (3.8 μM for 30, 60, and 120 min)	STHdh$^{111/111}$ Huntington's disease striatal-derived cells	↓ Cell susceptibility to apoptosis	Pepe et al. (2020)
Type 2 diabetes mellitus	Curcumin nanoparticles (30 mg/mL or 60 mg/mL for 30 days)	Male albino rats	↓ Glucose level, MDA levels ↑ TAC	Abu-Taweel et al. (2020)
Type 2 diabetes mellitus	Nanocurcumin (100 and 200 mg/kg)	Male Wistar rats	↓ Insulin resistance, serum levels of FBS, VLDL, LDL, TG, and cholesterol	Shamsi-Goushki et al. (2020)

(continued)

Table 6.11 (continued)

Age-related diseases	Co-delivery system	Cell lines and animal models	Outcomes	References
Rheumatoid arthritis	Curcumin-loaded oil–water nanoemulsions or curcumin suspension (orally administered 50 mg/kg body weight once a day for 14 days)	Male Sprague Dawley rats	TNF-α and IL-1β levels in synovial fluid of curcumin-loaded oil–water nanoemulsions-treated group were more than two-fold lower than the suspension group	Zheng et al. (2015)

CA casein, *CCNP* CUR nanoparticles, *CK-MB* creatine kinase myocardial band, *CMC* carboxymethyl cellulose, *CUR* curcumin, *CurNisNp* CUR and nisin (antimicrobial peptide) based poly lactic acid nanoparticles, *FA* folic acid, *FBS* fasting blood sugar, *HepG2* hepatocarcinoma cells, *Huh7* hepatocarcinoma cells, *IL-1β* interleukin-1beta, *LDL* low-density lipoprotein, *MDA-MB-231* breast adenocarcinoma cells, *MDA* malondialdehyde, *MEL-39* melanoma cancer cell line, *NGs* nanogels, *TAC* total antioxidant capacity, *TG* triglycerides, *TNF-α* tumor necrosis factor-α, *VLDL* very-low-density lipoprotein

that the stability of curcumin should be revised carefully before considering GSK-3β activity as a therapeutic target of curcumin. So far, many curcumin nanoformulations have been developed to enhance the effectiveness of curcumin, tissue specificity, and cellular uptake (Gera et al. 2017). However, most of the nanoformulation studies are only performed in the preclinical models. The efficacy and toxicology of curcumin nanoformulation in humans have to be researched and performed in comparative randomized clinical trials before introducing to the pharmaceutical market.

6.6.2 Epigallocatechin Gallate

Green tea has become the second largest drink after water (La et al. 2019). It is one of the popular beverages consumed worldwide (Namita et al. 2012). Green tea is produced by exposing the fresh leaves of *Camellia sinensis* to hot steam or heat after plucking to minimal polyphenol oxidation (Gianfredi et al. 2018). The predominant bioactive compounds of green tea are polyphenolic components and caffeine. (−)-epigallocatechin-3-gallate (EGCG) is the most abundant catechins found in green tea (Du et al. 2012), representing nearly a third of the solid content (Potenza et al. 2007). In particular, catechins comprised 30–42% of the total dry weight of green tea (Dufresne and Farnworth 2001). In general, a cup of green tea containing nearly 150–200 mg of total flavonoids, in which 90–100 mg is catechins (Hodgson and Croft 2010).

EGCG is the physiologically active polyphenols, known for its broad spectrum of health benefits, including anti-atherogenic, anti-inflammatory, and anticancer activity (Chu et al. 2017; Yamagata 2020). Substantial studies have revealed that green tea consumption possesses a protective effect against several types of cancers (Abe and Inoue 2020; Musial et al. 2020). Preclinical studies from *in vivo* and *in vitro* studies have demonstrated that green tea polyphenols exert anticarcinogenic activity via suppression of cell proliferation and induction of apoptosis (Man et al. 2020; Yoshimura et al. 2019; Chen et al. 2020). An *in vitro* study showed that co-treated with EGCG (50 μM) for 24 h improved the sensitivity of human colon carcinoma cell line (DLD1 and HCT-116) to 5-fluorouracil (5-FU) (La et al. 2019). This study further showed that EGCG improved the activity of 5-FU by modulating the glucose-regulated proteins 78 (GRP78)/NF-κB/multidrug resistance mutation 1 (MDR1) signaling pathway in colorectal cancer cells (La et al. 2019). The data from xenografts model have also shown a similar effect, in which co-treatment with EGCG (25 mg/kg) and 5-FU (20 mg/kg) for 14 days markedly suppressed the tumor growth (La et al. 2019), implied that EGCG may synergistically enhance the activity of 5-FU by reducing the tumor burden via downregulation of drug resistance-associated protein-MDR1 (La et al. 2019). Data from a meta-analysis involving 8 cohort studies and 5 case-control studies suggested that drinking 5 cups of green tea/day can reduce breast cancer risk (Gianfredi et al. 2018) (Table 6.12). Such anticancer effect has been accredited to its antioxidant activity. Evidence from experimental studies shows that long-term exposure to polyphenols may decrease oxidative stress and chronic inflammation, and thereby suppressed the diffusion, reproduction, and proliferation of cancer cells (Mao et al. 2017; Ma et al. 2018). Importantly, accumulating evidence from *in vivo* studies highlights the inhibitory effects of EGCG on triple-negative breast cancer (TNBC) cell growth (Bimonte et al. 2020). TNBC is accounting for 15–20% of breast cancer and does not express human epidermal growth factor receptor 2 (HER2) negative (neu) markers, progesterone receptor (PR), and estrogen receptor (ER) (Bianchini et al. 2016). A high concentration of EGCG (100 μM) inhibits cell proliferation (Fig. 6.8) by inducing apoptosis via stimulation of ROS production in TNBC (Hs578T) cell lines (Braicu et al. 2011). The animal model study further showed that feeding TNBC mouse model with green tea polyphenols (1%) and EGCG (1 mg/animal in 100 μL of distilled water) for 10 weeks induced apoptosis and reduced tumor growth (Thangapazham et al. 2007).

With regard to the potential of EGCG in the treatment of Alzheimer's disease, compelling evidence from *in vivo* and *in vitro* studies has suggested that EGCG may play a neuroprotective role in Alzheimer's disease (Cascella et al. 2017; Wei et al. 2019). Wei et al. (2019) found that feeding rats with EGCG (100 mg/kg body weight for 4 weeks) significantly reduced β-amyloid ($A\beta_{1-42}$) plaque formation in brains and alleviated cognitive impairments in the aging rats with cognitive impairments (Fig. 6.8). In the brain, EGCG act as an anti-inflammatory, the signaling pathway modulatory agent, and a potent antioxidant. In a further study focused on inflammation outcome, Biasibetti et al. (2013) showed that EGCG (10 mg/kg/day for 4 weeks) improved the cognitive deficit by mediating NO metabolites in rats. Data from

Table 6.12 The effects of EGCG on age-related diseases in clinical studies

Age-related diseases	Study conditions	Treatment	Outcomes	References
Breast cancer	Observational study (8 cohort studies and 5 case-control studies)	5 cups of green tea/day	↓ Breast cancer risk	Gianfredi et al. (2018)
Cognitive dysfunction	Non-blinded, non-placebo controlled design, pilot study	2 g/day for 3 months	Improved cognitive performance	Ide et al. (2014)
Alzheimer' disease	Double-blind, placebo-controlled, cross-over study	Single dose (300 mg)	↑ Theta, beta, and alpha activity, particularly in central and midline frontal regions	Scholey et al. (2012)
Type 2 diabetes mellitus	Meta-analysis of 27 randomized controlled trials	Green tea catechins ranged from 80 to 1344 mg/day for 3 weeks to 12 months	↓ Fasting blood glucose level No effect on HOMA-IR, HbA1c, and FBI	Xu et al. (2020a)
Type 2 diabetes mellitus	Meta-analysis of 8 randomized controlled trials	Green tea (400–10,000 mg/day for 8 weeks-9 months)	↓ CRP levels No effect on plasma levels of MDA and TAC	Asbaghi et al. (2019)
Type 2 diabetes mellitus	Meta-analysis of 11 randomized controlled trials	Green tea catechins (varied from ˂400 mg/day to ≥400 mg/day for ˂8 weeks to ≥8 weeks)	No effect on plasma CRP levels	Serban et al. (2015)
CVD	Meta-analysis of 10 cohort studies and seven case-control studies	3 cups per day (1 cup = 237 mL)	↓ Incidence rate of myocardial infarction by 11%	Peters et al. (2001)
CVD	Prospective cohort study	>2 cups/day, about 7 oz/day for 10 years	↓ Mortality risk of CVD by 22–33%	Kuriyama et al. (2006)
CVD	Meta-analysis of 9 randomized controlled studies	Drinking ≥3 cups of tea/day (green or black)	↓ 21% risk of ischemic stroke compared to those consuming <1 cup/day	Arab et al. (2009)

(continued)

Table 6.12 (continued)

Age-related diseases	Study conditions	Treatment	Outcomes	References
CVD	Randomized, double-blind, placebo-controlled clinical trial	1500 mg of decaffeinated green tea extract/day for 4 weeks	↓ Total cholesterol levels	Lu and Hsu (2016)
CVD	Randomized, double-blind, cross-over and placebo-controlled clinical trial	Green tea extract (one capsule 30 min after meal, 3 times/day for 6 weeks), EGCG amounted to 856.8 mg/day	↓ LDL-C levels ↑ Leptin No effect on TC, TG, and HDL-C levels	Huang et al. (2018)
CVD	Systematic review and meta-analysis analyzed of 31 randomized controlled trials	Green tea (varied from 80 to 2488.7 mg/day for 3 weeks to 12 months)	↓ LDL-C, TC, and TG levels No effect on HDL-C	Xu et al. (2020b)
Obesity	Randomized controlled trials	EGCG (800 mg/day for 8 weeks)	No changes in body fat percentage and BMI	Brown et al. (2009)
Obesity	Meta-analysis of 8 randomized controlled trials	EGCG (varied from 300 to 800 mg/day for 8–12 weeks and 300–600 mg/day for 2–3 days)	↑ Energy expenditure ↓ Respiratory quotient	Kapoor et al. (2017)

BMI body mass index, *CRP* C-reactive protein, *CVD* cardiovascular disease, *EGCG* (−)-epigallocatechin-3-gallate, *FBI* fasting blood insulin, *HDL-C* high-density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment of insulin resistance, *LDL-C* low-density lipoprotein cholesterol, *MDA* malondialdehyde, *TAC* total antioxidant capacity, *TC* total cholesterol, *TG* triglycerides

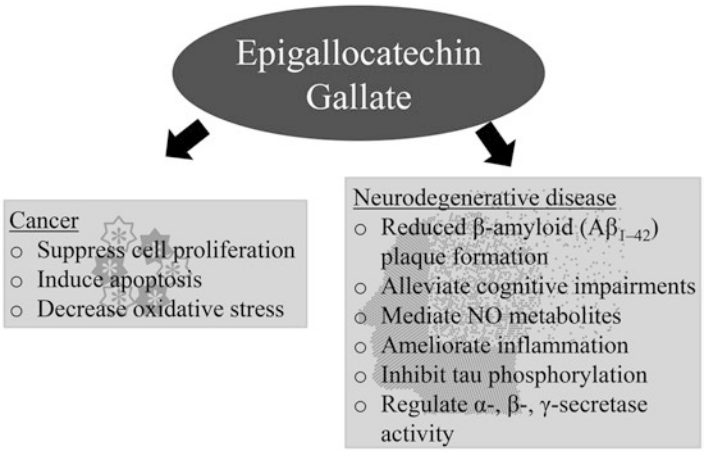

Fig. 6.8 Mechanisms of epigallocatechin gallate in the modulation of cancer and neurodegenerative disease. *NO* nitric oxide

systematic review and meta-analysis of the animal model included randomized controlled trials from inception to November 2019 have demonstrated that EGCG is inversely associated with Alzheimer's disease (Zhang et al. 2020). EGCG is thought to protect against Alzheimer's disease by suppressing acetylcholinesterase (AChE) activity, ameliorating inflammation, inhibiting tau phosphorylation, and regulating α-, β-, γ-secretase activity (Zhang et al. 2020). These findings are in line with the earlier study reported *in vitro* for MC65 cell lines, in which EGCG (20 μM) downregulates Aβ levels by reducing the nuclear translocation of c-Abl and improving the endogenous amyloid precursor protein (APP) proteolysis (Lin et al. 2009). Indeed, tau accumulation promotes load on clearance in the machinery of neurons, which may collapse, and ultimately leading to neuronal death (Keller et al. 2000; Keck et al. 2003). Notably, EGCG (64.2 μM) was shown to dissolve tau fibrils and oligomers and inhibit the heparin-triggered full-length tau aggregation (Sonawane et al. 2020). The vital role played by EGCG such as quenching the oligomers and disassembling tau filaments, implied that EGCG may be a promising tool for the amelioration of Alzheimer's disease. Consistent with the findings from preclinical studies, the evidence from a clinical study has revealed that consumption of green tea (2 g/day for 3 months) significantly improved cognitive performance in subjects with cognitive dysfunction (Ide et al. 2014) (Table 6.12). Another double-blind, placebo-controlled, cross-over study consistently reported a neurocognitive potential of administration single dose of EGCG (300 mg) (Scholey et al. 2012). From the study reviewed, Scholey et al. (2012) found that EGCG stimulates theta, beta, and alpha activity, particularly in central and midline frontal regions. In general, alpha activity is characterized by large rhythmic waves that are linked to relaxation and less in the active cognitive process. Beta activity is alleviated by movement and stimulates behavioral arousal and focused attention. Theta activity is mainly linked to quiet wakefulness (Cantero et al. 2003). Further, EGCG treatment can also decrease self-rated stress and increased self-rated calmness (Scholey et al. 2012), suggesting that EGCG may provide more attentive and relaxed conditions after consuming green tea. An extensive body of systematic review of the cohort, cross-sectional, cross-over studies, and randomized controlled trials has demonstrated a beneficial role of green tea supplementation (Mancini et al. 2017). From the study reviewed, it showed that green tea can influence brain function, cognition, and psychopathological symptoms (Mancini et al. 2017). Such finding highlights the neuroprotective effect of green tea may be modulated partly through synergistic/additive effects of the bioactive compounds in green tea (Mancini et al. 2017).

In addition to the effects demonstrated in cancer and Alzheimer's disease, the beneficial impact of EGCG in humans has also been observed on type 2 diabetes (Fig. 6.9). The animal model study showed that treatment of EGCG (5 mg/kg/day) for 4 days intraperitoneally decreased β-cells response to the elevation of glucose in diabetic rats (Yun et al. 2006). From the study reviewed, EGCG increases insulin-immunoreactivity in β-cells and stimulates the loss of islet cell mass (Yun et al. 2006), suggesting that EGCG had prooxidant properties in the β-cells. A recent meta-analysis with 27 randomized controlled trials involving 2194 subjects has revealed a significant role of green tea consumption on glycemic control (Xu et al.

2020a) (Table 6.12). It showed that adults who consume green tea for 3 weeks to 12 months with green tea catechins ranged from 80 to 1344 mg/day can significantly reduce fasting blood glucose levels (Xu et al. 2020a). The improvements in these indices could be attributed to the tea catechins, which are one of the prominent antioxidants to alleviate oxidative stress (Mustata et al. 2005). Tea catechins are thought to decrease carbohydrate absorption from the intestine through the suppression of α-glucosidase, α-amylase, and intestinal sucrose (Collins et al. 2007). Glucose metabolism and insulin sensitivity were improved in rodents after supplemented with tea catechins and thus provide a useful approach for decreasing the type 2 diabetes risk (Wolfram et al. 2006). Further, tea catechins may also suppress hepatic gluconeogenesis by modulating protein-tyrosine phosphorylation and altering gluconeogenic gene expression in the mouse liver (Waltner-Law et al. 2002). In another meta-analysis involving 614 type 2 diabetes patients have shown that green tea (400–10,000 mg/day for 8 weeks-9 months) was effective in reducing the CRP levels (Asbaghi et al. 2019), which is known as an important inflammatory mediator to predict the incidence of CVD (Ridker 2003; Eslampour et al. 2019). This finding indicates that green tea may decrease the risk of CVD in type 2 diabetes mellitus patients by reducing CRP levels. However, a meta-analysis of 11 randomized controlled trials revealed that green tea catechins (varied from $<$400 mg/day to $\geq$400 mg/day for $<$8 weeks to $\geq$8 weeks) had no significant effect on plasma CRP levels (Serban et al. 2015). Intriguingly, both of the studies of meta-analyses showed an inconsistent finding of the effects of green tea on CRP levels. This could be partly due to the different participants included in these meta-analyses. Indeed, most of the meta-analyses had no specific on the types of subjects, for instance, healthy individuals or patients with certain types of metabolic ailments. Further, the human interindividual polymorphism may affect the metabolic rate and bioavailability of the tea flavonoids (Serban et al. 2015). In addition, Xu et al. (2020a) did not identify a significant effect of green tea (80–1344 mg/day for 3 weeks–12 months) on homeostasis model assessment of insulin resistance (HOMA-IR), HbA1c, and fasting blood insulin (FBI). A study by Asbaghi et al. (2019) also found that green tea consumption (400–10,000 mg/day for 8 weeks to 9 months) had no significant effect on plasma levels of MDA and total antioxidant capacity in type 2 diabetes mellitus patients aged 52 years old and above.

EGCG supplementation not only decreases cancer, neurodegenerative disorder, and diabetes but also induces protective cardiometabolic effects (Fig. 6.9). Meta-analysis of population studies concerning tea consumption suggests that drinking 3 cups of tea/day decreases the risk of ischemic stroke and myocardial infarction by 21% and 11%, respectively (Peters et al. 2001; Arab et al. 2009) (Table 6.12). A recent systematic review and meta-analysis analyzed of 31 randomized controlled trials from inception to September 2019 including 3321 individuals showed that green tea consumption (varied from 80 to 2488.7 mg/day for 3 weeks to 12 months) significantly reduced low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and TG levels (Xu et al. 2020b). Nonetheless, Xu et al. (2020b) did not identify an association between green tea consumption and HDL-C. Consistent with the study reported by Xu et al. (2020b), Lu and Hsu (2016) and Huang et al. (2018) also

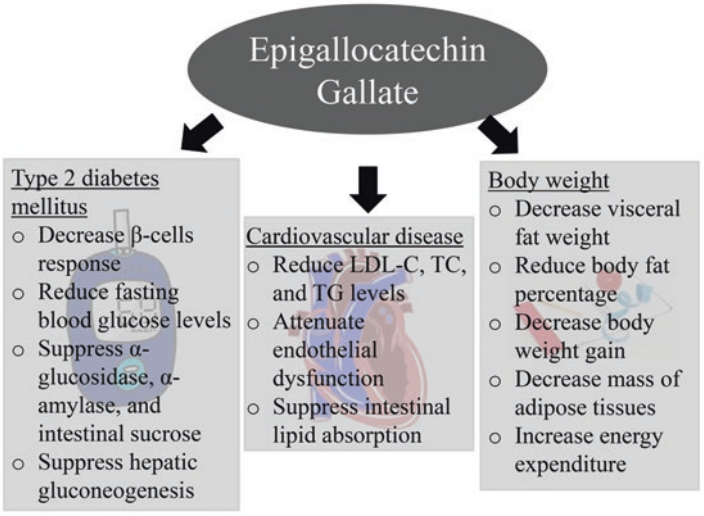

Fig. 6.9 Mechanisms of epigallocatechin gallate in the modulation of type 2 diabetes mellitus, cardiovascular disease, and body weight. *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglycerides

found that no association between green tea intake and HDL-C levels. Further, some observational study has emerged to suggest that green tea is negatively linked to the risk of CVD (Xu et al. 2020b). The previous study stated that compared to the non-tea drinkers, the mortality risk of CVD was reduced by 22–33% in middle-aged individuals from Japan who consuming green tea (>2 cups/day, about 7 oz/day for 10 years) (Kuriyama et al. 2006). Green tea is believed to have hypolipidemic activity by attenuating the endothelial dysfunction triggered by ox-LDL through the Jagged-1/Notch signaling pathway in human umbilical vein endothelial cells and thereby suppressing the atherosclerotic plaque formation (Wang et al. 2018c). Further, green tea may also suppress intestinal lipid absorption by interrupting micelle formation (Koo and Noh 2007).

Several studies have revealed that genetically obese or high-fat diet (HFD) rodents who consume EGCG or green tea extract are negatively associated with adiposity or body weight gain compared to those who never receive EGCG (Li et al. 2018). Compelling evidence has corroborated these data and found that dietary supplementation of EGCG (3.2 g/kg diet for 16 weeks) significantly decreased visceral fat weight, body fat percentage, and body weight gain (Fig. 6.9) in mice compared to those who never receive EGCG (Bose et al. 2008). Further, Lee et al. (2009) compared different groups of C57BL/6J mice fed with HFD treated with 0.2 or 0.5% EGCG (w/w) and a high-fat control diet for 8 weeks. The data showed that EGCG significantly decreased the mass of adipose tissues and body weight (Lee et al. 2009). Consistent with the studies reported by Lee et al. (2009), Li et al. (2018) also found that feeding HFD mice with EGCG (50 mg/kg and 100 mg/kg per day for 20 weeks) reduced epididymal fat and obesity. From the study reviewed,

administration of EGCG increased the concentration of HDL-C and reduced the levels of LDL-C, cholesterol, and TG (Li et al. 2018). An emerging role of EGCG in relation to lipid metabolism has been demonstrated and the effect of AMPK on lipolysis, lipogenesis, and adipogenesis has been proposed (Yang et al. 2016). Research evidence indicates that EGCG (100 mg/kg per day for 20 weeks) is of benefit in the upregulation of AMPK activity in epididymal and subcutaneous adipose tissues, indicates that EGCG may mediate the lipid metabolism partly via AMPK activation in adipose tissues (Li et al. 2018). Moreover, data from systematic review and meta-analysis of randomized controlled trials have demonstrated that EGCG supplementation (varied from 300 to 800 mg/day for 8–12 weeks and 300 to 600 mg/day for 2–3 days) moderately increase energy expenditure and decrease respiratory quotient (Kapoor et al. 2017) (Table 6.12). Despite some evidence have demonstrated an inverse association between EGCG and body weight gain, not all studies showed such a link. Brown et al. (2009) did not identify the changes in body fat percentage and BMI among individuals who consumed high concentration of EGCG (800 mg/day), which is about 2.5 times that applied in other randomized controlled trials for 8 weeks of the period. In this regard, the intakes of as low as 300 mg of EGCG/day may have the potential to stimulate fat metabolism (Kapoor et al. 2017). Indeed, the concentration of 300 mg EGCG/day is listed in the established list of plants authorized in food supplements in French regulatory (Guillaume 2014). It has also been reported as an acceptable dosage by the Japanese Consumer Affairs Agency under the health claim laws of the labeling system (White Paper on Consumer Affairs 2015). Overall, the aforementioned findings suggest that EGCG may become a useful approach to improve age-related chronic diseases.

6.6.3 Resveratrol

Resveratrol is a stilbenoid known as *trans*-3,4′,5-trihydroxystilbene, comprised of two aromatic rings which are bound with a methylene bridge (Salehi et al. 2018). Resveratrol is found naturally in over 70 different plant species including legumes, pines, and grapevines (Soleas et al. 1997). In brief, resveratrol is a naturally occurring polyphenol, which is widely found in pomegranates, soybeans, and peanuts (Sinha et al. 2016) (Fig. 6.10). Botrytis cinerea infection in grapes can cause the exclusive synthesis of resveratrol in the grape skins and leaf epidermis (Hasan and Baek 2013). Indeed, grape skins are not undergone fermentation during white wine production, and thus only red wines contain remarkable levels of resveratrol (Fuhrman et al. 2001). Resveratrol exists as *cis*/*trans* isoforms, in which the *trans* isomer is the predominant form (Gambini et al. 2015).

Substantial evidence suggests that resveratrol exhibits a broad range of health-promoting effects including neuroprotective, vasorelaxant, cardioprotective, anticarcinogenic, immune-modulator, anti-hyperlipidemic, antioxidant, and anti-inflammatory activity (Bo et al. 2013; Andrade et al. 2018; Colica et al. 2018; Pannu and Bhatnagar 2019; Xiao et al. 2019). Resveratrol acts as a potent

antioxidant by reducing oxidative stress, one of the predominant contributors to chronic diseases, via several redox-related signaling pathways (Petrella et al. 2020; Wang et al. 2020). For instance, resveratrol promotes the phosphatase and tensin homolog (PTEN) and subsequently leading to the downregulation of Akt phosphorylation, and ultimately increased the antioxidant enzymes such as SOD and catalase (Ingles et al. 2014). Further, resveratrol is also enhanced the antioxidant defense system by mediating antioxidant enzymes via decreased ERK stimulated by ROS (Singh and Vinayak 2017). A systematic review and meta-analysis of 6 randomized clinical trials involving 299 participants revealed that supplementation of resveratrol (varied from ≤500 mg/day and ≥500 mg/day of resveratrol for 1.5 to 5 months) increased the circulating GPx levels; whereas no association was reported between resveratrol supplementation and MDA, total antioxidant capacity, or SOD levels (Omidian et al. 2020). In a further study focused on oxidative stress markers, Seyyedebrahimi et al. (2018) showed that patients with type 2 diabetes mellitus who received resveratrol (800 mg/day for 2 months) had no effect on MDA levels. Despite resveratrol is absorbed rapidly, yet the systemic bioavailability is ˂1% (Goldberg et al. 2003; Walle et al. 2004). In general, the antioxidant activities of resveratrol include (1) inducing autophagy through transcription factor EB (TFEB)-dependent or mammalian target of rapamycin (mTOR)-dependent pathway (Zhou et al. 2019); (2) upregulating the gene expression involved in mitochondrial energy biogenesis, primarily via PTEN/Akt, ERK/p38 MAPK, and AMPK/Sirtuin 1 (SIRT1)/Nrf2 signaling pathways (Ungvari et al. 2011); (3) enhancing endogenous antioxidant enzymes (Tung et al. 2014); (4) scavenging free radicals (Cicero et al. 2019); (5) decreasing RNS/ROS production (Lorenz et al. 2003; Zhu et al. 2020).

The antidiabetic potential of resveratrol in diabetes mellitus has been described by Oyenihi et al. (2016) and Öztürk et al. (2017). Emerging research evidence on animal models indicates that resveratrol exerts glucose-lowering effects by improving clinical and biochemical parameters of diabetes-induced liver injury (Hamadi et al. 2012; Hussein and El-Maksoud 2013), diabetes-induced CVD (Turan et al. 2012; Guo et al. 2014; Mohammadshahi et al. 2014), diabetes-induced hypertension (Allah and El-Debakey 2010; Vella et al. 2015), diabetic retinopathy (Hua et al. 2011; Kubota et al. 2012; Kim et al. 2012; Soufi et al. 2012), diabetic neuropathy (Kumar et al. 2007, 2013; Bastianetto et al. 2015), and diabetic nephropathy (Xu et al. 2014; Wu et al. 2012; Elbe et al. 2015). These findings implied that resveratrol may mediate pancreatic β cells and improve insulin action (Fig. 6.11), and thus prevent the complications of diabetes mellitus (Szkudelski and Szkudelska 2015).

A randomized, double-blind, placebo-controlled clinical trial evaluated resveratrol administration in relation to diabetic nephropathy. The study showed that resveratrol supplementation (500 mg/day for 90 days) significantly decreased the mean of urine albumin/creatinine ratio and increased serum antioxidant enzymes in patients with type 2 diabetes and albuminuria (Sattarinezhad et al. 2019). From the study reviewed, resveratrol administration failed to show any benefit in improving the estimated glomerular filtration rate (eGFR) and serum creatinine level (Sattarinezhad et al. 2019). The finding in this study suggests that resveratrol may be an effective adjunct to angiotensin receptor blockers (ARBs) for decreasing

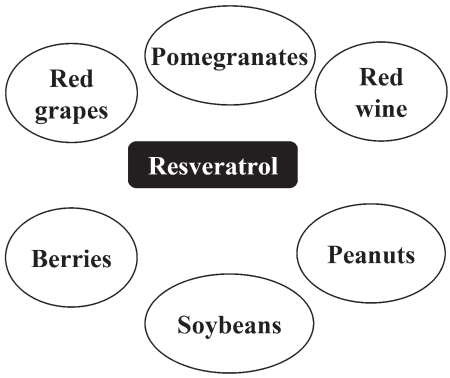

Fig. 6.10 Sources of dietary resveratrol

urinary albumin excretion in patients with diabetic nephropathy. Resveratrol has shown a hypoglycemic effect by activating the SIRT1 signaling pathway (Yun et al. 2012). The previous study has stated that administration of resveratrol significantly reduced SIRT1 expression and activity *in vitro* and *in vivo* models of diabetes mellitus (Lagouge et al. 2006; Milne et al. 2007; De Kreutzenberg et al. 2010; Yar et al. 2011). Resveratrol regulates glucose homeostasis by activating the AMPK. Indeed, AMPK mediates several prominent intracellular processes including cellular homeostasis, mitochondrial function, and energy metabolism (Herzig and Shaw 2018). Under hyperglycemic circumstances, the dysregulation of AMPK activity is linked to hyperglycemic-related tissue damage and insulin resistance, suggesting an interrelated stimulation of the AMPK and type 2 diabetes mellitus (Oyenihi et al. 2016). Table 6.13 summarizes the clinical studies of resveratrol on several age-related diseases.

Besides its effects on diabetes mellitus, a beneficial effect of resveratrol supplementation has also been demonstrated on the CVD risk (Fig. 6.11). In randomized, double-blind, cross-over trial involving 50 healthy adult smokers revealed that resveratrol (500 mg/day for 30 days) significantly increased total antioxidant status and decreased TG and CRP levels (Bo et al. 2013). A 1-year follow-up study including 75 patients further supported that intake of 8 mg of resveratrol for the first 6 months and a double concentration for the next 6 months demonstrated that resveratrol-rich grape supplement improved the fibrinolytic status and inflammation in patients who were on statins and at high CVD risk (Tomé-Carneiro et al. 2012). Similarly, a double-blind, placebo-controlled trial including 40 post-infarction Caucasian patients showed that intakes of resveratrol (10 mg/day for 3 months) decreased LDL-C levels, improved endothelial function, enhanced left ventricle diastolic function, and protected against unfavorable hemorheological changes in patients with coronary artery disease (Magyar et al. 2012), suggesting the cardioprotective potential of resveratrol. Although most of the studies have reported a negative link between resveratrol and CVD risk, not all findings showed such a link. Compared to those who received 300 mg and placebo group, a high concentration of resveratrol (1000 mg/day for 90 days) increased the biomarkers of CVD risk

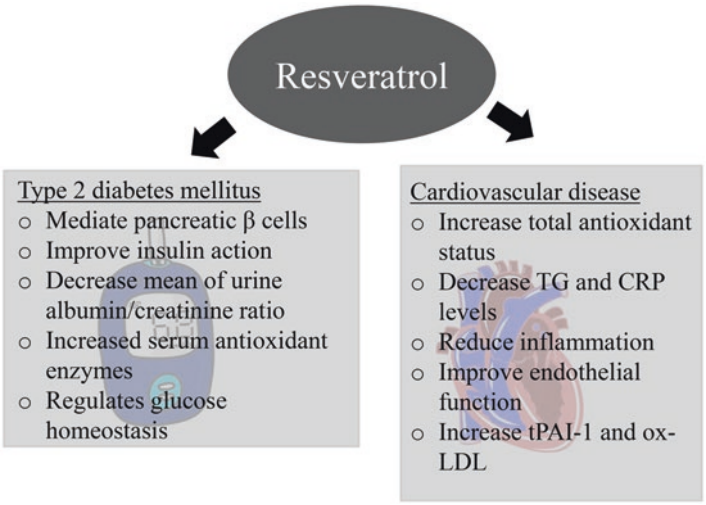

Fig. 6.11 Mechanisms of resveratrol in the modulation of type 2 diabetes mellitus and cardiovascular disease. *CRP* C-reactive protein, *ox-LDL* oxidized low-density lipoprotein, *TG* triglycerides, *tPAI-1* total plasminogen activator inhibitor-1

including total plasminogen activator inhibitor-1 (tPAI-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble E-selectin 1 (sE-selectin 1), and ox-LDL in overweight individuals aged 65 years old and above (Mankowski et al. 2020). Consistent with the study reported by Mankowski et al. (2020), administration of 150 mg/day of resveratrol for 4 weeks in overweight individuals also failed to show any benefit in improving the metabolic risk markers, for instance, inflammation or endothelial function, which are linked to cardiovascular health risk (van der Made et al. 2015, 2017). Inconclusive findings could be due to the pharmacokinetics and bioavailability of resveratrol, health status of the subjects, varying of the gut microbiota, and the concentration of resveratrol. Other factors such as the form of administration (gel caps, powder, and tablet), lifestyle, gender, and age may also confound the findings. In this regard, future studies should be conducted in a similar study design and compared in the same study (Ramírez-Garza et al. 2018; Shaito et al. 2020).

Emerging evidence has suggested that resveratrol protects against neural degeneration and injuries in dementia and Alzheimer's disease. In the brain, resveratrol acts as a potent anti-oxidative and anti-inflammatory agent by modulating different signaling pathways including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), SIRT1, and AMPK (Kulkarni and Cantó 2015). These metabolic regulators have been demonstrated to be involved in the onset of neurodegenerative disorders (Pasinetti et al. 2015). Indeed, brain tissues are susceptible to oxidative stress due to their low concentration of antioxidants, less regenerative capability, high amounts of peroxidizable fatty acids, and high rate of oxygen consumption (Salim 2017). Free radicals have been considered as the underlying factor

Table 6.13 The clinical studies of resveratrols on age-related diseases

Age-related diseases	Study conditions	Treatment	Outcomes	References
Type 2 diabetes mellitus	Randomized, double-blind, placebo-controlled	500 mg/day for 90 days	↓ Mean of urine albumin/creatinine ratio	Sattarinezhad et al. (2019)
			↑ Serum antioxidant enzymes	
			No effect on eGFR and serum creatinine level	
CVD	Randomized, double blind, cross-over study	500 mg/day for 30 days	↑ Total antioxidant status	Bo et al. (2013)
			↓ TG and CRP levels	
CVD	Triple-blinded, randomized, parallel, dose-response, placebo-controlled, 1-year follow-up trial	8 mg for the first 6 months and a double concentration for the next 6 months	Improved the fibrinolytic status and inflammation	Tomé-Carneiro et al. (2012)
CVD	Double-blind, placebo controlled trial	10 mg/day for 3 months	↓ LDL-C levels	Magyar et al. (2012)
			Improved endothelial function	
			Enhanced left ventricle diastolic function	
			Protected against unfavorable hemorheological changes	
CVD	Randomized placebo-controlled trial	150 mg/day for 4 weeks	No effect on inflammation and endothelial function	van der Made et al. (2015, 2017)
CVD	Randomized, placebo-controlled trial	1000 mg/day for 90 days	↑ Biomarkers of CVD risk such as tPAI-1, sVCAM-1, sICAM-1, sE-selectin 1, and ox-LDL	Mankowski et al. (2020)
Alzheimer's disease	Randomized, placebo-controlled, double-blind, multi-site, phase 2 trial	500 mg/day with 500 mg increments every 13 weeks up to 52 weeks, ending with 1000 mg twice/day	↓ MMP-9 expression	Moussa et al. (2017)
			Attenuated the declines in cerebrospinal fluids Aβ42 and Aβ40 levels	

(continued)

Table 6.13 (continued)

Age-related diseases	Study conditions	Treatment	Outcomes	References
Alzheimer's disease	Randomized, double-blind, placebo-controlled trial	500 mg/day with 500 mg escalation every 13 weeks up to 52 weeks, ending with 1000 mg twice/day	Attenuated the decline in plasma Aβ40 and cerebrospinal fluid Aβ40 ↑ brain volume loss	Turner et al. (2015)
Colorectal Cancer	Intervention study	8 daily doses at 0.5 or 1.0 g prior to surgical resection	↓ Tumor cell proliferation by 5%	Patel et al. (2010)
Colorectal cancer	Phase I pilot clinical trial	Freeze-dried grape powder (80 g/day containing 0.07 mg of resveratrol for 2 weeks)	↓ Wnt target genes of the normal mucosa No effect on the cancerous tissues	Nguyen et al. (2009)
Cancer	Prospective cohort study	24-h urinary resveratrol metabolites	No association between 24 h total urinary resveratrol metabolite and cancer or inflammatory markers such as IL-1β, IL-6, and CRP	Semba et al. (2014)
Prostate cancer	Randomized, placebo controlled clinical study	Two doses, 1000 mg/day for 4 months	↓ Serum levels of the androgen precursors DHEAS, DHEA, and androstenedione No association between resveratrol and dihydrotestosterone, free testosterone, testosterone, circulating levels of PSA or prostate size	Kjaer et al. (2015)

CRP C-reactive protein, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *DHEA* dehydroepiandrosterone, *DHEAS* dehydroepiandrosterone-sulphate, *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein cholesterol, *MMP-9* matrix metalloproteinase-9, *ox-LDL* oxidized-low density lipoprotein, *PSA* prostate-specific antigen, *sE-selectin 1* soluble E-selectin 1, *sICAM-1* soluble intercellular adhesion molecule-1, *sVCAM-1* soluble vascular cell adhesion molecule-1, *TG* triglycerides, *tPAI-1* total plasminogen activator inhibitor-1

for the pathogenesis of brain aging and neurodegenerative diseases (Islam 2017). The previous study found that resveratrol possesses scavenging properties by reducing free radicals production in tissues (Fu et al. 2018). A study reported by Huang et al. (2011) showed that resveratrol (100 μM for 7 days) downregulated Aβ-induced iNOS expression (Fig. 6.12), which is involved in the HO-1 inhibition and Aβ-induced lipid peroxidation, and subsequently suppress Aβ-induced neurotoxicity in rats, suggesting that resveratrol may exert neuroprotectant against Aβ. Amyloid β peptide is one of the predominant components of amyloid plaques that interacts with several toll-like receptors (TLRs) including TLR4 and thereby stimulate microglial activation (Chen et al. 2017). The previous study has demonstrated that resveratrol can prevent the LPS-induced activation of microglial BV-2 cells and murine RAW 264.7 macrophages (Capiralla et al. 2012; Ge et al. 2019). Resveratrol was found to prevent the proinflammatory activity of Aβ on macrophages by suppressing stimulation of signal transducer and activator of transcription 3 (STAT3) and STAT1 and inhibiting the NF-κB activation by modulating the IκB and IKK phosphorylation (Capiralla et al. 2012). A study in the animal model has revealed that feeding mice with 350 mg/kg body weight of resveratrol for 15 days decreased cerebral amyloid deposition and reduced Aβ related to microglial activation (Capiralla et al. 2012). Despite the animal studies showed a promising result, the clinical trials evaluated the effect of resveratrol on Alzheimer's disease remain scarce. Clinical studies from Phase II trial have shown that resveratrol is beneficial to be consumed in patients with mild to moderate Alzheimer's disease (Turner et al. 2015; Moussa et al. 2017). The previous study showed that Alzheimer's disease patients who supplemented with resveratrol (500 mg/day with 500 mg increments every 13 weeks up to 52 weeks, ending with 1000 mg twice/day) downregulated matrix metalloproteinase-9 (MMP-9) expression (Moussa et al. 2017). Notably, a greater reduction of cerebrospinal fluids Aβ42 and Aβ40 expression for those who consumed placebo compared to the resveratrol group, implied that resveratrol attenuated the declines in cerebrospinal fluids Aβ42 and Aβ40 levels (Moussa et al. 2017). The decrease in MMP-9 levels suggested that resveratrol may protect the central nervous system by decreasing the permeability and thus limit the proinflammatory agents and infiltration of leukocytes into the brain (Moussa et al. 2017). Further, ameliorating of cerebrospinal fluid Aβ40 and Aβ42 levels in Alzheimer's disease patients who received resveratrol indicates a lower accumulation of Aβ in the brain (Thordardottir et al. 2017). Consistent with the study reported by Moussa et al. (2017), Turner et al. (2015) also found that resveratrol treatment (500 mg/day with 500 mg escalation every 13 weeks up to 52 weeks, ending with 1000 mg twice/day) attenuated the decline in plasma Aβ40 and cerebrospinal fluid Aβ40. From the study reviewed, resveratrol administration increased the brain volume loss compared to those who consumed placebo (Turner et al. 2015). Nonetheless, the underlying mechanisms of brain volume loss require further elucidation; the experimental study indicates that they are not related to functional or cognitive decline (Turner et al. 2015).

Numerous studies revealed that resveratrol administration is linked to the lower risk of several types of cancer. Resveratrol prevents cancers via a few mechanisms including suppress tumor proliferation, metastasis, and angiogenesis, induce

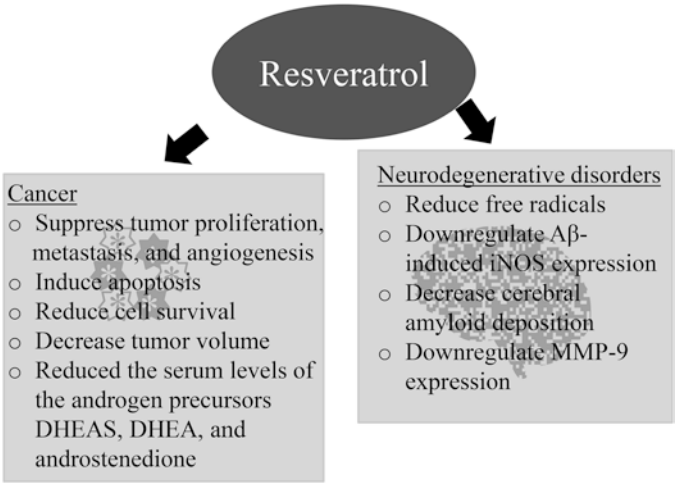

Fig. 6.12 Mechanisms of resveratrol in the modulation of cancer and neurodegenerative disorders. *DHEA* dehydroepiandrosterone, *DHEAS* dehydroepiandrosterone sulphate, *iNOS* inducible nitric oxide synthase, *MMP-9* matrix metalloproteinase-9

apoptosis, and reduce cell survival (Ferraz da Costa et al. 2018; Ko et al. 2017; Wu et al. 2018; Rodríguez-Enríquez et al. 2019) (Fig. 6.12). A study found that feeding 40 mg/kg/day of resveratrol orally for 30 days decreased tumor volume in cigarette smoke condensate transformed MCF-10A-Tr cells-mediated tumors in female xenograft BALB/c mice (Mohapatra et al. 2014). In a further study focused on ovarian cancer, Tan et al. (2016) showed that resveratrol (160 mg/kg intraperitoneally per day for 14 days) suppressed tumor regrowth after cisplatin in a xenograft mouse model of ovarian cancer compared to the vehicle control group, suggesting that resveratrol has the potential to prolong disease-free survival. In line with this, data from population-based studies further demonstrated that patients with colorectal cancer who consumed eight daily doses of resveratrol (0.5 or 1.0 g) before surgical resection reduced tumor cell proliferation by 5%, suggesting that administration of resveratrol at 0.5 or 1.0 g may sufficient elicit anticarcinogenic effect (Patel et al. 2010). The Wnt signaling pathway is known to be involved in the development of colon carcinogenesis (Kirsanov et al. 2020). Nguyen et al. (2009) found that freeze-dried grape powder (80 g/day containing 0.07 mg of resveratrol for 2 weeks) downregulated the Wnt target genes of the normal mucosa, but had no effect on the cancerous tissues. This finding suggests that freeze-dried grape powder of resveratrol may prevent colon cancer rather than the treatment of colon cancer. In a further study focused on prostate cancer, Kjaer et al. (2015) evaluated the effects of resveratrol (two doses, 150 mg or 1000 mg/day for 4 months) on sex steroid hormones, PSA, and prostate size in middle-aged men with metabolic syndrome. The study showed that administration of 1000 mg resveratrol/day for 4 months significantly reduced the serum levels of the androgen precursors dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), and androstenedione compared

to the control group (Kjaer et al. 2015). However, Kjaer et al. (2015) did not identify an association of resveratrol and dihydrotestosterone, free testosterone, testosterone, circulating levels of PSA, or prostate size. In this regard, evidence from this study failed to show any benefit in delaying the pathologic process of benign prostate hyperplasia during 4 months of administration of resveratrol (Kjaer et al. 2015). Intriguingly, a follow-up study for 9 years including 783 community-dwelling women and men aged 65 years and above had revealed that 24 h total urinary resveratrol metabolite was not associated with cancer or inflammatory markers such as IL-1β, IL-6, and CRP (Semba et al. 2014). Resveratrol is metabolized rapidly predominantly into sulfate conjugates and glucuronide that are excreted through urine (Ko et al. 2017). Due to the poor bioavailability of resveratrol, a high dosage (up to 5 g/day) has been used in the studies. A study found that participants who received resveratrol >1 g/day can lead to adverse outcomes such as abdominal pain, nausea, and diarrhea (Patel et al. 2011). Poor bioavailability of resveratrol is a major issue in extrapolating its effects. Therefore, different strategies have been developed to improve its bioavailability (Smoliga and Blanchard 2014), for instance, nanotechnology formulation (Cláudia Santos et al. 2019), micronized powders (Howells et al. 2011; Popat et al. 2013), using prodrug approach (Liang et al. 2013), and combination with phytochemical piperine (Johnson et al. 2011). Taken together, resveratrol might be a useful approach for ameliorating age-related diseases. The crucial role played by resveratrol on chronic diseases worth further elucidation in long-term randomized clinical trials.

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Chapter 7
The Role of Antioxidant on Health and Age-Related Diseases in Aging

7.1 Low Molecular Weight Antioxidant

Low molecular weight antioxidant (LMWA), for instance, phenolic compounds, glutathione, carotenoids, vitamins E and C, lipoic acid, and uric acid are critical antioxidative defense mechanisms of organisms and cells (Grune et al. 2005; Tan et al. 2018). LMWA is a small molecule (˂900 daltons) biological compound that mediates the physiological process in the body (Macielag 2012; Veber et al. 2002). LMWA exerts preventive ability toward oxidative damage by stabilizing the redox potential of transition metals and scavenging free radicals (Kohen 1999). In particular, tocopherol (vitamin E) and ascorbic acid (vitamin C) are crucial LMWA cannot be synthesized by the human (Podda and Grundmann-Kollmann 2001). Many compounds are synthesized in the body which exerts an antioxidant potential such as coenzyme Q, keto acids, uric acid, glutathione, melanins, melatonin, taurine, and lipoic acid (Sifuentes-Franco et al. 2017).

LMWA is one of the efficient agents for the skin defense mechanism toward environmental factors, for instance, pollutants, pesticides, cigarette smoke, ozone, and ultraviolet light (Kohen and Gati 2000). The LMWA protects skin tissues by neutralizing the free radicals or chelating the metallic ions (Martins et al. 2020). In particular, vitamin E, ascorbic acid, ubiquinol, uric acid, and glutathione are detectable in the stratum corneum. The gradient capacity of LMWA in keratinocytes is inversely associated with carcinogenesis risk (Martins et al. 2020). Grammenandi et al. (2016) explored the concentration of LMWA in both nonmelanoma skin carcinomas and normal-looking adjacent. The study found that normal-looking skin showed higher ascorbic acid and uric acid concentration compared to nonmelanoma skin carcinomas. The deficiency of hydrophilic LMWA such as uric and ascorbic acids in tumor samples is likely due to the decrease of the water levels in a cancer area and thereby leading to the reduction of the solubility of hydrophilic antioxidants. Ultimately, their activities are further decreased (Grammenandi et al. 2016).

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Nonetheless, Grammenandi et al. (2016) did not identify an association of lipophilic LMWA (α-tocopherol, ubiquinol, and β-carotene) between nonmelanoma skin carcinomas and normal-looking skin. Further, aging and exposure to oxidative stress caused a significant reduction in skin water-soluble LMWA activity and levels (Kohen and Gati 2000). The skin is the outermost barrier of the body, which is susceptible to exposure to oxidative stress such as UV-irradiation (Strozyk and Kulms 2013). Oxidative stress has been implicated in the development of skin aging, namely photo-aging (Gu et al. 2020). In this regard, direct topical application or through high intake of vegetables and fruits are thought to increase amounts of LMWA and thereby may protect against oxidative stress and modulate the development of skin aging (Podda and Grundmann-Kollmann 2001).

Besides its effects on cancer and skin aging, a relatively low LMWA was also found in the rat embryos and yolk sacs cultured for 28 h under the diabetic condition *in vitro* (Ornoy et al. 1999). It has been demonstrated that diabetes caused an increase in uric acid and a decrease in vitamin E and ascorbic acid *in vitro*, indicates that dysregulation of LMWA may increase diabetes and anomalies (Ornoy et al. 1999). Moreover, research evidence also indicates that patients with type 2 diabetes mellitus had a relatively low level of LMWA (Farhood et al. 2019). Of all LMWA, glutathione is one of the predominant cellular antioxidants (Narayanankutty et al. 2019).

7.2 Glutathione

Glutathione (GSH) (Fig. 7.1) is a pleiotropic tripeptide, comprised of glutamic acid, cysteine, and glycine (Huang and Yin 2020). GSH is a crucial antioxidant present in plants, microorganisms, and animals, which is involved in the modulation of cellular homeostasis (Lushchak 2012). The synthesis of GSH involved two

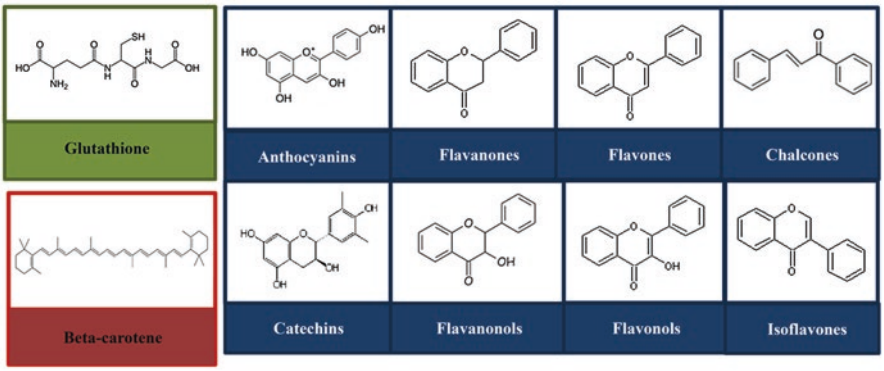

Fig. 7.1 Molecular structures of glutathione, polyphenols (anthocyanins, flavanones, flavones, chalcones, catechins, flavanonols, flavonols, and isoflavones), and beta-carotene

ATP-dependent enzymatic steps catalyzed by glutathione synthase (GS) and glutamylcysteine synthase (GCS) (Halliwell and Gutteridge 1989). GCS forms a peptide bond between cysteine and glutamate, the glycine is added with the facilitation of GS (Lu 2013). Despite GS is not crucial in the mediation of GSH synthesis, numerous evidence indicates that GS may play a pivotal role in specific tissues and/or under stressful circumstances (Luo et al. 1998). GSH contains non-protein intracellular thiol and reaching a concentration of millimolar in the intracellular region. The active thiol group exists as part of the cysteine residue and allows the GSH to serve as an antioxidant.

The function and biological role of GSH depends on the chemical structure (Calabrese et al. 2017). GSH plays a predominant role in the detoxifying of endogenous compounds and xenobiotics (Desari et al. 2018). These compounds are electrophiles and formed a conjugate with GSH catalyzed by GSH-S-transferases (GST), either enzymatically or spontaneously (Meister 1988). GSH prevents the cellular damage induced by ROS and RNS via detoxification or through GSH-dependent peroxidase-catalyzed reactions (Circu and Aw 2012). Elevation of GSH appears to be a universal cellular response against oxidative stress. By contrast, reduced GSH seems to be aggravated the development of many diseases (Ballatori et al. 2009). Nearly 90% of intracellular GSH is detected in the cytosol, while about 10–15% of intracellular GSH is found within mitochondria and the endoplasmic reticulum contains a small percentage of GSH (Lu 2009). However, impairment of the mitochondrial ETC is linked to the deficiency of GSH (Hargreavas et al. 2005). In this regard, mitochondrial depletion of GSH may lead to an elevation of ROS and depletion of ATP. Alteration of GSH levels may cause a detrimental health impact, for instance, dysregulation of transcription of detoxification enzymes, cell growth, and apoptosis (Townsend et al. 2003). Importantly, compromised GSH concentration could be a crucial indicator of various diseases due to its ability in modulating the redox balance in the body (Bhattacharjee et al. 2017). When ROS levels increased during immune response and metabolism, antioxidant including GSH concentration is increased to compensate (Nita and Grzybowski 2016; Mak et al. 2017). Subsequently, the upstream regulators are needed to mediate the recycling molecules and *de novo* synthesis to maintain optimal GSH concentration (Vomhof-Dekrey and Picklo 2012; Habib et al. 2015; Lin et al. 2016a). Nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the pivotal antioxidant regulators (Gong and Yang 2020). Nrf2 is a transcription factor linked to the antioxidant response element (ARE), a promoter region of several genes coding for antioxidant-related enzymes (Vomhof-Dekrey and Picklo 2012). During redox equilibrium, Nrf2 is restricted to the cell cytoplasm by Kelch-like ECH-associated protein 1 (Keap1). Therefore, this mechanism prevents Nrf2 from increase the transcription of antioxidant-related enzymes. By contrast, Nrf2 is dissociated to Keap1 is favored by Keap1 inhibitors. Subsequently, Nrf2 is translocated into the cell nucleus and bound with the ARE of the antioxidant-related gene promoters (Li et al. 2013; Steele et al. 2013; Pekovic-Vaughan et al. 2014; Vomund et al. 2017). The elevation of these transcriptions promotes the upregulation of GSH to mediate the redox equilibrium.

In human study, a significant decrease in blood GSH concentration was found in the healthy elderly, particularly in individuals aged 60–79 years (Lang et al. 1992). Low GSH in the elderly may increase the risk of metabolic ailments due to the reduced capacity to maintain various detoxification and metabolic reactions modulated by GSH (Lang et al. 1992). Compared with young individuals, elderly people had a relatively low GSH concentration and high plasma oxidative stress (Sekhar et al. 2011). Deficiency of GSH was linked to the increased oxidative stress in the elderly, which indicates that the primary contributor to low GSH and high oxidative stress in aging is a decreased rate of GSH synthesis, which could be due to the low availability of its precursor amino acids (Sekhar et al. 2011; Jahoor et al. 2019). Dietary supplementation of GSH precursors glycine (1.33 mmol/kg/day) and cysteine (0.81 mmol/kg/day) for 14 days is effective at restoring GSH in the elderly to the levels similar to young subjects, suggesting that replenish the supply of glycine and cysteine can restore the GSH synthesis and decrease the oxidant damage (Sekhar et al. 2011). GSH is a tripeptide of glycine, cysteine, and glutamate (Minich and Brown 2019). Elderly people have adequate glutamate concentration because amino acid nitrogen is recycled by regulating the glutamate that serves as an intermediary (Sekhar et al. 2011). Importantly, the flux of a nonessential amino acid comprises its release from *de novo* synthesis and protein breakdown (Zhang et al. 2017a). Reduced intracellular glycine and cysteine levels in the elderly could be due to the reduced *de novo* synthesis or delayed body protein turnover (Sekhar et al. 2011). Research evidence indicates the aging promotes the reduction of protein turnover, suggesting that glycine and cysteine are reduced with aging (Young et al. 1975; Golden and Waterlow 1977). Several studies revealed that feeding animals with a diet low in GSH precursor amino acids, particularly cysteine, increased the development of GSH deficiency (Grimble et al. 1992; Jahoor et al. 1995; Bella et al. 1999). In this regard, these findings showed that deficiency of intracellular GSH in aging is likely due to the reduced *in vivo* synthesis secondary to a reduced supply of the GSH precursors cysteine and glycine (Sekhar et al. 2011). Table 7.1 summarizes the effects of GSH on age-related diseases in *in vivo* and human studies.

In malignant and normal cells, the elevation of GSH concentration is linked to the proliferative response, which is required for cell cycle progression (Messina and Lawrence 1989; Lu and Ge 1992). Holmgren (1981) demonstrated that the mechanisms underlying GSH in DNA synthesis are complex and might relate to the regulation of thioredoxin and reduced glutaredoxin, which is needed for the ribonucleotide reductase activity. As opposed to the beneficial effects of the other antioxidants, GSH has a complex role in relation to cancers. GSH exhibits a dual role in cancer by inducing cancer proliferation or through safeguarding cell homeostasis from proneoplastic oxidative damage (Desideri et al. 2019). The concentration of GSH was associated with cellular proliferation and metastasis of melanoma cells and liver cancer (Gamcsik et al. 2012; Carretero et al. 1999; Huang et al. 2001; Marengo et al. 2010). An animal study has demonstrated that intrasplenic inoculation of B16 melanoma (B16M) cells into C57BL/6J mice triggered metastatic foci formation (Carretero et al. 1999). The size and number of metastatic foci were markedly increased when B16M cells with high GSH concentration were inoculated *in vivo*

Table 7.1 Effects of glutathione on age-related diseases in *in vivo* and human studies

Age-related diseases	Experimental model	Outcomes	References
Breast cancer	Breast cancer women aged 30–99 years (mean 58 years)	Associated with the clinical progression of the breast cancer	Jardim et al. (2013)
Ovarian cancer	Women with ovarian cancer	Combination of GSH and cisplatin increased the quality of life	Smyth et al. (1997)
Cancer	Systematic review of dietary supplementation of GSH in patients receiving chemotherapy with or without radiation for various malignancies	Counteract detrimental effects of cancer-induced antioxidant depletion	Ladas et al. (2004)
Type 2 diabetes mellitus	Type 2 diabetic, prediabetic, and normoglycemic subjects	Prediabetic and type 2 diabetes mellitus patients had higher erythrocyte GPx	Gunawardena et al. (2019)
Type 2 diabetes mellitus	Patients with type 2 diabetes mellitus (7 without and 9 with microvascular complications)	Diabetic patients with microvascular complications had lower erythrocyte GSH levels	Lutchmansingh et al. (2018)
CVD	Apolipoprotein E-deficient mice fed with 50 mg/kg/day of liposomal coated GSH for 2 months	Upregulated GSH concentration and decreased lipid peroxides and ox-LDL levels	Rosenblat et al. (2007)
CVD	A prospective cohort study involving 909 atrial fibrillation patients during a mean follow-up of 43.4 months	Patients with atrial fibrillation had relatively low amounts of serum GPx3	Pastori et al. (2016)
Atherosclerosis	245 type 2 diabetes mellitus patients	High concentration of GPx3 decreased the carotid plaque and carotid intima-media thickness	Ling et al. (2020)

CVD cardiovascular disease, *GPx* glutathione peroxidase, *GSH* glutathione, *ox-LDL* oxidized-low density lipoprotein

(Carretero et al. 1999). Intriguingly, high percentages of tumor cells with high GSH levels were able to proliferate in the presence of oxidative and nitrosative stress (Carretero et al. 2001). Hence, maintenance of a high intracellular concentration of GSH is crucial for the extravascular proliferation of metastatic cells (Carretero et al. 2001). Godwin et al. (1992) and Mulcahy et al. (1994) found that elevation of GSH concentration is related to the drug resistance in tumor cells. GSH is a predominant contributor to chemoresistance by participating in DNA repair processes, preventing the DNA or protein damage, interacting with ROS, and reacting with drugs (Traverso et al. 2013). A retrospective study evaluated the breast cancer tumor fragments in women aged 30 to 99 years revealed that estrogen receptor (ER)-positive

had a relatively higher GSH protein concentration compared to ER-negative (Jardim et al. 2013). Further, GPx and GSH were found to be associated with the clinical progression of breast cancer. Breast cancer patients with high GPx levels were significantly correlated with a high rate of mortality (Jardim et al. 2013). Elevation of GSH is characterized as an indicator of low response toward chemotherapy, which may further lead to the development of metastasis. It has been suggested that high amounts of ROS are produced upon exposure to doxorubicin that is responsible for the antioxidant synthesis including GPx and GSH, and thus causing the cells to be more resistant to oxidative damages (Gaudiano et al. 2000), indicated that high expression of GPx in breast cancer patients may link to the development of chemotherapy resistance (Jardim et al. 2013). Although research has revealed the detrimental impact of GSH in cancer, not all studies showed such a link. Ladas et al. (2004) found that dietary supplementation of GSH during chemotherapy was effective to counteract the detrimental effects of cancer-induced antioxidant depletion. Several studies by Nunes and Serpa (2018) have suggested that GSH could have a potential co-adjuvant of chemotherapy in ovarian cancer patients. In support of this, a clinical trial has demonstrated that the combination of GSH with cisplatin increased the quality of life in patients with advanced-stage ovarian cancer (Smyth et al. 1997).

Besides its effects on cancer, GSH also plays a crucial role in type 2 diabetes mellitus. A study by Lutchmansingh et al. (2018) evaluated the GSH in relation to type 2 diabetes mellitus with microvascular complications. The data showed that patients with type 2 diabetes mellitus showed reduced absolute synthesis rates and lower erythrocyte GSH levels, particularly to those diabetic patients with microvascular complications, compared to non-diabetic controls (Lutchmansingh et al. 2018). Circulating concentration of proinflammatory cytokines and ROS are increased in type 2 diabetes mellitus with macro- and microvascular complications, which may further decrease the GSH levels (Brownlee 2001; Nguyen et al. 2014). This finding could be attributed to the irreversible loss of GSH in diminishing the rate of synthesis and decreasing GSH levels (Lutchmansingh et al. 2018). Indeed, an irreversible utilization of GSH in diabetes may also occur with activated activity and high oxidative stress via the polyol pathway (Lutchmansingh et al. 2018). In addition, prediabetic and type 2 diabetes mellitus patients had higher erythrocyte GPx activity compared to an individual with normoglycemic (Gunawardena et al. 2019). Further, high GPx activity was also found in patients with type 2 diabetes mellitus with poor glycemic control, suggesting a compensatory adaptive response for poor glycemic control concomitantly with markedly increased lipid peroxidation (Gunawardena et al. 2019). GPx has been identified as an initial protective response to control H_2O_2 levels after oxidative damage and under normal physiological conditions (Lee et al. 2008). GPx plays a critical role in mediating the H_2O_2 balance. When the level of H_2O_2 is markedly increased through the lipid peroxidation pathway, it may elevate GPx activity (Gunawardena et al. 2019). Moreover, the study also showed that GPx is positively correlated with HbA1c of type 2 diabetes mellitus (Gunawardena et al. 2019).

GSH plays a crucial etiological role in the development of CVD and cardiometabolic disease (Bajic et al. 2019). The progression and development of CVD are characterized by substantial changes in the GSH levels and oxidation state (Espinosa-Díez et al. 2018). Rosenblat et al. (2007) exploring the impact of GSH on atherosclerosis using liposomes. The data showed that feeding atherosclerotic apolipoprotein E-deficient mice with 50 mg/kg/day of liposomal coated GSH for 2 months decreased lipid peroxides and ox-LDL levels and upregulated the GSH concentration. This favorable effect is likely due to the ability of GSH to increase the 7 alpha-hydroxylase cholesterol levels, and subsequently promotes the biosynthesis of bile acids from cholesterol (Hassan et al. 1993; Lin et al. 2004). A 43.4-month follow-up prospective cohort study conducted from September 2007 to October 2015 involving 909 patients with atrial fibrillation showed that patients with atrial fibrillation had relatively low amounts of GPx3 in serum compared to those without cardiovascular disease (Pastori et al. 2016). The study further demonstrated that GPx3 activity progressively declines with aging, with a marked reduction in elderly aged ≥70 years (Pastori et al. 2016). These findings suggest that decreasing natural antioxidants could be a predisposing factor to cardiovascular events in the elderly (Pastori et al. 2016). Of all glutathione peroxidase isoforms, GPx3 is the predominant form of antioxidant in plasma and only identified in the extracellular space (Holley et al. 2016). Data from the animal study further revealed that deficiency of GPx3 increased occluded vessels, enhanced platelet-rich thrombi, and stimulated platelet activation to a greater extent compared to wild-type (Jin et al. 2011). The association between thrombosis and GPx3 levels could be attributed to H_2O_2, which is a stimulus for thromboxane A_2 production (Pignatelli et al. 1998). Thromboxane A_2 is a potent aggregating molecule derived from COX-1 stimulation (Smyth 2010). Indeed, high serum GPx3 levels are associated with the decrease in carotid plaque and carotid intima-media thickness, suggesting that reduced GPx3 concentration may act as an independent predictor for carotid atherosclerosis in type 2 diabetes mellitus (Ling et al. 2020). Taken together, GSH plays a crucial role in cell redox homeostatic mode of action. It was evident that GSH involved in many intracellular homeostatic functions, hence there has been a tremendous potential to be used as a biomarker in diseases suffered by the elderly. The primary role played by GSH in pathophysiology conditions underlying age-related diseases worth further elucidation in long-term clinical trials.

7.3 Polyphenol

Polyphenol or known as polyhydroxyphenols, are characterized by several phenol structural units (Nascimento-Souza et al. 2018). Polyphenols are non-nutrient (Goñi and Hernández-Galiot 2019) or secondary metabolites (Pandey and Rizvi 2009) produced by plants, which are usually found in vegetables and fruits (Lima et al. 2014). In general, the features and number of these phenol structures contribute to the unique characteristics of the polyphenol compounds in terms of physical,

chemical, and biological (Estrela et al. 2017). Apart from that, polyphenols can affect the color, odor, and flavor which may contribute to the sensory perception of food (Pandey and Rizvi 2009). These phenolics are responsible for the attractive color of flowers, fruits, and leaves (Mikulic-Petkovsek et al. 2015). Among the polyphenolic compounds, the flavonoid is the most common class of polyphenol (Kumar and Pandey 2013). Phenolics comprised of around 8000 naturally occurring components, in which all of them exert one common structural feature, namely a phenol (Leopoldini et al. 2011). Further classification divides them into simple phenols and polyphenols, based on the number of phenol subunits. Polyphenols exert at least two phenol subunits such as stilbenes, flavonoids, and compounds that possess at least three phenol subunits, for instance, tannins. Phenolic acids are phenols that exert one carboxylic acid. It contains two distinctive constitutive carbon, namely hydroxybenzoic and hydroxycinnamic acids (Kumar and Goel 2019).

Flavonoids are the most studied group of polyphenol. The diphenylpropane skeleton is the basic structure of flavonoid, consist of two benzene rings (rings B and A) bound with three-carbon chains and formed a closed pyran ring (a heterocyclic ring containing oxygen, ring C) (de Castro Peixoto et al. 2019). The structures of flavonoids are denoted as C6-C3-C6. The B ring is connected to position 3/4. Flavonoids, for instance, genistein, fisetin, isorhamnetin, kaempferol, and quercetin are widely found in vegetables and fruits (Dou et al. 2014; Ganai and Farooqi 2015; Chin et al. 2018; Kanberoglu et al. 2019; Imran et al. 2021). In nature, flavonoid components are products derived from plants, which are found in several parts of the plants (Stankovic et al. 2011). It belongs to the category of low-molecular-weight phenolic compounds that are extensively found in the plant kingdom. Flavonoids are widely found in beverages and foods of plant origin, for instance, wine, cocoa, tea, vegetables, and fruits; hence they are also known as dietary flavonoids (Panche et al. 2016). Flavonoids are further classified into several subgroups (anthocyanins, flavanones, flavones, chalcones, catechins, flavanonols, and flavonols) (Fig. 7.1) according to the degree of unsaturation, the carbon of the ring C bound to the ring B, and the oxidation of the ring C (Panche et al. 2016). Indeed, the physiological function of the flavonoid is depends on the pattern of hydroxylation and glycosylation of the three rings and the structural characteristics (Halbwirth 2010). This subgroup has unique major sources. For instance, tea and onions are the predominant dietary sources of flavones and flavonols (Maiti et al. 2019; Li et al. 2020).

Isoflavones (Fig. 7.1) are one of the flavonoid in which the B ring is bound to the position 3 of the C ring. The B ring is linked to position 2 of the C ring, which can be further categorized into several subgroups, namely chalcones, flavones, flavonols, flavanones, and anthocyanins (Fig. 7.1 and Table 7.2).

There are nearly 6000 flavonoids that form the colorful pigments of vegetables, fruits, medicinal plants, and herbs (Kumar 2017; Li et al. 2018a). Flavonoids have long been recognized to be synthesized in certain parts and are responsible for the aroma and color of flowers (Samanta et al. 2011). The health-promoting potentials of flavonoids have been demonstrated in preclinical and clinical studies (Revathy et al. 2018; Rodríguez-García et al. 2019; Dükel et al. 2021). Substantial evidence revealed an inverse relationship between plasma or serum total antioxidant capacity

Table 7.2 Subgroups of flavonoids (Hano and Tungmunnithum 2020)

Subgroups	Characteristics
Chalcones	The absence of ring C, or known as open-chain flavonoids
Flavones	Containing a ketone on the ring C at position 4 and a double bond between positions 2 and 3. Majority of them comprised of a hydroxyl group in position 5 of ring A; whereas hydroxylation in other positions, usually at positions 3′ and 4′ of the B ring or position 7 of the A ring
Flavonols	-The largest and the most common flavonoid subgroup, comprised of a hydroxyl and a ketone group in position 3 of the ring C
	-Exhibit different patterns of glycosylation, methylation, and hydroxylation
	-Constitute the building blocks of proanthocyanin
Flavanones	Fully saturated ring C
Anthocyanins	Pigments responsible for the coloring of fruits, flowers, and plants, varying depends on the acylation or methylation of the hydroxyl groups on the rings B and A as well as the pH

and both the progression and onset of age-related diseases (Wu et al. 2017; Mullan et al. 2018). It has been suggested that antioxidant supplementation could be served as a promising therapy based on the Free Radical Theory of Aging (FRTA) (Harman 1956, 2006).

The biochemical, medicinal, and pharmacological properties of phenolics have been widely reported (Semaming et al. 2015; Kiokias et al. 2020). The anti-inflammatory, antimutagenic, anticarcinogenic, and antioxidative properties as well as their abilities to mediate prominent cellular enzyme function have drawn interest from the medicinal, pharmaceutical, cosmetic, and nutraceutical industries. Indeed, most interest has been attributed to their antioxidant activity of flavonoids by scavenging free radicals and reducing free radical formation (Treml and Šmejkal 2016).

Flavonoids are also known as potent inhibitors for enzymes including phosphoinositide 3-kinase, lipoxygenase, COX, and XO (Tronina et al. 2017; Ibrahim et al. 2018; Santi et al. 2018; Zhang et al. 2019a). A study reported by Cos et al. (1998) evaluated the structure-function activity of flavonoids. The data showed that flavonoid luteolin (tetrahydroxyflavone) is the most potent inhibitor of XO (Cos et al. 1998). XO is a source of oxygen free radicals (Dowell et al. 1993). In this regard, the ability of flavonoids in chelating trace metals plays a crucial role in oxygen metabolism (Malešev and Kuntić 2007).

Flavonoids have beneficial antioxidant activity and biochemical effects in relation to oxidative stress-induced diseases in the elderly such as neurodegenerative disease (Devi et al. 2021), diabetes mellitus (Hussain et al. 2020), CVD (Yamagata and Yamori 2020), and cancer (Liskova et al. 2020) (Tables 7.3 and 7.4). Some flavonoids such as tea catechins (Rahman et al. 2020), apigenin (Adham et al. 2021), and quercetin (Raja et al. 2017) have been found to have anti-inflammatory activity via suppressing iNOS and COX-2. The effectiveness of flavonoids in the prevention of neurodegenerative disease has been reported in recent decades (Cirmi et al. 2016; Flanagan et al. 2018; Borowiec and Michalak 2021). In particular, the study is concerned about Alzheimer's disease, Parkinson's disease, and dementia (Jung and

Table 7.3 *In vitro* and *in vivo* studies conducted in polyphenols and their effects on age-related diseases

Age-related diseases	Cell lines/ animal models	Source of polyphenols	Dosages	Findings	References
Parkinson disease	6-OHDA lesion rat model	Tangeretin, a citrus flavonoid	20 mg/kg/day for 4 days	Protect nigrostriatal pathway induced by neurotoxic substance 6-OHDA	Datla et al. (2001)
Colon and breast cancers	LoVo and MCF-7 cell lines	Peel-flavonoids (Peel-F) and flesh flavonoids (Flesh-F) extracted from Pink Lady apples	LoVo cells (Peel-F = 110.33 ± 2.52 mg/mL and Flesh-F = 378.14 ± 1.64 mg/mL)	↓ Proliferation of LoVo and MCF-7 cells	Yang et al. (2015)
			MCF-7 cells (Peel-F = 58.42 ± 1.39 mg/mL and Flesh-F = 296.06 ± 3.71 mg/mL)		
Colon cancer	Pirc rats (F344/NTac-Apc^{am1137})	Flavonoid-rich extract from bergamot juice	35 mg/kg and 70 mg/kg body weight for 12 weeks	↓ Colon preneoplastic lesions MDF	Navarra et al. (2020)
CVD	Male Wistar rats	EGCG	10 mg/kg intravenously	↓ Myocardial damage by reducing NF-κB activity and AP-1 pathway	Aneja et al. (2004)
CVD	Sprague-Dawley rats	Quercetin	5 μM for 30 min	↓ Vasoconstrictor sensitivity in rat aortic ring	Khoo et al. (2010)
Diabetes mellitus	Systematic review and meta-analysis of animal studies	Quercetin	10, 25, and 50 mg/kg	↓ Serum glucose levels	Bule et al. (2019)
Diabetes mellitus	32 male albino Wistar rats	Apple peel extract or apple juice	Apple peel extract (1 g/kg) or cloudy apple juice (15 mL/kg) for 21 days	Improved antioxidant enzyme activity	Fathy and Drees (2016)
				↓ Lipid peroxidation levels	
Osteoporosis	Three-month-old female Sprague Dawley rats	Total flavonoids of *Herba Taxilli*	400, 200, and 100 mg/kg/day for 28 days	↑ Serum calcium (Ca^{2+}) level	Li et al. (2019a)

(continued)

Table 7.3 (continued)

Age-related diseases	Cell lines/ animal models	Source of polyphenols	Dosages	Findings	References
Osteoporosis	Systematic review (including 11 animal studies and 1 human study) (between January 2016 to October 2019)	Flavonoids	–	Exert a positive effect on osteoporotic fracture healing	Chiavarini et al. (2020)

AP-1 activator protein-1, *CVD* cardiovascular disease, *EGCG* (−)-epigallocatechin-3-gallate, *LoVo* human colon cancer cell line, *MCF-7* human breast cancer cell line, *MDF* mucin-depleted foci, *NF-κB* nuclear factor-kappa B, *6-OHDA* 6-hydroxydopamine

Kim 2018; Shishtar et al. 2020; Uddin et al. 2020). Flavonoids appear to mediate neuronal function (Jaeger et al. 2018). Diets high in flavonoids were found to be beneficially affecting the human neuronal function, probably via enhancement of their regeneration and function (Cirmi et al. 2021). RNS and ROS are involved in the progression and development of neurodegenerative diseases; while dietary flavonoids have been demonstrated to combat oxidative neuronal damage (Khan et al. 2020). A study reported by Panche et al. (2015) and Jager and Saaby (2011) evaluated different plant metabolites in relation to neurodegenerative diseases. The data showed that flavonoids may perform a crucial role in receptor and key systems in the brain as well as exert a significant effect on the central nervous system. Substantial studies have been conducted on flavonoids in Alzheimer's disease using molecular docking. The study found that flavonoid is a potent acetylcholinesterase (AChE) inhibitor (Hu et al. 2009). Interestingly, flavonoids showed more potent inhibitory activity against AChE compared to rivastigmine, an Alzheimer's disease drug (Hu et al. 2009). AChE is a crucial enzyme in the central nervous system and suppression of this enzyme could result in the elevation of neural acetylcholine levels. In this regard, suppression of cholinesterases is one of the predominant focuses for drug development to combat Alzheimer's disease (Sharma et al. 2020). It has been demonstrated that a strong relationship between flavonoids and suppression of NF-κB pathway (Spagnuolo et al. 2018). The extract from *Ginkgo biloba* plant, rich in flavonoids, may beneficially affect Alzheimer's disease and dementia (Singh et al. 2019). A study in the animal model study has suggested that tangeretin (20 mg/kg/day for 4 days), a citrus flavonoid, could protect the nigrostriatal pathway induced by neurotoxic substance 6-hydroxydopamine (Datla et al. 2001). In support of this, the Personnes Age'es QUID (PAQUID study) involving 1640 subjects aged 65 years and above suggested that regular consumption of dietary

Table 7.4 The clinical studies of polyphenols on age-related diseases

Age-related diseases	Study conditions	Source of polyphenols	Durations	Outcomes	References
Dementia	Prospective epidemiologic study (1640 nondemented participants aged 65 years and above)	Flavonoids (Fruit juice, soup, coffee, tea, chocolate, oats flakes, sweet pepper, asparagus, French beans, spinach, cabbage, dried fruits, other fruits, kiwi, and/or citrus fruits)	14.33 mg/day over a 10-year period	Improved cognitive function	Letenneur et al. (2007)
Lung cancer	Case-control study (649 incident cases of primary lung cancer among women diagnosed from February 1992 to January 1994 and control group of 675 women)	Green tea	>1500 g/year	↓ Lung cancer risk in non-smoking women	Zhong et al. (2001)
Lung cancer	Meta-analysis of epidemiological studies (5 cohort and 12 case-control studies) involving 12,276 cases and 102,516 controls	Coffee	≤1 cup/day, 2–3 cups per day, or ≥3 cups/day	↑ Lung cancer risk	Xie et al. (2016)

Lung cancer	Prospective cohort study (34,708 post-menopausal women)	Flavonoids-containing foods including red wine, chocolate, tea, soy, citrus juices and fruits (orange juice, oranges, grapefruit juice, grapefruits), bran added to foods, broccoli, grapes and raisins, berries (blueberries and strawberries), and fresh pears and apples	Median intake of total flavonoids = 239.2 mg/day	↓ Lung cancer risk, particularly in women who had stopped smoking and current smokers	Cutler et al. (2008)
Lung cancer	Prospective cohort study (63,257 Singaporean Chinese men and women)	Black tea	At least 2 cups/day, with an average of 17.7 years of follow-up	↓ 33% of lung cancer risk in men compared to those who never or less-than-weekly black tea drinkers	Seow et al. (2020)
Lung cancer	Prospective cohort study (63,257 Singaporean Chinese men and women)	Green tea	More than 2 cups/day, with an average of 17.7 years of follow-up	No effect	Seow et al. (2020)
Lung cancer	Prospective cohort study (63,257 Singaporean Chinese men and women)	Coffee	One or more cups/day	↑ Risk of lung cancer compared to rarely or non-daily coffee drinkers	Seow et al. (2020)

(continued)

Table 7.4 (continued)

Age-related diseases	Study conditions	Source of polyphenols	Durations	Outcomes	References
Cancer	Cohort study (A total of 3234 incident cancer cases among 38,408 women aged 45 years and above)	Foods rich in flavonoids including tofu, onion, broccoli, apple, and tea	Median intake = 8.88–47.44 mg/day during 11.5 years of follow-up	No significant association	Wang et al. (2009)
Cancer	Cohort study (1063 women aged 75 years old and above)	Total flavonoids (from black tea, onions, pears, apples, tea, fruit juice, and oranges)	≥813 mg/day over the 5 years follow-up period	↓ Risk of cancer mortality	Ivey et al. (2015)
Gastric cancer	European Prospective Investigation into Cancer and Nutrition (EPIC) study (477,312 subjects (29.8% men) aged 35–70 years old from 10 European countries)	Total flavonoid, flavanols, flavones, flavonols, and anthocyanidins	Total flavonoid = (433.8 ± 330.6 mg/day), flavanols (350.8 ± 304.1 mg/day), flavones (3.46 ± 3.92 mg/day), flavonols (26.70 ± 17.38 mg/day), and anthocyanidins (29.51 ± 22.75 mg/day) during an average follow-up of 11 years	↓ Gastric adenocarcinoma risk in women	Zamora-Ros et al. (2012)
Gastric cancer	Prospective cohort study (1297 gastric cancer cases)	Flavonoids from 124 food items	≤84.1 mg/day or 84.2–4211.2 mg/day over a mean of 12 years follow-up	No effect	Sun et al. (2017)
Gastric cancer	Case-control study using 334 cases and 334 matched controls aged 35–75 years	Total flavonoid from black soybeans, tofu, and green tea	105.2 ± 77.9 mg/day	↓ Gastric cancer risk in women but not in men	Woo et al. (2014)
Breast cancer	A meta-analysis of case-control and prospective cohort studies (9513 cases and 181,906 controls)	Total flavonoids, flavanones, or flavan-3-ols	Total flavonoids (median intake = 19.13–29.1 mg/day), flavanones (median intake = 31.2–33.7 mg/day), or flavan-3-ols (median intake = 7.9–162 mg/day)	No significant association	Hui et al. (2013)

Breast cancer	A meta-analysis of case-control and prospective cohort studies (9513 cases and 181,906 controls)	Flavones and flavonols	Flavones (median intake = 0.13–2.5 mg/day) and flavonols (median intake = 9.8–27.8 mg/day) intake	↓ Breast cancer risk in postmenopausal women	Hui et al. (2013)
Colorectal cancer	Spanish case-control study (424 cases with incident colorectal cancer and 401 hospital-based controls)	Total flavonoid intake from vegetables, legumes, wine, and fruits	Median = 196.4 mg/day	↓ Colorectal cancer risk	Zamora-Ros et al. (2013)
Colorectal cancer	Case-control study in a Chinese population (1632 colorectal cancer cases and 1632 frequency-matched controls)	Flavonoids from fruits and vegetables	Flavones (3.67 mg/day) from lettuce, peppers, pumpkin, leaf mustard, and Chinese celery, flavanones (3.76 mg/day) from tomato, white wine, citrus juice, citrus fruits, and leaf mustard, and anthocyanidins (20.64 mg/day) from banana, apple, grapes, and vegetables (radish and eggplant)	↓ Colorectal cancer risk	Xu et al. (2016)
Colorectal cancer	Prospective cohort study from 2519 colorectal cancer cases (1061 in men, 1458 in women)	Flavonoid subclasses (anthocyanins, flavan-3-ols, flavanones, flavones, and flavonols) from onions, tea, red wine, oranges, blueberries, strawberries, pears, and apples	116–769 mg/day and 107–808 mg/day during 26 years of follow-up	No association	Nimptsch et al. (2016)
Prostate cancer	Case-control study (118 histopathological-verified prostate cancer cases and 222 controls)	Catechins and flavonols	Catechins (36.18 mg/day) and flavonols (37.14 mg/day)	↓ Prostate cancer risk	Reale et al. (2018)

(continued)

Table 7.4 (continued)

Age-related diseases	Study conditions	Source of polyphenols	Durations	Outcomes	References
Prostate cancer	Case-control study (118 histopathological-verified prostate cancer cases and 222 controls)	Flavanones	81.32 mg/day	↑ Prostate cancer risk	Reale et al. (2018)
Thyroid cancer	Prospective study of European Prospective Investigation into Cancer and Nutrition (EPIC) study	Coffee or tea	100 mL/day	No association with the total differentiated thyroid cancer	Zamora-Ros et al. (2019)
Coronary heart disease	Zutphen Elderly Study (805 males aged 65–84 years)	Flavonoids-containing foods such as apples, onions, or tea	Followed-up for 5 years	↓ Mortality of coronary heart disease	Hertog et al. (1993)
Stroke	Cohort study from 42 cases of first fatal or nonfatal stroke (552 men aged 50–69 years)	Flavonoids	≥28.6 mg/day	↓ Stroke incidence in elderly	Keli et al. (1996)
Stroke	Cohort study from 42 cases of first fatal or nonfatal stroke (552 men aged 50–69 years)	Flavonoid from tea	≥4.7 cups	Protect against stroke	Keli et al. (1996)
CVD	Meta-analysis of randomized controlled trials	Catechin supplements	20–300 mg/day	↑ Flow-mediated dilation ↓ Pulse wave velocity No changes in endothelial function markers	Shafabakhsh et al. (2020)

CVD	Randomized, double-blind, controlled, cross-over design, 19 healthy men	Black tea	Twice daily containing 800 mg tea flavonoids/day for 1 week	Improved flow-mediated dilatation in healthy men	Grassi et al. (2009)
CVD	33 male and female patients with coronary artery disease submitted to elective PCI (between 18 and 75 years)	Flavonoid-based antioxidant-rich diet such as grapes, cherry tomatoes, onions, and cruciferous vegetables	40 mg/day antioxidant compounds for 6 months	↓ LDL-C Not related to the decreasing of inflammatory and oxidative stress markers	Cammerer et al. (2018)
Diabetes mellitus	Meta-analysis of 6 prospective cohort studies involving 18,146 cases and 284,806 participants	Total flavonoids	An increased in 500 mg/day	↓ 5% in diabetes mellitus risk	Liu et al. (2014a)
Diabetes mellitus	Meta-analysis involving 8 prospective studies (312,015 subjects with 19,953 developed type 2 diabetes mellitus during the follow-up periods of 4–28 years)	Total flavonoids	≥550 mg/day	↓ Incident of type 2 diabetes mellitus	Xu et al. (2018)

(continued)

Table 7.4 (continued)

Age-related diseases	Study conditions	Source of polyphenols	Durations	Outcomes	References
Osteoporosis	Meta-analysis of 16 studies (7 cohort and 9 case-control studies) involving 772,707 participants with 37,166 fracture cases	Tea	≥3 cups/day	↓ Fractures risk	Xiang et al. (2019)
Osteoporosis	Systematic review and meta-analysis of 52 randomized controlled trials	Soy isoflavones	˂90 mg/day	Effective in the prevention of osteoporosis-related bone loss in overweight/obese individuals	Akhlaghi et al. (2020)
Osteoporosis	Systematic review and meta-analysis of 63 randomized controlled trials involving 6427 postmenopausal women	Ipriflavone (600 mg/day) and genistein (54 mg/day)	Ipriflavone (600 mg/day) and genistein (54 mg/day)	Improved bone mineral density	Sansai et al. (2020)

CVD cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *PCI* percutaneous coronary intervention

flavonoids (mean flavonoid intake is 14.33 mg/day for 10 years) in fruit juice, soup, coffee, tea, chocolate, oats flakes, sweet pepper, asparagus, French beans, spinach, cabbage, dried fruits, other fruits, kiwi, and/or citrus fruits could be beneficial on cognitive function during aging (Letenneur et al. 2007). Flavonoids are believed to be mediated by regulating the neuronal signal cascade through suppression of cell apoptosis, and thereby promote neuronal differentiation and survival (Vauzour et al. 2008). Flavonoids also seem to possess beneficial effects on the central and peripheral nervous system by changing the central blood flow (Socci et al. 2017). Folch et al. (2018) demonstrated that flavonoids may reduce the progression and development of Alzheimer's disease-like pathophysiology by inducing α-secretase (A disintegrin and metalloproteinase 10 (ADAM10)), interfering amyloid β protein production, and suppressing of β-secretase (β active site cleavage enzyme-1 (BACE-1)) (Fig. 7.2). Despite regular consumption of foods rich in flavonoids seems to decrease the risk of neurodegenerative diseases and combat the onset of age-related cognitive disorders, the mechanisms of actions remain obscure. Overall, it remains unknown which of the substances could produce the strongest protection of the nervous system and when to use it to produce the optimal effectiveness. Therefore, further study is necessary to conclusively resolve the question behind these effects.

Notably, data from epidemiological and clinical studies found that flavonoids may reduce the risk of cancer (Storelli et al. 2019; Sun et al. 2021). In the promotion

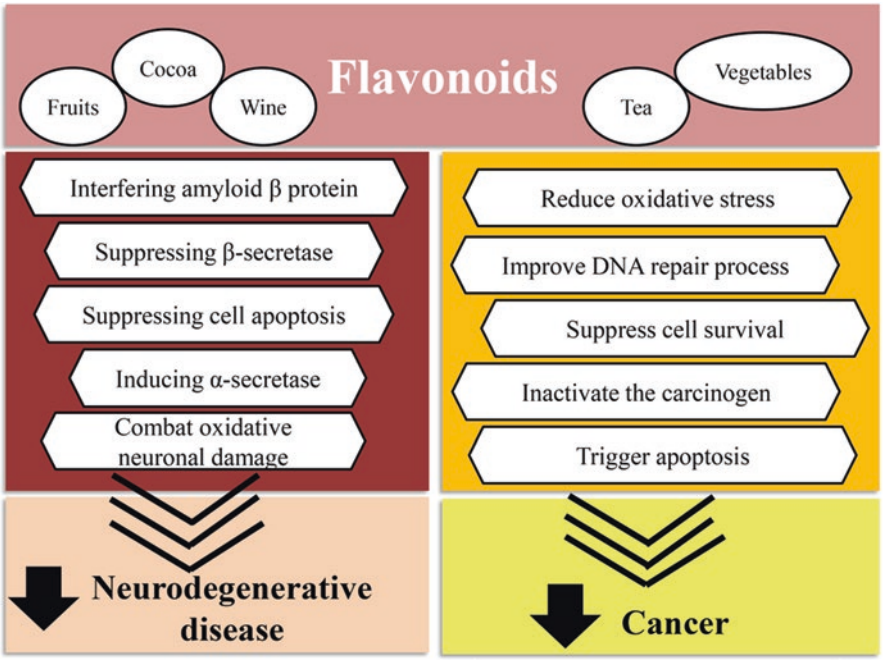

Fig. 7.2 Mechanisms of flavonoids in the modulation of neurodegenerative disease and cancer

and initiation stages, flavonoids decrease the proliferation of cancerous cells through several mechanisms including reduction of oxidative stress, improvement of DNA repair process, suppression of cell survival, and inactivation of the carcinogen (Zaidun et al. 2018; Zhang et al. 2018a) (Fig. 7.2). While in the progression phase, flavonoids may show cytostatic or cytotoxic activity against cancer cells, exhibit antioxidant activity, suppress angiogenesis, and trigger apoptosis (Sp et al. 2017; Loung et al. 2019; Elhady et al. 2020). Prevention of metabolic stimulation of procarcinogens is associated with flavonoids interaction with Phase I enzymes, which is responsible for the metabolism of several exogenous and endogenous substrates (Batra and Sharma 2013). Such findings could be attributed to the suppression of the cytochrome P450 enzymes, for instance, CYP1A2 and CYP1A1. In addition, flavonoids may protect against cellular damage arising from the stimulation of carcinogenic factors through reinforcement of mutagen detoxification by inducing phase II enzymes, for instance, UDP-glucuronyl transferase (UDP-GT) and glutathione S-transferase (GST) (Shih et al. 2007; Jiang and Hu 2012). Flavonoids were shown to negatively associate with several types of cancers in animal and human studies. Apples are a rich source of flavanoids (Tu et al. 2017). It has been demonstrated that peel-flavonoids (Peel-F) and flesh flavonoids (Flesh-F) extracted from Pink Lady apples suppressed the colon cancer (LoVo) (Peel-F = 110.33 ± 2.52 mg/mL and Flesh-F = 378.14 ± 1.64 mg/mL) and breast cancer (MCF-7) (Peel-F = 58.42 ± 1.39 mg/mL and Flesh-F = 296.06 ± 3.71 mg/mL) cells (Yang et al. 2015). Further, consumption of at least one apple/day decreased the risk of colorectal cancer (Jaganathan et al. 2014). An animal study has shown that a flavonoid-rich extract from bergamot juice (35 mg/kg and 70 mg/kg body weight for 12 weeks) reduced colon preneoplastic lesions mucin-depleted foci (MDF) in Pirc rats (F344/NTac-Apc^{am1137}) (Navarra et al. 2020). The data further revealed that feeding rats with a flavonoid-rich extract from bergamot juice (70 mg/kg body weight for 12 weeks) downregulated inflammation-related genes (*Arginase 1*, *IL-10*, *IL-6*, *IL-1β*, *iNOS*, and *COX-2*) and upregulated *p53* levels (Navarra et al. 2020). Likewise, Ivey et al. (2015) also demonstrated that high total flavonoids intake (from black tea, onions, pears, apples, tea, fruit juice, and oranges) (≥813 mg/day) reduced the risk of cancer mortality in women aged 75 years old and above compared to those with low total flavonoids intake (˂525 mg/day) over the 5 years follow-up period. The Iowa Women's Health Study conducted from 1986 to 2004 involving 34,708 post-menopausal women revealed that regular consumption of flavonoids-containing foods including red wine, chocolate, tea, soy, citrus juices and fruits (orange juice, oranges, grapefruit juice, grapefruits), bran added to foods, broccoli, grapes and raisins, berries (blueberries and strawberries), and fresh pears and apples (median intake of total flavonoids = 239.2 mg/day) significantly decreased the risk of lung cancer, particularly among past and current smokers (Cutler et al. 2008). Compared to those who never or less-than-weekly black tea drinkers, individuals who consume black tea (at least 2 cups/day) significantly reduced 33% of lung cancer risk in men (Seow et al. 2020). A possible explanation for the protective effect observed only in men is that they may have high oxidative stress levels compared to women (Barp et al. 2002; Ide et al. 2002; Matarrese et al. 2011), and thus the antioxidant effect of black tea to

restore balance may be more significant among men. Although several meta-analyses found that green tea reduced the risk of lung cancer (Zhong et al. 2001; Wang et al. 2014), the recent study failed to show any significant association between lung cancer risk and green tea consumption (more than 2 cups/day) (Seow et al. 2020). In another study involving 38,408 women aged 45 years and above further revealed that no significant association between the risk of cancer and consumption of foods rich in flavonoids including tofu, onion, broccoli, apple, and tea over 11.5 years of follow-up (median intake = 8.88–47.44 mg/day) (Wang et al. 2009). The same effect was also observed in the prospective study. European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that coffee or tea consumption (100 mL/day) was not associated with total differentiated thyroid cancer (Zamora-Ros et al. 2019).

Compared to those who rarely or non-daily coffee drinkers, individuals who consume one or more cups of coffee per day have a relatively high risk of lung cancer (Seow et al. 2020). Similarly, three recent meta-analyses found that coffee consumption (≤1 cup/day, 2–3 cups per day, or ≥3 cups/day) was positively associated with the risk of lung cancer (Xie et al. 2016; Galarraga and Boffetta 2016; Wang et al. 2016a). The increased cancer risk from drinking coffee is possibly modulated by intermediate compounds and mechanisms, for instance, pyrogallol and gallic acid, and thus leading to DNA damage (Hossain et al. 2013). In the context of breast cancer, a meta-analysis of epidemiological studies involving 9513 cases and 181,906 controls revealed that no significant association between total flavonoids (median intake = 19.13–29.1 mg/day), flavanones (median intake = 31.2–33.7 mg/day), or flavan-3-ols (median intake = 7.9–162 mg/day) intake and breast cancer risk (Hui et al. 2013). Nonetheless, the study found that flavones (median intake = 0.13–2.5 mg/day) and flavonols (median intake = 9.8–27.8 mg/day) intake is negatively associated with breast cancer risk in postmenopausal women (Hui et al. 2013). This finding could be attributed to the flavonoids that have a similar chemical composition as oestrogens, and thus flavonoids possess an ability to decrease menopause symptoms (Gardeazabal et al. 2019). However, further study is necessary to investigate the effects of flavonoid consumption in post- and pre-menopause breast cancer risk. Furthermore, a population-based case-control study reported by Reale et al. (2018) evaluated flavonoids in relation to prostate cancer risk in Sicilian men from January 2015 to December 2016. The data found that a high intake of catechins (36.18 mg/day) and flavonols (37.14 mg/day) reduced the prostate cancer risk. Notably, the study found that high consumption of flavanones (81.32 mg/day) increased prostate cancer risk (Reale et al. 2018). In addition to the effects mentioned above, total flavonoid intake (105.2 ± 77.9 mg/day) from black soybeans, tofu, and green tea reduced the gastric cancer risk in women but not in men (Woo et al. 2014). A similar finding was also observed in the EPIC study, who reported that total flavonoid intake (433.8 ± 330.6 mg/day during an average follow-up of 11 years) is negatively associated with gastric adenocarcinoma risk in women (Zamora-Ros et al. 2012). Such relationship was also observed in several flavonoid subgroups, for instance, flavanols (350.8 ± 304.1 mg/day), flavones (3.46 ± 3.92 mg/day), flavonols (26.70 ± 17.38 mg/day), and anthocyanidins (29.51 ± 22.75 mg/day) (Zamora-Ros

et al. 2012). However, Sun et al. (2017) failed to show any protective effect between flavonoid intake (≤84.1 mg/day or 84.2–4211.2 mg/day over 12 years of follow-up) and gastric cancer risk. In the context of colorectal cancer, several studies reported by Hazafa et al. (2020) have shown that flavonoids exert their efficacy in the inhibition of colon cancer *in vitro*. In support of this, Xu et al. (2016) showed that flavonoid consumption such as flavones (3.67 mg/day) from lettuce, peppers, pumpkin, leaf mustard, and Chinese celery, flavanones (3.76 mg/day) (tomato, white wine, citrus juice, citrus fruits, and leaf mustard), and anthocyanidins (20.64 mg/day) (banana, apple, grapes, and vegetables (radish and eggplant)), is negatively linked to the colorectal cancer risk. Zamora-Ros et al. (2013) further revealed that total flavonoid intake (median = 196.4 mg/day) from vegetables, legumes, wine, and fruits is inversely associated with colorectal cancer risk in a Spanish population. Nonetheless, a prospective study evaluated the association of daily flavonoids consumption (116–769 mg/day and 107–808 mg/day during 26 years of follow-up) (from onions, tea, red wine, oranges, blueberries, strawberries, pears, and apples) and colorectal cancer has demonstrated that no association between flavonoid intake and colorectal cancer risk (Nimptsch et al. 2016). Overall, the protective effects of flavonoids on cancer in epidemiological studies remain controversial. Indeed, these findings may vary from diet and geographical location. Therefore, further studies are required to confirm the effects of flavonoids on certain types of cancers.

Flavonoids not only modulate neurodegenerative diseases and cancers but also decrease CVD (Mahmoud et al. 2019). Inflammation plays a prominent role in atherosclerosis (Moriya 2019). Flavonoids exert bioactivity that beneficially influence cardiovascular risk factors, for instance, blood platelet aggregation, endothelial dysfunction, dyslipidemia, and lipoprotein oxidation (Mulvihill et al. 2016; Malakul et al. 2018; Rolnik et al. 2020) (Fig. 7.3). The cardioprotective effect of flavonoids could be due to its lipid-lowering properties, anti-thrombogenic properties, and antioxidant activities (Nijveldt et al. 2001; Zeka et al. 2017). Several epidemiological studies reported by Ponzo et al. (2015) and Dalgaard et al. (2019) examined flavonoids in relation to CVD risk. Considerable studies showed that flavonoid intake can decrease total mortality and the risk of CVD (Kim and Je 2017). In Zutphen Elderly Study involving 805 males aged 65–84 years and followed-up for 5 years revealed that the mortality of coronary heart disease was reduced after consuming flavonoids-containing foods such as apples, onions, or tea (Hertog et al. 1993), suggesting that regularly consuming food rich in flavonoids may decrease the risk of mortality from coronary heart disease in elderly men. A 15-year follow-up study further reported that high consumption of flavonoids (≥28.6 mg/day) such as black tea can decrease the stroke incidence in the elderly (Keli et al. 1996). Notably, data from a meta-analysis of randomized controlled trials included a study from inception to March 2019 that evaluated catechin supplementation in relation to endothelial function (Shafabakhsh et al. 2020). The study showed that catechin supplementation (20–300 mg/day) significantly increase flow-mediated dilation and reduce pulse wave velocity, but did not change endothelial function markers (Shafabakhsh et al. 2020). By contrast, some research has emerged to suggest that flavonoids can modulate endothelial function (Bondonno et al. 2018; Zhang et al. 2018b).

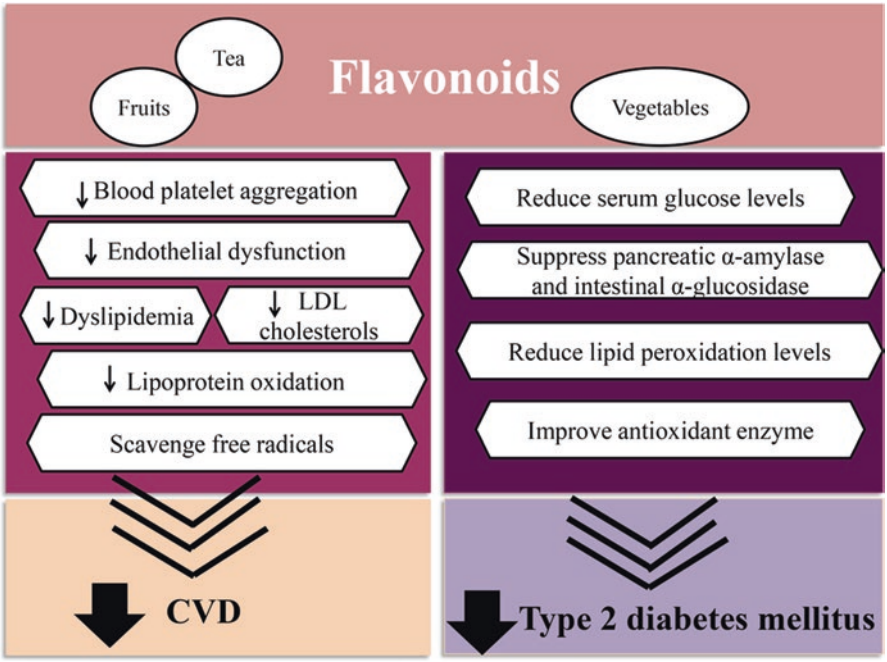

Fig. 7.3 Mechanisms of flavonoids in the modulation of cardiovascular disease and type 2 diabetes mellitus. *CVD* cardiovascular disease, *LDL* low-density lipoprotein

Endothelial-derived NO via the activity of constitutive NO synthase is crucial for maintaining the dilation of blood vessels (Sandoo et al. 2010). However, a high dosage of NO produced by iNOS in macrophages can result in oxidative damage (Xue et al. 2018). It has been suggested that flavonoids can scavenge the free radicals by decreasing the formation of peroxynitrite, and thereby leading to less damage (Nugroho et al. 2017). Furthermore, flavonoids decreased the ischemia-reperfusion injury by disrupting iNOS activity (Cebova and Pechanova 2020). In this regard, NO scavenging is hypothesized to play a crucial role in the therapeutic effects of tea flavonoids (Panat et al. 2016). A study reported by Grassi et al. (2009) evaluated the effects of tea flavonoids in relation to flow-mediated dilatation of the brachial artery. The data showed that black tea (twice daily containing 800 mg tea flavonoids/day for 1 week) improved flow-mediated dilatation in healthy men (Grassi et al. 2009). The endothelium is the inner lining of the blood vessels (Favero et al. 2014). It plays an important role in selectively permeable barriers between tissues and blood. Tea catechins have been shown to mediate the redox-sensitive transcriptional activity, for instance, AP-1 and NF-κB in cardiovascular cells (Aneja et al. 2004). NF-κB has been demonstrated to be involved in the mediation of several oxidative-stress related vascular activities (Pierce et al. 2009). The previous study found that EGCG administration (10 mg/kg intravenously) is beneficial for the treatment of reperfusion-induced myocardial damage by reducing NF-κB activity and AP-1 pathway (Aneja

et al. 2004). A beneficial role of flavonoids has also been observed on lipid profiles. Data from a randomized clinical trial showed that flavonoid-based antioxidant-rich diet such as grapes, cherry tomatoes, onions, and cruciferous vegetables (40 mg/day antioxidant compounds for 6 months) significantly decrease the LDL cholesterols in patients with coronary artery disease submitted to elective percutaneous coronary intervention (PCI) (Cammerer et al. 2018). The data further showed that a flavonoid-based antioxidant-rich diet (40 mg/day antioxidant compounds for 6 months) is not related to the decreasing of inflammatory and oxidative stress markers 6 months after PCI (Cammerer et al. 2018). Notably, the micellar solubilization of hydrolyzed lipids is important for the absorption and uptake of lipids by the enterocyte (Robert et al. 2020). Green tea may affect the uptake of other lipids and cholesterols by the enterocyte via the interaction with transporters, especially exposure to the intestinal lumen (Koo and Noh 2007). Sakakibara et al. (2019) and Kobayashi and Ikeda (2017) showed that tea catechins, for instance, gallate esters can reduce cholesterol absorption by decreasing the bile acid-induced micellar solubility and forming insoluble co-precipitates of cholesterols. It has been reported that green tea catechins are potent and selective inhibitors in rats' squalene epoxidase, a rate-limiting enzyme for cholesterol biosynthesis (Abe et al. 2000). The presence of galloyl moiety has been suggested to be crucial for squalene epoxidase suppression activity (Abe et al. 2000). In this regard, the hypocholesterolemic effect of tea catechins could be attributed to the inhibitory activity on cholesterol biosynthesis and absorption to improve cholesterol excretion (Kobayashi and Ikeda 2017). Taken together, the experimental studies suggest that flavonoids may beneficial to the cardiovascular system and decrease the CVD risk. Despite substantial evidence on flavonoids are promising, many studies are still needed to prove the efficacy of CVD treatment and prevention. The potential implication of flavonoids on CVD worth further investigation in long-term clinical studies.

Diabetes mellitus is a chronic disorder characterized by increased levels of blood glucose, and thereby resulted in the damage of nerves, kidneys, eyes, blood vessels, and heart (World Health Organization 2020). Nearly 422 million people have diabetes worldwide, with 1.6 million deaths are attributed to diabetes annually (World Health Organization 2020). Data from systematic review and meta-analysis of animal studies included a study between July 2018 and August 2018 have demonstrated that quercetin with a dose of 10, 25, and 50 mg/kg could reduce the serum glucose levels (Bule et al. 2019) (Fig. 7.3). Another common flavonoid, anthocyanidins are commonly found in radishes, red cabbage, and apples (Rodriguez-Amaya 2019; Yuste et al. 2019). Cyanidin and its glycosides, which belong to anthocyanins, have been shown to suppress pancreatic α-amylase and intestinal α-glucosidase *in vitro* (Akkarachiyasit et al. 2010) (Fig. 7.3). Further, the animal study showed that feeding rats with apple peel extract (1 g/kg) or cloudy apple juice (15 mL/kg) for 21 days improved antioxidant enzyme activity and reduced lipid peroxidation levels, suggesting that apple juice/extract may have protective effects against the deleterious complication of diabetes mellitus (Fathy and Drees 2016). Notably, emerging epidemiological studies in Europe and United States suggested that dietary flavonoids can protect against diabetes mellitus (Mondal and Rahaman

2020). Several prospective cohort studies in a meta-analysis have corroborated this finding and found that an increase in the total flavonoid consumption of 500 mg/day was linked to a 5% reduction in type 2 diabetes mellitus (Liu et al. 2014a). Consistent with the study reported by Liu et al. (2014a), a meta-analysis involving 8 prospective studies (312,015 subjects with 19,953 developed type 2 diabetes mellitus during the follow-up periods of 4–28 years) revealed that high consumption of total flavonoids (≥550 mg/day) is inversely associated with the incident of type 2 diabetes mellitus (Xu et al. 2018). The study further demonstrated that the type 2 diabetes mellitus risk was reduced by 5% for every 300 mg/day increment in total flavonoid consumption (Xu et al. 2018). These improvements could be due to the antioxidant properties of flavonoids that protect the body against deleterious effects of hyperglycemia in type 2 diabetes mellitus via modulation of aldose reductase, glucose co-transporter, or α-glucosidase (Fang et al. 2019).

Substantial studies have suggested that flavonoids could decrease the risk of osteoporosis (Qi et al. 2019; Liu et al. 2020). Feeding rats with total flavonoids of *Herba Taxilli* (400, 200, and 100 mg/kg/day for 28 days) was shown an ability in treating osteoporotic rats induced by retinoic acid (Li et al. 2019a). This efficacy could be attributed to the reduction of tartrate-resistant acid phosphatase (TRAP) and alkaline phosphatase (ALP) and elevation of serum Ca^{2+} level (Li et al. 2019a) (Fig. 7.4). Data from a systematic review reported by Chiavarini et al. (2020) involving 11 animal studies and 1 human study (between January 2016 to October 2019)

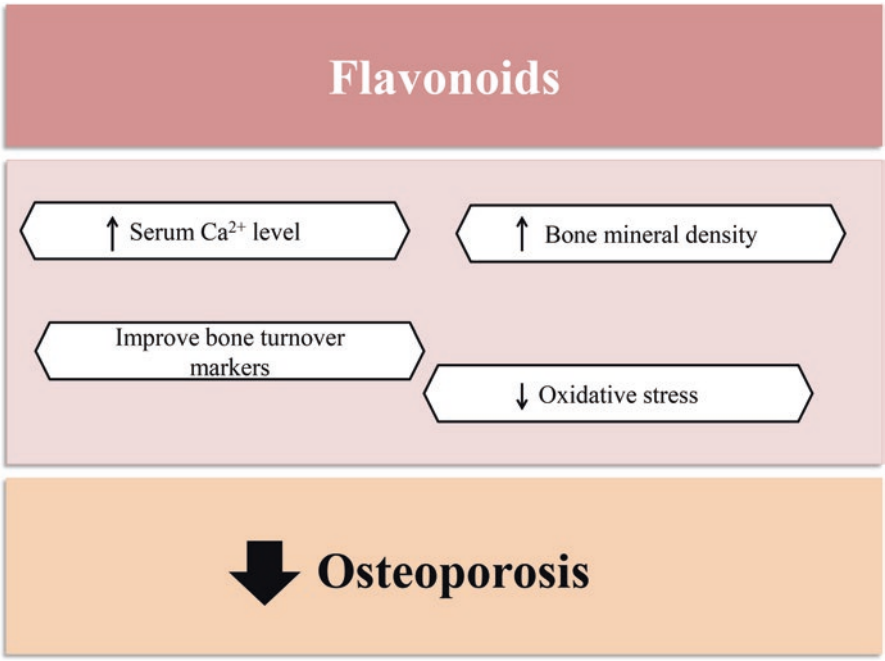

Fig. 7.4 Biological mechanism of flavonoids in relation to osteoporosis

further revealed that flavonoids exert a positive effect on osteoporotic fracture healing. This finding indicates that flavonoids could be used as a therapeutic agent for fracture healing. Likewise, a meta-analysis of 772,707 participants with 37,166 fracture cases demonstrated that tea consumption (≥3 cups/day) may be linked to the reduced risk of fractures (Xiang et al. 2019). In another systematic review and meta-analysis including 8 studies from inception to 9th January 2019 demonstrated that puerarin could enhance the bone mineral density in ovariectomy-induced postmenopausal osteoporosis in the murine model (Yang et al. 2020a) (Fig. 7.4). Puerarin is an isoflavone that exerts health-promoting properties (Zhang et al. 2019b; Jeon et al. 2020; Chen et al. 2021). Similarly, a systematic review and meta-analysis of randomized controlled trials further revealed that bone turnover markers (C-telopeptides, pyridinoline, and osteoprotegerin) were favorably affected by soy isoflavones (Akhlaghi et al. 2020). Notably, the data from bone markers analysis further demonstrated that isoflavones at dosage ˂90 mg/day show a better preventive effect in osteoporosis-associated bone loss in overweight/obese individuals (Akhlaghi et al. 2020). In the context of bone mineral density in postmenopausal women, a systematic review and meta-analysis of 63 randomized controlled trials involving 6427 postmenopausal women revealed that ipriflavone (600 mg/day) and genistein (54 mg/day) shows a beneficial effect on bone mineral density (Sansai et al. 2020). In this regard, these findings imply that flavonoids may improve bone mineral density and reducing the symptoms of osteoporosis. Taken together, flavonoids might be a promising approach for the prevention of age-related diseases and amelioration of oxidative stress. The crucial role played by flavonoids and their subclasses is worth attention to and further evaluated in randomized clinical trials.

7.4 Carotenoids

Carotenoids are tetraterpene pigments that absorb wavelengths from 400 to 550 nanometers, and thus the compounds are shown in red, orange, and yellow color (Maoka 2020). It is a naturally occurring pigment and is usually found in animals, plants, algae, fungi, several species of archaea, and photosynthetic bacteria (Ahrazem et al. 2016; Liang et al. 2018). In general, carotenoids are comprised of eight isoprene units and a 40-carbon skeleton (Maoka 2020). The general structures usually consist of a polyene chain with nine conjugated double bonds and an end group at both ends of the polyene chain (Maoka 2020). The end group and structure of the polyene chain of carotenoid are illustrated in Fig. 7.1. Carotenoids are divided into two categories, namely xanthophylls and carotenes (Maoka 2020). There are nearly 50 carotenes are present in nature (Khachik 2006; Tan and Norhaizan 2019). Carotenes, for instance, lycopene, γ-carotene, β-carotene, and α-carotene are carotenoids containing hydrocarbons (Fig. 7.1) (Mezzomo and Ferreira 2016); whereas xanthophylls such as peridinin, fucoxanthin, astaxanthin, zeaxanthin, lutein, and β-cryptoxanthin, are carotenoids containing oxygen atoms, for instance, furanoxide, epoxide, carboxylic, aldehyde, and carbonyl groups (Maoka 2020). Several

xanthophylls are present as protein complexes, sulfates, glycosides, and fatty acid esters. There are nearly 800 xanthophylls that have been naturally discovered up until 2018 (Maoka 2009).

Carotenoids are essential components found in chlorophylls of photosynthetic plants, algae, and bacteria that are involved in photoprotection and photosynthesis (Maoka 2020). It produces light energy and converts this energy to chlorophylls via singlet-singlet excitation transfer (Kvíčalová et al. 2016). This conversion is a low energy state transfer used during photosynthesis. Conversely, carotenoids absorb unrestricted energy from chlorophylls via triplet-triplet conversion and generate excessive energy through polyene vibration (Maoka 2020). This triplet-triplet transfer is a high-energy state that is involved in photoprotection. During photosynthesis, ROS including superoxide anion radicals, hydroxyl radicals, and singlet oxygen are released from light and oxygen (Phaniendra et al. 2015). Notably, carotenoids with more than 11 conjugated double bonds have demonstrated an ability to scavenge singlet oxygen (Fiedor and Burda 2014). This mechanism is a physical reaction, in which carotenoids take up the thermal energy from singlet oxygen and produce this energy through polyene vibration (Maoka 2020). During the xanthophyll cycle, it involves the enzymatic removal of epoxy groups from xanthophylls (lutein epoxide, antheraxanthin, and violaxanthin) to produce de-epoxy xanthophylls (lutein and zeaxanthin) (Maoka 2020). This enzymatic cycle plays a crucial role in activating the energy liberation within light-harvesting antenna proteins through non-photochemical scavenging by decreasing the energy levels that reach the photosynthetic reaction centers (Polívka and Frank 2010).

Besides photosynthetic, carotenoids also appeared in non-photosynthetic organs of plants including flowers, roots, seeds, pericarps, and fruits (Maoka 2020). Carotenoids in non-photosynthetic organs serve as precursors of plant hormones, color attractants, antioxidants, and photo-protectors (Maoka 2020). During the ripening stage, seeds and fruits turn to purple or red color. This color changes could be due to the formation of anthocyanins and/or carotenoids (Fernández-López et al. 2020). For instance, the color of the pericarp of tomato changed to deep red from greenish-yellow color during the ripening process (Carrillo-López and Yahia 2014). This change is due to the conversion of phytoene to lycopene in the pericarp of the tomato (Fraser et al. 2007). Phytoene is a colorless compound found predominantly in greenish-yellow tomato and is converted to neurosporene (orange) and lycopene (red) by phytoene desaturase (Britton et al. 1998, 2008). Lycopene is a carotenoid that exerts some photoprotection and singlet oxygen scavenging activities (Britton et al. 1998, 2008).

Carotenes are one of the first intermediates in the synthesis of carotenoids, and thus these components exist in all photosynthetic organisms and are abundantly found in our diets (Maoka 2020). There are nearly 50 carotenoids found in human foods, in which 20 of them ingested from food are found in the serum or plasma (Maoka 2020). Of all of these carotenoids, zeaxanthin, lutein, β-cryptoxanthin, lycopene, α-carotene, and β-carotene are the major compounds that make up more than 90% of the total carotenoids (Maoka 2020). Carotenoids ingested from the diet are absorbed by the small intestine (Reboul 2019); whereas xanthophyll esters are

hydrolyzed by esterase or lipase and absorbed (Breithaupt et al. 2007). The provitamin A carotenoids are converted by β-carotene-15,15′-dioxygenase into the retinal in the mucous of the small intestine (von Lintig 2012). Subsequently, the absorbed carotenoids are incorporated into chylomicrons and transported to the liver and other organs in the bloodstream (Reboul 2013).

Many studies have shown that carotenoids exert beneficial antioxidant and biochemical effects on animals and humans (Sajjadi and Bathaie 2017; Cui et al. 2019; Deding et al. 2020; Lin et al. 2020). Data from epidemiological studies revealed a negative link between high consumption of carotenoids and the risk of chronic diseases (Tan and Norhaizan 2019; Umigai et al. 2020). These favorable effects could be mediated via several mechanisms, for instance, regulation of cell growth (Moccia et al. 2020), enhancement of immune system (Liu et al. 2019), and modulation of cell differentiation, apoptosis, and cell cycle (Sheng et al. 2020). Carotenoids are highly lipophilic molecules that reside intracellularly to protect the membranes from oxidative stress (Fiedor and Burda 2014). Carotenoids are well-known as an eye-sight protecting agent (Bungau et al. 2019). These carotenoids are categorized as pro-vitamin A which comprised of the unsubstituted β-ionone ring such as γ-carotene, β-cryptoxanthin, β-carotene, and α-carotene, and thereby converted into retinal (Grune et al. 2010). Substantial evidence highlights that zeaxanthin and lutein are crucial dietary carotenoids in decreasing and preventing age-related macular degeneration (AMD) and cataracts (Maci and Santos 2015; Eisenhauer et al. 2017). AMD is the most common cause of blindness in adults aged 65 years old and above (Wong et al. 2014). Oxidative stress within the retina is implicated in the development and progression of AMD (Abokyi et al. 2020). Zeaxanthin and lutein have been identified as the major components of the macular pigments (Ma et al. 2012a). Studies have demonstrated a significant correlation between high concentrations of lutein in serum or ocular tissues and decreased risk of AMD (Korobelnik et al. 2017; Arslan et al. 2019; Rinninella et al. 2018). The preventive role of lutein toward AMD is more likely due to the antioxidant effect. Lutein can inhibit ROS and inflammatory mediator production, and thereby reduce NADPH oxidase subunit Nox4 (Tuzcu et al. 2017; Yanai et al. 2018). Data from the meta-analysis showed that serum lutein and zeaxanthin levels were inversely linked to the risk of nuclear cataracts (Liu et al. 2014b) (Table 7.5). The preventive role of lutein and zeaxanthin is more likely due to their blue-light filtering activities and antioxidant properties (Chitchumroonchokchai et al. 2004). The lens of the eye is prone to oxidative damage which subsequently promotes high-energy short-wavelength light exposure and increases the production of ROS. The ROS produced leads to aggregation or cross-linking of the crystalline proteins in the lens of epithelial cells, and ultimately caused the generation of cataracts (Gao et al. 2011). In particular, isomer zeaxanthin and lutein are concentrated in the lens, indicates that they may have a preventive role in the vital ocular tissues (Mares 2016). A systematic review and meta-analysis of 6 cohort studies comprising a total of 2477 incident AMD cases and follow-up from 5 to 18 years revealed that dietary intake of lutein and zeaxanthin can affect the risk of AMD (Ma et al. 2012b). The data showed that increased dietary intake of lutein and zeaxanthin may protect against late AMD (Ma et al.

Table 7.5 The clinical studies of carotenoids on age-related diseases

Age-related diseases	Study conditions	Source of carotenoids	Durations	Outcomes	References
Nuclear cataract	Meta-analysis (7 cross-sectional studies and 1 cohort study)	Serum lutein and zeaxanthin	–	↓ Nuclear cataract risk	Liu et al. (2014b)
AMD	Systematic review and meta-analysis of 6 cohort studies comprising a total of 2477 incident AMD cases and follow-up from 5 to 18 years	Dietary intake of lutein and zeaxanthin	–	Protect against late AMD Not associated with a reduced risk of early AMD	Ma et al. (2012b)
Age-related cataract	Dose-response meta-analysis (6 prospective cohort studies involving 4416 cases and 41,999 participants)	Zeaxanthin/lutein	Each 300 μg/day increment	↓ Risk of posterior subcapsular cataract and nuclear cataract by 3%	Ma et al. (2014)
AMD	The multicenter Eye Disease Case-Control Study (356 case subjects who were diagnosed with the advanced stage of AMD within 1 year prior to their enrollment, aged 55 to 80 years old, and 520 control subjects)	Lutein from dark green, leafy vegetables	~6 mg/day	↓ Risk of AMD	Seddon et al. (1994)
AMD	Meta-analysis of 8 randomized controlled trials involving 1176 AMD patients	Zeaxanthin/lutein supplements	Each 1 mg/day increment (ranged from 6 to 36 months)	↓ 0.003 of visual acuity scale	Liu et al. (2015)
AMD	Meta-analysis (9 prospective, randomized controlled trials involving 855 patients diagnosed with AMD)	Lutein supplements	10 or 20 mg/day for more than 6 months	Improved visual acuity and MPOD in AMD patients	Feng et al. (2019a)
CVD	Systematic review and meta-analysis including from inception to August 2016, involving 634 participants	Lycopene-containing food such as tomato	70–400 g/day, followed-up for 2 months on average, range from 1 to 180 days	↓ IL-6 levels and LDL-cholesterol Improved flow-mediated dilation	Cheng et al. (2017)
CVD	Placebo-controlled, randomized, double-blind, cross-over trial with 16 postmenopausal women	100% watermelon juice	Daily dose of 14.4 ± 0.34 mg lycopene for 4 weeks	No effect on serum lipids or antioxidant capacity ↑ Circulating lycopene levels	Crowe-White et al. (2020)
CVD	Diet-control-led, repeated measures cross-over design with 10 healthy subjects	Tomato or watermelon juice	Tomato juice (122 g each at dinner and breakfast, 18.4 mg lycopene/day) or watermelon juice (260 g each at dinner, lunch, and breakfast, 20.1 mg lycopene/day) for 3 weeks	No effect on plasma cholesterol levels or antioxidant status	Collins et al. (2004)

(continued)

Table 7.5 (continued)

Age-related diseases	Study conditions	Source of carotenoids	Durations	Outcomes	References
CVD	Prospective cohort of 39,876 middle-aged and older women	Tomato-based products (pizza, tomato sauce, tomato juice, and tomatoes)	≥7 servings/week during a median follow-up of 7.2 years	↓ CVD risk by 30%	Sesso et al. (2003)
Hypertension	Quasi-experimental study with pretest-posttest control group design, he Community Health Center of Magelang in July 2016–January 2017, pregnant women in trimester I, II, and III with high blood pressure	Tomato juice	250 mL/day	↓ 2.81 mmHg diastolic pressure ↓ 8.26 mmHg systolic pressure	Anita et al. (2017)
Atherosclerosis	Case-control study involving 125 subjects with early atherosclerosis and 107 controls aged 45–68 years old	Serum levels of lutein and β-carotene	–	Serum lutein level showed a greater early protection against atherosclerosis compared to serum β-carotene level	Zou et al. (2011)
Coronary artery disease	PBMC from patients with stable angina	Lutein	25 μM for 48 h	Inhibits LPS-induced IL-6, TNF, and IL-1β mRNA levels	Chung et al. (2017)
Colorectal cancer	Case-control study with 1846 controls and 923 colorectal cancer patients	Carrot, persimmon, peach, pumpkin, and ginger	49.4 ± 45.4 g/day	↑ Risk of colorectal cancer in men	Lee et al. (2017)
Lung cancer/prostate cancer	Randomized, double-blind, placebo-controlled primary-prevention trial involving 29,133 male smokers 50–69 years old	Alpha-tocopherol or β-carotene	Alpha-tocopherol (50 mg/day) alone, beta carotene (20 mg/day) alone and follow-up for 5–8 years	No reduction in the incidence of lung cancer among male smokers High incidence of lung cancer in men who received β-carotene compared those who did not received Induce prostate cancer among individuals who received α-tocopherol than those who did not	The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group (1994)

Bladder cancer	Meta-analysis involving 516,740 adults included a study from inception to April 2019	Circulating concentration of zeaxanthin, lutein, β-carotene, and α-carotene	–	↓ Bladder cancer risk by 56% for every 1 μmol/L increase in daily circulating concentration of zeaxanthin and lutein	Wu et al. (2020)
		Dietary β-cryptoxanthin intake		↓ Bladder cancer risk by 27% for every 1 μmol/L elevation in circulating concentration of β-carotene	
				↓ Bladder cancer risk by 76% for every 1 μmol/L increase in circulating concentration of α-carotene	
				↓ Bladder cancer risk by 42% for every 1 mg increase in β-cryptoxanthin intake	
Alzheimer's disease	Case-control study performed from August 2006 to 2008	Serum carotenoids (zeaxanthin, lycopene, lutein, β-cryptoxanthin, β-carotene, and α-carotene)	–	Patients with Alzheimer's disease showed lower levels of serum carotenoids compared to cognitively normal participants	Mullan et al. (2017)
Parkinson's disease	Cohort study involving a total of 1036 cases (482 Nurses' Health Study and 554 Health Professionals Follow-up Study)	Dietary carotenoids (nuts, vegetables, and fruits)	Median intake of dietary carotenoids = 7502–26,940 mg/day over 12 years of follow-up	No effect	Hughes et al. (2016)
Alzheimer's disease and dementia	Community-based cohort of older adults (927 participants free from Alzheimer' disease and dementia at baseline)	Total carotenoids	6.7–24.8 mg/day during the follow-up for a mean of 7 years	Less global Alzheimer's disease and dementia pathology	Yuan et al. (2021)

AMD age-related macular degeneration, *CVD* cardiovascular disease, *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein cholesterol, *LPS* lipopolysaccharide, *MPOD* macular pigment optical density, *PBMC* peripheral blood mononuclear cells, *TNF-α* tumor necrosis factor-α

2012b). However, Ma et al. (2012b) did not identify an association between dietary lutein and zeaxanthin and early AMD. Ma et al. (2014) showed that every 300 μg/day increments of zeaxanthin/lutein decreased posterior subcapsular cataract and nuclear cataract risk by 3%. In addition, zeaxanthin/lutein supplementation was also significantly improved contrast sensitivity and visual acuity (Liu et al. 2015). The study showed that each 1 mg/day increment in zeaxanthin/lutein is linked to the 0.003 reductions on a visual acuity scale (Liu et al. 2015). Of all carotenoids, zeaxanthin and lutein, which are predominantly obtained from dark green leafy vegetables, were strongly related to the decreased risk of AMD (Seddon et al. 1994). The intake of lutein ~6 mg/day is sufficient to reduce the risk of AMD (Seddon et al. 1994). In support of this, a meta-analysis conducted by Feng et al. (2019a) showed that dietary intake of lutein (10 or 20 mg/day) for more than 6 months can significantly improve visual acuity and macular pigment optical density (MPOD) in AMD patients. In the context of toxicity, a systematic risk assessment of lutein supplements is safe up to 20 mg/day (Shao and Hathcock 2006). The AREDS2 trial showed that no adverse effects were reported (except skin yellowing) after supplementation of zeaxanthin and lutein (2 and 10 mg/day, respectively) for 5 years in patients with intermediate AMD (Age-Related Eye Disease Study 2 Research G 2013). Despite the data for safety is available for lutein, future studies are needed to evaluate the chronic intake of high lutein-containing supplements in a certain population. Table 7.5 summarizes the clinical studies of carotenoids on age-related diseases.

Carotenoids have been reported to prevent several chronic diseases induced by oxidative stress such as coronary artery disease (Chung et al. 2017) and CVD (Costa-Rodrigues et al. 2018). Oxidative stress can activate signaling pathways, predominantly through NF-κB, and thus leading to stimulation of IL-6 and TNF-α (Brasier 2010; Fischer and Maier 2015; Panahi et al. 2018). The implication of carotenoids in relation to the pathogenesis of CVD has been widely evaluated in both *in vivo* and *in vitro* models (Hajizadeh-Sharafabad et al. 2019). Increased plasma low-density lipoprotein (LDL) levels and oxidation state of LDL fraction increased the prevalence of CVD (Zhang et al. 2019c). Despite many therapeutic methods such as angioplasty or thrombolysis are available today, special attention needs to be paid to the diet (Tong et al. 2016). The prevalence of cardiovascular disorders is unevenly distributed in developed countries; while Southern Europe seems to be protected by having less incidence of CVD. This effect could be attributed to the dietary factors, for instance, the Mediterranean diet, which is containing olive oil and tomatoes (Krasinska et al. 2017). Watermelon, tomato sauce, and tomatoes are crucial sources of lycopene and may surrogate for the Mediterranean diet to a certain degree (Naz et al. 2014). Lycopene is a carotenoid with high antioxidant activity, which can modulate inflammation and apoptosis (Thies et al. 2017). Many studies evaluated lycopene in relation to cardiovascular risk. Although the findings are inconsistent, most of the studies showed that consumption of lycopene-containing food such as tomato (70–400 g/day for 1–180 days) significantly improved flow-mediated dilation and decreased IL-6 and LDL-cholesterol (Cheng et al. 2017), suggesting the tomatoes may protect against the development of CVD. Despite lycopene shows a high antioxidant activity but in certain

circumstances, its cardiovascular preventive role appears to be likely linked to the anti-inflammatory properties than to the suppression of the LDL oxidation (Muller et al. 2016). This phenomenon could be attributed to the elevation of hydrophobicity in lycopene; hence it is more likely to be found in the nuclear hydrophobic core of the lipoprotein (Muller et al. 2016). Research evidence has suggested that intakes of one or more servings/day of tomato-rich products, such as pizza, tomato sauce, tomato juice, and tomatoes, reduced the CVD risk by 30% in middle-aged and older women (Sesso et al. 2003). The effects were not only observed in lycopene consumption, the serum concentration may also affect the cardiovascular risk (Mozos et al. 2018). Low adipose tissue and serum lycopene levels were correlated with major acute cerebrovascular and acute coronary diseases and early atherosclerosis and demonstrated to be more reliable in risk assessment compared to daily consumption of lycopene (Kim et al. 2011). A placebo-controlled, randomized, double-blind, cross-over trial involving 16 postmenopausal women demonstrated that watermelon juice (14.4 ± 0.34 mg lycopene for 4 weeks), one of the rich sources of dietary lycopene, was significantly increased circulating lycopene (Crowe-White et al. 2020). However, the study showed that consumption of watermelon juice did not improve antioxidant capacity or serum lipids (Crowe-White et al. 2020). In support of this, intakes of lycopene from tomato juice (122 g each at dinner and breakfast, 18.4 mg lycopene/day) or watermelon juice (260 g each at dinner, lunch, and breakfast, 20.1 mg lycopene/day) for 3 weeks did not affect the plasma cholesterol levels or antioxidant status among middle-aged adults (Collins et al. 2004). Oxidative stress causes endothelial dysfunction due to oxidative injury of the endothelial cells and uncoupling of the NO synthase (Mozos and Luca 2017), in which both of these are linked to the inflammation. By decreasing ROS and oxidative stress, lycopene decreased lipids, protein, and mitochondrial damage, enhances endothelium-dependent vasodilation, and promotes the bioavailability of NO (Nakamura et al. 2017). For instance, watermelon promotes plasma L-arginine and enabling NO production due to the presence of L-citrulline (Figueroa et al. 2017). The previous study stated that lycopene supplementation enhanced the endothelial-modulated vasodilation in CVD patients, but not in healthy individuals, implied the crucial role of lycopene in secondary cardiovascular prevention (Costa-Rodrigues et al. 2018). These favorable effects of lycopene could be attributed to the suppression of intracellular adhesion molecule-1 expression, TNF-α-induced NF-κB activation, and interaction of endothelial cells and monocytes (Hung et al. 2008). Further, lycopene can also suppress T lymphocyte activation and decrease the secretion of metalloproteinases by macrophages (Thies et al. 2017). The animal study showed that lycopene (30 mg/kg/day for 8 weeks) prevents transplant vasculopathy and reduces the smooth muscle cell proliferation and intimal hyperplasia in allograft vessels via modulating the NO/cyclic guanosine monophosphate (cGMP) pathways and decreasing Rho-associated kinases (He et al. 2016). Importantly, lycopene is a regulator for cholesterol levels by modulating a few mechanisms including down-regulation of kexin type 9/proprotein convertase subtilisin mRNA levels and suppression of HMG-CoA reductase, suggesting that lycopene supplementation could be beneficial for patients with statin intolerance (Alvi et al. 2017). In addition,

lycopene possesses an antihypertensive effect by enhancing the production of NO in the endothelium, decreasing oxidative stress induced by angiotensin-II, and suppressing an angiotensin-converting enzyme in the endothelium (Belovic et al. 2016). This finding is supported by the study reported by Anita et al. (2017), who found that women who drank 250 mL of tomato juice/day can result in diastolic pressure drop by 2.81 mmHg and systolic pressure to decrease by 8.26 mmHg. Besides lycopene, lutein has also emerged as a potential atheroprotective agent in recent decades (Chung et al. 2017). In a study by Zou et al. (2011) focusing on serum lutein and β-carotene in relation to atherosclerosis, serum lutein level was shown to have a greater likelihood of early protection against atherosclerosis compared to serum β-carotene. The protective role of the cardiovascular system is more likely due to the ability to mediate cholesterol metabolism and antioxidative activity (Palloza et al. 2012), and thus lead to the prevention of LDL cholesterol oxidation (Hu et al. 2008). Further, the data from *ex-vivo* have also been demonstrated that lutein exerts anti-inflammatory effects on human peripheral blood mononuclear cells (PBMC) (Chung et al. 2017). Administration of lutein (25 μM for 48 h) in PBMC inhibits the LPS-induced IL-6, TNF, and IL-1β mRNA levels (Chung et al. 2017). Several studies have also reached a similar finding, in which high intake of carotenoids reduced the incidence of hypertension, stroke, myocardial infarction, and all-cause mortality (Yang et al. 2011). Although epidemiological studies have demonstrated an inverse relationship between β-carotene and the risk of CVD, several large randomized trials failed to observe any negative association between β-carotene and CVD. For instance, Women's Antioxidant Cardiovascular Study (WACS) (Cook et al. 2007), α-tocopherol and β-carotene (ATBC) study (Rapola et al. 1997), and MRC/BHF Heart Protection Study (Heart Protection Study Collaborative Group 2002) failed to show any beneficial effects. Although some controversy was reported in certain effects of carotenoids on cardiovascular health, most of the evidence showed the unequivocal benefits of lycopene consumption on vascular, cardiac, and endothelial health and function.

In addition to the effects observed on vision health and CVD, a beneficial effect of carotenoid supplementation has also been reported on cancer, demonstrating the enormous functional potential of carotenoids (Saini et al. 2020). Lycopene has gained attention for its health benefits including the treatment and prevention of cancer (Cha et al. 2017; Lim and Wang 2020). It has been suggested that the intake of lycopene from food or by itself may decrease cancer risk (da Costa Pereira Soares et al. 2019). Carotenoids were found to negatively link to several types of cancer (Gong et al. 2018; Kim et al. 2019; Mirahmadi et al. 2020). The anticancer ability of carotenoids is modulated via a few mechanisms including modulation of phase II detoxification enzyme and anti-inflammatory activities, regulation of angiogenesis and metastasis, and mediation of apoptosis induction, cell cycle arrest, and growth factor signaling (Trejo-Solís et al. 2013). These findings indicate the unique chemical structure of the carotenoids, which confers a strong antioxidant property (Mezzomo and Ferreira 2016). A meta-analysis involving 644 animals showed that lycopene (1.1–15 mg/kg/day or 20 mg/kg for 3x a week, range from 4 to 70 weeks via diet) significantly decreased the growth, number, and incidence of

hepatocellular carcinoma (HCC) (Mekuria et al. 2020) (Table 7.6). Lycopene has been demonstrated to suppress liver tumor initiation through several mechanisms including stimulating antioxidant defense system, scavenging oxygen free radicals, and inhibiting the cytochrome P450 2E1 enzymes (Aizawa et al. 2016; Wang et al. 2010; Stice et al. 2018). The former could be due to its ability to activate the Nrf2 which is known to be an important regulator for the cellular response to oxidative

Table 7.6 Effects of carotenoids on age-related diseases *in vitro* and *in vivo*

Age-related diseases	Cell lines/Animal models	Source of carotenoids	Dosages	Findings	References
CVD	Male Brow-Norway (BN) rats (n = 16) and male Lewis rats (n = 32)	Lycopene	30 mg/kg/day for 8 weeks	Prevents transplant vasculopathy	He et al. (2016)
Cancer	Systematic review and meta-analysis involving 644 animals (Long-Evans Cinnamon rats, ferrets, C57BL/6J mice, C3H/HeN mice, WT/BCO2-KO mice, Sprague-Dawley rats, Wistar rats, and BALB/c mice), studies between 2001 and 2018	Lycopene	1.1–15 mg/kg/day or 20 mg/kg for 3x a week, range from 4 to 70 weeks via diet	↓ Growth, number, and incidence of HCC	Mekuria et al. (2020)
Dementia	Female Sprague-Dawley rats (n = 60)	Lycopene	100 mg/kg for 2 months	↑ SOD activity in the hippocampus ↓ NRSF levels	Zhu et al. (2020)
Alzheimer's disease	P301L transgenic mice	Lycopene	5 mg/kg for 8 weeks	↓ The increase of tau phosphorylation at Ser396, Ser262, Ser235, and Thr231 in brain tissues	Yu et al. (2017)
Alzheimer's and Parkinson's diseases	Microglial cells	Crocetin and crocin	Crocetin (10 and 20 μM) and crocin (10 and 20 μM)	Inhibit the generation of NO and proinflammatory cytokines	Nam et al. (2010)
Cognition	Male Wistar rats	Lycopene	4 mg/kg/day for 90 days	↓ Cognitive impairment of the $AlCl_3$-induced hippocampal lesions	Cao et al. (2019)

HCC hepatocellular carcinoma, *NO* nitric oxide, *NRSF* neuron-restrictive silencer factor, *SOD* superoxide dismutase

stress (Bartolini et al. 2018). Nrf2 can stimulate detoxifying or antioxidant enzymes, for instance, catalase, HO-1, GPx, glutathione-S-transferase (GST), and SOD (Gupta et al. 2013; Bhatia et al. 2018). Further, lycopene exerts an anti-inflammatory effect by suppressing HCC progression and development (Bhatia et al. 2018). This is largely modulated by suppression of the oncogenic transcriptional NF-κB and downstream cascades (Ip et al. 2013; Bhatia et al. 2018), and thus resulting in the suppression of the NF-κB induced expression of inflammatory cytokines, for instance, IL-6 and TNF-α, that influence the proliferation and survival of premalignant cells (Vendrell et al. 2015; Todoric et al. 2016). The beneficial effect of lycopene was not only observed in liver cancer, the anticancer effect was also reported in bladder cancer. Data from a meta-analysis involving 516,740 adults included a study from inception to April 2019 demonstrated that bladder cancer risk was reduced by 56% for every 1 μmol/L increase in daily circulating concentration of zeaxanthin and lutein, by 27% for every 1 μmol/L elevation in circulating concentration of β-carotene, by 76% for every 1 μmol/L increase in circulating concentration of α-carotene, and by 42% for every 1 mg increase in β-cryptoxanthin intake (Wu et al. 2020). Orange/yellow fruits and vegetables are thought to be an excellent source of carotene, which can act as provitamin A (Liu 2004). Carotenoids may exert a positive effect against cancer by inhibiting the metastasis and proliferation of cancer cells (Reczek and Chandel 2015). However, intake of orange/yellow fruits and vegetables including carrot, persimmon, peach, pumpkin, and ginger (49.4 ± 45.4 g/day) are linked to an increased risk of colorectal cancer in men (Lee et al. 2017). The possible mechanisms underlying the increased risk of colorectal cancer in men should be further elucidated to confirm these relationships.

Notably, high blood concentration and dietary consumption of carotenoids were linked to the reduced risk of total cancer and all-cause mortality (Aune et al. 2018). However, the negative association between blood concentration and dietary intake of antioxidants is not likely due to the single antioxidants but due to the combination of bioactive compounds present in vegetables and fruits (Aune et al. 2018). Such findings support the recommendation to increase consumption of vegetables and fruits, but not antioxidant supplements for chronic disease prevention (Aune et al. 2018). However, randomized clinical trials are consistently shown no clear benefits of antioxidant supplements in relation to chronic disease risk as well as potential harms of supplementation of β-carotene and vitamin E on lung cancer risk and mortality, respectively (The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994; Bjelakovic et al. 2012, 2013). The study evaluated the use of supplements with a single of several antioxidants; whereas the observational studies have assessed these nutrients based on the dietary intake of food or blood concentrations. The dietary sources of these antioxidants found in vegetables and fruits also exert a broad spectrum of bioactive constituents that may have synergistic effects. The findings from the observational studies could reflect a small number of bioactive constituents that have not been assessed in randomized trials. In support of this, the randomized intervention study evaluated the intake of kiwi fruit (3 kiwi fruits/day added to the regular diet) and using gene expression profiles as a proxy outcome, the study showed that phytochemicals work in concert rather than individually (Bøhn et al. 2010).

An emerging role of carotenoids in relation to neuroinflammation and the occurrence of its positive effects on Alzheimer's disease pathophysiology has been extensively evaluated in both *in vivo* and *in vitro* models (Nazem et al. 2015; Ardura-Fabregat et al. 2017). Neuroinflammation is a response of the nervous system during autoimmune disorders, trauma, and neurodegeneration (Stephenson et al. 2018). Carotenoids have been shown to decrease proinflammatory cytokine release and lipid peroxidation by inhibiting the stimulation of the NF-κB pathway in the presence of oxidative stressors (Kim et al. 2012; Wu et al. 2015; Liu et al. 2017a). The animal study showed that feeding rats with lycopene (100 mg/kg for 2 months) increased SOD activity in the hippocampus and reduced the neuron-restrictive silencer factor (NRSF) levels in the vascular dementia rats (Zhu et al. 2020), indicating that the memory and learning impairment of vascular dementia rats could be alleviated by lycopene. NRSF plays a crucial role in numerous cellular processes in the nervous systems (Warburton et al. 2015), in which the NRSF levels are markedly increased under stress-associated conditions of Alzheimer's disease and aging. A study reported by Yu et al. (2017) further demonstrated that administration of lycopene (5 mg/kg for 8 weeks) can reduce the increase of tau phosphorylation at Ser396, Ser262, Ser235, and Thr231 in brain tissues of P301L transgenic mice, implied that suppression of tau protein phosphorylation may modulate the Alzheimer's disease. In addition to lycopene, the beneficial effects of dietary carotenoids, for instance, crocetin, crocin, astaxanthin, and fucoxanthin have been investigated in recent decades (Lin et al. 2016b; Finley and Gao 2017; Tribuzi et al. 2017; Yuan et al. 2020; Hafez et al. 2021). The previous study has demonstrated that crocetin (10 and 20 μM) and crocin (10 and 20 μM) can inhibit the generation of NO and proinflammatory cytokines stimulated by β-amyloid (Aβ), interferon-γ, and LPS in microglial cells (Nam et al. 2010). Astaxanthin has also been demonstrated to protect neurons in Parkinson's disease (Lee et al. 2011; Ye et al. 2012, 2013) and Alzheimer's disease (Lobos et al. 2016). Consistent with the beneficial effects of carotenoids treatment on the neurodegenerative study on cell culture and animal studies, the cohort study has also shown the correlation between the intakes of total carotenoids (6.7–24.8 mg/day during the follow-up for a mean of 7 years) and had less global Alzheimer's disease and dementia pathology (Tan and Norhaizan 2019; Yuan et al. 2021). A study evaluated zeaxanthin and lutein in relation to cognitive performance among 2011–2014 National Health and Nutrition Examination Survey (NHANES) among US adults aged ≥60 years old (Christensen et al. 2020). The data showed that a high intake of zeaxanthin and lutein from foods and supplements may prevent or delay cognitive decline (Christensen et al. 2020). In support of this, a case-control study further revealed that patients with Alzheimer's disease showed lower serum levels of carotenoids (zeaxanthin, lycopene, lutein, β-cryptoxanthin, β-carotene, and α-carotene) compared to cognitively normal subjects (Mullan et al. 2017). Despite experimental and human studies have proposed a possible relationship between increased consumption of both nonprovitamin A carotenoid and provitamin A species and the decreased risk of Parkinson disease; however, the risk reduction was small and did not always reach statistical significance (Guest and Grant 2016). A study reported by Hughes et al. (2016) showed that intake of carotenoids from nuts, vegetables, and fruits (median intake of dietary

carotenoids = 7502–26,940 mg/day over 12 years of follow-up) was not related to the risk of Parkinson's disease. Carotenoids may suppress the onset of neurodegenerative diseases via a few mechanisms. It has been suggested that carotenoids may alleviate oxidative stress and mitochondrial dysfunction by regulating amyloid oligomer-induced signaling, modulating anti-amyloid aggregation activity and anti-neuroinflammatory effects, upregulating of antioxidant enzyme, and scavenging of ROS (Lakey-Beitia et al. 2017; Lin et al. 2017; Xiang et al. 2017; Zhao et al. 2017). Notably, the mechanisms of action of carotenoids are likely to be regulated simultaneously. For instance, feeding with a diet containing lycopene (4 mg/kg/day for 90 days) ameliorated cognitive impairment of the hippocampus in aluminium chloride ($AlCl_3$)-induced rats by inhibiting oxidative stress-mediated apoptosis and inflammation (Cao et al. 2019). Such an effect was accompanied by an elevation of SOD and GSH activity and decreased 8-hydroxy-2′-deoxyguanosine and MDA levels (Cao et al. 2019). The study further revealed that administration of lycopene resulted in the concomitant upregulation of *Nrf2* and *HO-1*, downregulation of NF-κB protein and TNF-α mRNA levels, implies that lycopene ameliorates $AlCl_3$-induced hippocampal lesions by suppressing oxidative stress-mediated inflammation in rats (Cao et al. 2019). Although many studies showed the beneficial effects of carotenoids on neurodegenerative diseases, further studies are required to elucidate whether the anti-apoptotic and antioxidative activity of carotenoids in relation to Alzheimer's disease or Parkinson's disease is interconnected and whether modulation of neuroinflammatory response could result in the therapeutic effect of carotenoids. Taken together, carotenoids are a good antioxidant that is best obtained by consuming specific foods rich with carotenoids. High consumption of carotenoids should be included in the diet of the elderly through carotenoids-rich foods.

7.5 Dietary Minerals

Dietary minerals are essential components required by all living organisms for proper body metabolism (Gharibzahedi and Jafari 2017). Minerals are naturally occurring elements with definite chemical formulas and universal structures. Minerals play a key role in transmitting nerve impulses, secreting specific hormones, regulating heartbeat, and facilitating bone formation (Pravina et al. 2013). Minerals are not only can be obtained from drinking water and food, it can also found in mineral supplements (Akram and Rehman 2018; Ershow et al. 2018). Indeed, most of the minerals can be consumed through animal sources, fruits, and vegetables (Tasić et al. 2017; Wong et al. 2019; Czech et al. 2020). However, individuals who did not meet the daily dietary mineral intake can obtain the minerals through supplementation (Wan et al. 2019).

Minerals are classified into two classes, namely, trace minerals and macrominerals. Macrominerals are dietary minerals that are needed in a large amount, such as calcium, magnesium, chloride, phosphorus, sodium, and potassium; whereas trace minerals including fluoride, zinc, copper, iron, iodine, and selenium (Sousa et al. 2019). These trace elements are usually served as a functional part of the enzyme

(Yatoo et al. 2013). Nevertheless, consumption of a high amount of trace elements is noxious to both animals and humans (Counotte et al. 2019; Mehri 2020). For example, selenium is a crucial trace element that should be present in the diet to obtain an adequate intake. Selenium exerts anti-inflammatory and antioxidant actions and is responsible for immune response regulation (Ibrahim et al. 2019). However, long-term excessive selenium (2 and 6 mg/L for 85 days) supplementation significantly elevates the systolic blood pressure in male Wistar rats (Grotto et al. 2018) (Table 7.7). Selenium (200 μg/day) supplementation was also significantly increased the risk of type 2 diabetes mellitus in the elderly, suggesting that

Table 7.7 *In vivo* studies conducted in dietary minerals and their effects on age-related diseases

Age-related diseases	Animal models	Source of minerals	Dosages	Findings	References
Parkinson's disease	Male Wistar rats	Selenium	11.18 μg/L in drinking water	Effectively prevented the harmful effects of the toxin in locomotor activity, reducing bradykinesia, and DNA damage in leukocytes	Ellwanger et al. (2015)
Alzheimer's disease	Wistar rats	Selenium	1 mg/kg for 21 days	Attenuate lipid peroxidation and protect against aluminium chloride-induced Alzheimer's disease	Lakshmi et al. (2015)
Osteoporosis	Male Wistar rats	Zinc supplements	300 mg zinc/kg diet or 3000 mg zinc/kg diet for 4 weeks	Reduced bone mineral density	Suzuki et al. (2016)
Diabetic cardiomyopathy	Female Wistar rats	Normal basal diet (AIN-76) with the addition of zinc salt (zinc carbonate)	Five times (0.19 g/kg diet) and ten times (0.38 g/kg diet) for 6 weeks	Reduced hypercholesterolemia and hyperlipidemia, ameliorated hyperglycemia-induced oxidative stress, and showed cardioprotective effects	Barman and Srinivasan (2017)
Diabetic nephropathy	Male Wistar rats	Zinc supplemented diet	5 mg/kg in drinking tap water	Protect diabetic-induced renal damage in rats	Elsaed and Mohamed (2017)
Hypertension	Male Wistar rats	Selenium	2 and 6 mg/L for 85 days	Elevate systolic blood pressure	Grotto et al. (2018)
Huntington's disease	R6/1 mice	Dietary zinc	Zinc-deficient diet (chow: Specialty Feeds) for 15 weeks	Caused cognitive impairment and exacerbated hippocampal LTP deficit	Ayton et al. (2020)

AIN American Institute of Nutrition, *LTP* long-term potentiation

selenium supplementation may increase the development of diabetes (Thompson et al. 2016).

They are several minerals showed their antioxidant properties such as magnesium, selenium, zinc, and copper (Salmonowicz et al. 2014). For instance, zinc plays a crucial role in the body by suppressing the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) enzyme (do Nascimento Marreiro et al. 2017), acts as a cofactor for SOD enzymes (Cruz et al. 2015), regulating the GSH metabolism (Omata et al. 2013), and modulating the metallothionein expression (Ganger et al. 2016). Table 7.8 summarizes the roles and primary sources of macrominerals and trace minerals.

The deficiency of selenium, iodine, zinc, and iron affects about 15, 30, 30, and 60%, respectively, of the world population (Gharibzahedi and Jafari 2017). The mineral malnutrition in developing and industrial countries has drawn attention from the researchers, which attempts to design a technological and scientific study to overcome the minerals deficiency (Gharibzahedi and Jafari 2017). The deficiency of trace minerals can affect organs in the body (Zemrani and Bines 2020). In children and infants, the predominant causes of zinc deficiency are low zinc levels or malnutrition in breast milk, undernourishment, and parenteral nutrition (Livingstone 2015). Further, eating disorders, for instance, bulimia and anorexia nervosa may also cause zinc deficiency in both adults and children (Humphries et al. 1989). Malabsorption disorders also caused zinc deficiency (Prasad 2020). For example, inherited diseases such as cystic fibrosis and acrodermatitis enteropathica, as well as chronic inflammatory bowel diseases including ulcerative colitis and Crohn's disease may also lead to zinc malabsorption. Apart from that, high consumption of phytic acid, iron, or copper can also lead to dietary zinc malabsorption (Glutsch et al. 2019).

Dietary minerals have beneficial antioxidant and biochemical effects on several age-related diseases in the elderly (Tan et al. 2018; Skrajnowska and Bobrowska-Korczak 2019; Squitti et al. 2020) (Table 7.9). Zinc was found to negatively associate with CVD in humans based on several studies. Research evidence has revealed that zinc decreases TG, LDL-C, and TC and increases HDL-C levels (Li et al. 2010; El-Ashmony et al. 2012; Olechnowicz et al. 2018). A systematic review of prospective cohort studies comprising of 91,708 participants revealed that high serum zinc level was found to be associated with the reduced risk of cardiometabolic diseases, particularly in CVD (Chu et al. 2016). From the study reviewed, it showed that the protective effect of zinc was more pronounced in vulnerable individuals, specifically for those with coronary angiography or patients with type 2 diabetes mellitus (Chu et al. 2016). In support of this, low serum zinc levels (˂14.1 μmol/L) increased the incidence of myocardial infarction by 37% (Soinio et al. 2007). Notably, data from a prospective cohort study involving 20,460 Australian women aged 50–61 years revealed that consumption of food rich in zinc such as meat, dairy products, cereals, poultry, and fish, has a greater likelihood to increase the incidence of CVD in women (Milton et al. 2018). A recent systematic review and meta-analysis of 16 randomized controlled trials and 26 prospective cohort studies demonstrated that dietary calcium intake (72.2–4405 mg/day and follow-up for

Table 7.8 The roles and primary sources of macrominerals and trace minerals

Groups	Minerals	Main functions	Examples of food sources		
			Vegetables/Fruits	Animals	Others
Macrominerals	Calcium (Ca)	Blood pressure, blood clotting, immune system modulation, nerve functioning, muscles contraction and relaxation, and healthy teeth and bones maintenance	Legumes, mustard greens, and broccoli	Canned fish with bones (sardines and salmon), fortified soy milk and tofu, dairy products, and milk	–
	Magnesium (Mg)	Prevents constipation, nerve transmission, immune system health modulation, muscle contraction, and protein formation	Green and leafy vegetables, artichokes, legumes, seeds, and nuts	Seafood, dairy products, and milk	Drinking water and chocolate
	Chloride (Cl)	Essential for digestive (stomach) juices and body fluids maintenance	Olives, celery, lettuce, tomatoes, rye, and seaweed	Meat and trace amounts in milk	Breads, processed foods, soy sauce, and table salt
	Potassium (K)	Waste elimination, blood pressure maintenance, muscle contraction, nerve transmission, and fluid balance regulation	Legumes, whole grains, and dried and fresh vegetables and fruits	Yogurt (non-fat/skim, plain), milk, salmon fish, and meats	Acorn squash and baked potato
	Phosphorus (P)	Modulate nerve signaling and heartbeat, maintains acid-base balance, healthy teeth and bones maintenance, energy and ATP production, and required for protein synthesis	Legumes (lentils and beans), Brazil nuts, and squash and pumpkin seeds	Cheese, non-fat yogurt, milk, eggs, poultry, shellfish (scallops), salmon fish, and meats	Soya foods (tofu) and processed foods
	Sulfur (S)	Maintain structural integrity of skin, required for connective tissues development, and protect against toxic substances	Nuts, legumes, chives, leeks, onions, garlic, turnips, Brussels sprouts, kale, cabbage, cauliflower, and broccoli	Milk, eggs, fish, poultry, and meats	–
	Sodium (Na)	Nerve transition, muscle contraction, modulates some metabolic activities, heart function, and fluid and electrolyte balance	Canned vegetables (sweet peppers) and pickles (cucumber)	Cheese, trace amounts in milk, and cured fish and meat (bacon)	Fast foods, snacks, salted and roasted seeds and nuts (pumpkin seeds), instant soups, soy sauce, breads, and table salt

(continued)

Groups	Minerals	Main functions	Examples of food sources		
			Vegetables/Fruits	Animals	Others
Trace minerals	Chromium (Cr)	Regulates blood glucose levels, stimulates cholesterol and fatty acid synthesis, modulates body processes and brain function, and carbohydrates and fats metabolism	Molasses, black pepper, spinach, bananas, apples, green peppers, nuts, wheat germ, and whole grains	Butter, cheese, oysters, eggs chicken, liver, and beef	Unrefined foods and brewer's yeast
	Boron (B)	Important in modulating organ and cellular membrane functions, embryonic development, and improving the estrogen levels	Oat and wheat bran, legumes (beans and lentils), peanut butter, nuts, dried fruits (raisings and prunes), olives, avocados, apples, pears, peaches, red grapes, banana, potatoes, onions, carrots, and broccoli	–	Bee pollen, honey, and fruit juices
	Cobalt (Co)	Reduces neuromuscular, digestive, and fatigue	Figs, mushrooms (especially shitake), nuts, green leafy vegetables (spinach, turnip, lettuce, cabbage, and broccoli), and cereals (oats)	Shellfish, fish, mussels, oysters, milk, kidneys, liver, and meat	–
	Fluoride (F)	Delays bone density loss and maintain bone structure, decreases cavities in children, prevents tooth decay, teeth and bones development	Teas	Deboned chicken/meat, seafood (shellfish and fish)	Canned shellfish and fish, wine, beer, processed cereals, and drinking water
	Iodine (I)	Involved in several crucial component of hormones produced by the thyroid gland such as production of blood cells, muscle and nerve function, reproduction, metabolism, development, and growth	Organic potatoes, navy beans, strawberries, dried prunes, cranberries, and bananas	Boiled eggs, baked turkey breast, dairy products and milk, and seafood (lobster, shrimp, and cod fish)	Canned corn, tuna, baked potatoes, bread, and iodized salt
	Copper (Cu)	Neutralizes free radicals, promotes healing, repairs injured tissues, promotes immune system, required for proper functioning of organs and metabolic processes, and involved in protein metabolism	Avocados, dried fruit (prunes), mushroom, kale, whole grains, sesame seeds, cashew nuts, and legumes (chickpeas and cooked beans)	Goat cheese, oysters, and organ meats	Fermented soy foods (tempeh) and drinking water
	Iron (Fe)	An integrated part for crucial enzyme systems in several tissues, a transport medium for electrons within cells, needed for energy metabolism, and needed for the formation of hemoglobin in red blood cells	Dried fruits, dark leafy green vegetables, bran, whole grains, white beans, lentils, nuts, and pumpkin and squash seeds	Poultry, eggs, lamb, beef, clams, mussels, oysters, and liver (chicken)	Tofu, cereals, breads, cocoa powder, and dark chocolate
	Manganese (Mn)	Crucial for the nervous system activity and normal functioning of the brain, important for the growth of human bone structure, and preventing osteoporosis	Tea (black, brewed), whole grains (brown rice), spinach, beans, pumpkin seeds, and nuts	Fish and seafood	Tofu and bread (whole-wheat)
	Molybdenum (Mo)	Cell protection, produce energy within the cells, and produce enzymes that are required to remove waste from the body	Cucumber, wheat flour, sunflower seeds, nuts, leafy vegetables (spinach), whole grains, and legumes (lentils, peas, and beans)	Organ meats (lambs), cheese, milk, liver, and eggs	Breads and pasta
	Selenium (Se)	Assist in detoxification process, protect the organism from various viruses, stimulate the immune system, and protect the body from free radicals, heavy metals, and other harmful substances	Mushrooms, brown rice, lima/pinto beans, whole grains (rye), Brazil nuts, seeds (flaxseed, sesame, sunflower, and chia), and green and leafy vegetables (spinach, cabbage, and broccoli)	Pork, turkey and chicken, lamb and beef, fish, and seafood (oysters)	Selenium-enriched yeast and whole-wheat bread
	Zinc (Zn)	Important for protein synthesis and genetic materials, exert a key role in modulating the immune system, normal growth, fetal development, wound healing, and taste perception and improve digestion	White mushrooms, beans, nuts, squash and pumpkin seeds, spinach, wheat germ, and leavened whole grains	Pork, poultry, fish, lam and beef, and seafood (oyster)	Cocoa powder and chocolate

Source: Gharibzahedi and Jafari (2017)

Table 7.9 The clinical studies of dietary minerals on age-related diseases

Age-related diseases	Study conditions	Source of minerals	Durations	Outcomes	References
Type 2 diabetes mellitus	Phase III, randomized, placebo-controlled study	Selenium supplements	200 μg/day for 33.0 months (range from 0 to 82.6 months)	↑ Risk of type 2 diabetes mellitus in elderly	Thompson et al. (2016)
Type 2 diabetes mellitus	Systematic review of prospective cohort studies comprising of 334,387 participants	Zinc intake (dietary and/or supplements)	Median intake = 4.9–18.0 mg/day and follow-up for 4.8–24 years	No association	Chu et al. (2016)
Type 2 diabetes mellitus	Prospective cohort study involving 8921 women aged 45–50 years	Dietary zinc consumption from sugar, fat spreads, eggs, dairy products, bread, vegetables, and fruits	5.94–17.35 mg/day during 6 years of follow-up	↓ Risk of type 2 diabetes mellitus in women	Vashum et al. (2013)
CVD	Systematic review of prospective cohort studies comprising of 91,708 participants	Zinc (serum level)	≤14.1 μmol/L	↓ CVD risk	Chu et al. (2016)
CVD	Cohort study (20,460 Australian women aged 50–61 years)	Zinc-containing foods (meat, dairy products, cereals, poultry, and fish)	5.94–17.35 mg/day, with a mean intake of 10.66 mg/day and follow-up for 6 years	↑ Incidence of CVD in women aged 50 and above	Milton et al. (2018)
CVD	Systematic review and meta-analysis of 16 randomized controlled trials and 26 prospective cohort studies	Dietary calcium from dairy foods and nonalcoholic beverages	72.2–4405 mg/day and follow-up for 5.5–65 years	Do not increase the risk of CVD such as stroke and coronary heart disease	Yang et al. (2020b)
CVD	Systematic review and meta-analysis of 16 randomized controlled trials and 26 prospective cohort studies	Calcium supplements	1000–1500 mg/day during 6 months-7.1 years of follow-up	↑ Risk of myocardial infarction	Yang et al. (2020b)

(continued)

Age-related diseases	Study conditions	Source of minerals	Durations	Outcomes	References
Alzheimer's disease	10 patients (aged 54–93 years) with early or moderate AD, as well as 60 healthy people (aged 52–83 years)	Serum zinc and selenium	–	Low concentrations in Alzheimer's disease patients compared to healthy individuals	Socha et al. (2021)
Cognition	5435 community-dwelling men aged ≥65 years, a cohort study with a median follow-up for cognitive function of 4.6 years	Serum sodium	126–140 mmol/L	Low serum sodium increased risk of cognitive decline	Nowak et al. (2018)
Osteoporosis	12,794 community-dwelling individuals (6301 men and 6493 women) aged 40–74 years and follow-up for 5 years	Dietary calcium (fish, beans, vegetables, dairy products and milk, fruits, and cereals)	Women = 537 mg/day and men = 442 mg/day	Low calcium intake increased vertebral fractures and total fractures in women	Platonova et al. (2021)
Osteoporosis	Multicenter, hospital-based, and cross-sectional study involving 277 women with osteoporotic fractures.	Dietary calcium	Mean intake = 503.7 ± 274.7 mg/day, ranged from 36.4 to 2090.8 mg/day	Positive correlation on bone mineral density of femoral neck	Yoon et al. (2016)
Osteoporosis	Randomized controlled trial comprising a total of 1994 osteopenic postmenopausal women aged 65 years old and above during 6 years of follow-up	Dietary calcium	886 mg/day	No effect	Bristow et al. (2019)

CVD cardiovascular disease

5.5–65 years) from dairy foods and nonalcoholic beverages do not increase the risk of CVD such as stroke and coronary heart disease; whereas calcium supplementation (1000–1500 mg/day during 6 months-7.1 years of follow-up) may potentially lead to the development of coronary heart disease, particularly in myocardial infarction (Yang et al. 2020b). These findings suggest that intake of calcium should be included in the diet of the elderly via calcium-rich containing food. Table 7.9 summarizes the clinical studies of dietary minerals on age-related diseases.

Zinc is thought to play a crucial role in insulin secretion in peripheral tissues (Ruz et al. 2019). The binding of zinc to insulin is crucial for the maturation, crystallization, and biosynthesis of the hormone (Chabosseau and Rutter 2016). Zinc is transported to the insulin secretory granules of β-cells via ZnT8 (Chu et al. 2016). The previous study found that deletion or lack of ZnT8 reduces insulin secretion and crystallization (Wijesekara et al. 2010). Suppressing the stimulation of NF-κB, zinc leads to the inhibition of IL-6, TNF-α, and IL-1β secretion from macrophages and monocytes (Chasapis et al. 2020). A study reported by Vashum et al. (2013) evaluated dietary zinc in relation to type 2 diabetes mellitus. The data showed that high dietary zinc consumption (5.94–17.35 mg/day during 6 years of follow-up) from sugar, fat spreads, eggs, dairy products, bread, vegetables, and fruits is negatively associated with the type 2 diabetes mellitus in women (Vashum et al. 2013). Zinc intake has been linked to the decrease of oxidative stress through a few mechanisms. Indeed, zinc is involved in the insulin secretion, production, and action that served as a catalytic factor for the carboxypeptidase H enzyme. This enzyme facilitates the conversion from an inactive form of proinsulin into an active form of insulin. Moreover, zinc is also caused the phosphorylation of the insulin receptor by releasing more glucose into the cells (Norouzi et al. 2018). In a systematic review, zinc was found to improve insulin resistance in obese individuals (Cruz et al. 2017). Despite several studies have found an inverse association between dietary zinc and diabetes mellitus risk, not all findings showed such a link. Chu et al. (2016) did not identify an association between type 2 diabetes mellitus risk and zinc dietary/supplements intake (4.9–18.0 mg/day and follow-up for 4.8–24 years). Collectively, zinc plays a crucial role as an antioxidant nutrient that mediates insulin levels in type 2 diabetes mellitus.

In addition to the effects mentioned above, zinc has also shown a significant impact on brain function (Qi and Liu 2019). In particular, the hippocampus contains the highest zinc levels in the body (Frederickson 1989). The loss of zinc may compromise neuronal activity (Ayton et al. 2020). Low cortical zinc was shown to trigger cognitive impairment (Ayton et al. 2020). An animal study further demonstrated that dietary restriction of zinc exacerbated hippocampal long-term potentiation (LTP) deficit, suggesting that zinc may play a crucial role in maintaining the brain function of Huntington's disease (Ayton et al. 2020) (Table 7.7). Huntington's disease is characterized by cognitive decline and chorea motor impairment (Paulsen 2011), and typically occurred in mid-life, suggesting that aging may play a key role in the pathogenesis of Huntington's disease (Machiela and Southwell 2020). In the brain, abnormal metabolism of trace elements could modulate the mitochondrial functions and synaptic signaling pathways, induce inflammation, oxidative stress,

protein aggregation, and lead to synaptic dysfunction in the brain of Alzheimer's disease patients (De Benedictis et al. 2019). The previous study stated that patients with Alzheimer's disease had a relatively low concentration of serum zinc and selenium levels compared to healthy individuals (Socha et al. 2021). It has been found that proper zinc homeostasis is crucial in Alzheimer's disease because extremely high levels of zinc may lead to tau aggregation-induced toxicity and apoptosis and trigger the formation of granular tau aggregates in neuronal cells, which subsequently contributes to the hyper-phosphorylation of tau. By contrast, very low amounts of zinc can contribute to the development of amyloid fibril (Cristóvão et al. 2016; Hu et al. 2017). Frequent consumption of tea, jam, meat, poultry, honey, and flour products may positively correlated with serum zinc levels; whereas frequent intakes of cottage cheese, raw vegetables, sausages, and cakes may negatively link to the serum zinc concentration (Socha et al. 2021). A study reported by Nowak et al. (2018) evaluated the serum sodium level in relation to cognitive function in the community-dwelling older man. The data showed that low serum sodium levels (126–140 mmol/L) were related to the risk of cognitive decline in community-dwelling older men (Nowak et al. 2018). This finding could be attributed to the reducing extracellular sodium which may lead to the increases in oxidative stress markers (Barsony et al. 2011). Indeed, oxidative stress is one of the predominant factors that contribute to brain senescence, which can lead to cognitive decline (Forster et al. 1996).

Calcium is an essential nutrient crucial in modulating bone metabolism, and deficiency of calcium has been associated with osteoporosis (Park et al. 2017), particularly in East Asians (Balk et al. 2017). In a study by Platonova et al. (2021) focusing on dietary calcium-containing foods such as fish, beans, vegetables, dairy products and milk, fruits, and cereals (women = 537 mg/day and men = 442 mg/day) on osteoporotic fracture risk in middle-aged and elderly Japanese women and men, women were shown to have a greater likelihood of vertebral fractures and total fractures with low calcium intake compared to the men during a 5-year follow-up, suggesting that high intakes of dairy products and milk may be useful in women with low calcium consumption. In another cross-sectional study comprising 277 women with osteoporotic fractures showed that dietary intake of calcium (503.7 ± 274.7 mg/day) showed a positive effect on bone mineral density (Yoon et al. 2016). The beneficial role of calcium against osteoporosis is mediated through two main mechanisms, namely paracellular and transcellular pathways (de Barboza et al. 2015). Calcitriol ($1,25(OH)_2D_3$) is the major regulating hormone responsible for the intestinal Ca^{2+} absorption (de Barboza et al. 2015), which can change the function and structure of enterocytes (Tolosa de Talamoni et al. 1989; Alisio et al. 1997), and subsequently improve the Ca^{2+} transport across the intestine (de Barboza et al. 2015). Intriguingly, the data further revealed that nearly 80% of elderly Korean women with osteoporotic fractures had calcium intake below the recommended dietary intake (<700 mg/day) (Yoon et al. 2016). Despite research has demonstrated a beneficial effect of calcium intake and osteoporosis, not all studies showed such a relationship. A recent study by Bristow et al. (2019) did not identify an association between dietary calcium (886 mg/day) intake and postmenopausal bone loss during

6 years of follow-up in osteopenic postmenopausal women aged 65 years old and above. This finding suggests that an increase in calcium consumption is unlikely to reduce bone loss in the elderly. Overall, minerals are a good antioxidant to be consumed by ingesting specific food high with their chemical elements of interest. The crucial role played by minerals required further elucidation. Nonetheless, an overdose of mineral consumption is not recommended and may lead to an adverse outcome to health.

7.6 Ascorbic Acid

Ascorbic acid ($AscH_2$) or known as vitamin C, is a water-soluble ketolactone comprised of two ionizable hydroxyl groups (Du et al. 2012) (Fig. 7.5). Under physiological pH, the ascorbate monoanion, $AscH^-$, is the predominant form of vitamin C (Du et al. 2012). Ascorbate serves as a reducing agent and is readily to undergo two consecutive reactions, namely one-electron oxidation to form ascorbate radical ($ASc^{\bullet -}$) and dehydroascorbic acid (DHA) (Zhitkovich 2020). Due to the resonance stabilization of the unpaired electron, the ascorbate radical is relatively unreactive and is readily dismute to ascorbate and DHA (Du et al. 2012). In this regard, these properties make ascorbate an effective donor antioxidant (Padayatty et al. 2003). In general, there are three primary biological functions of ascorbic acid including acceptor/donor in electron transport either at the chloroplasts or plasma membrane, radical scavenger, and enzyme cofactor (Davey et al. 2000). Ascorbic acid is comprised of 4 –OH groups that can donate hydrogen to an oxidizing agent. Ascorbic acid is prone to chelate metal ions (Fe^{++}) due to the presence of –OH groups toward the carbon atoms (Timoshnikov et al. 2020). Pure ascorbic acid is a white crystalline powder, which is highly soluble in water and thus contributes to a colorless solution (Du et al. 2012). At high amounts of ascorbic acid (>1000 mg/kg), it tends to change the balance between ferrous (Fe^{2+}) and ferric iron (Fe^{3+}) and thus suppress oxidation and scavenge the oxygen (Timoshnikov et al. 2020). Ascorbic acid serves as a cofactor for several enzyme-catalyzed reactions, for example, mediating the hematopoiesis and leukocyte activity, hydroxylation of proline and lysine, neuroprotection, improving the iron absorption and collagen biosynthesis, and modulating the vascular and connective tissue's integrity (Kishimoto et al. 2013; May and Harrison 2013; Lane et al. 2016; Carr and Maggini 2017; Bonnet 2019).

Most of the animals and plants synthesize ascorbate from glucose (Drouin et al. 2011). In reptiles, amphibians, and primitive fish, the synthesis of ascorbate takes place in the kidney; while the site of synthesis in mammals is in the liver (Ching et al. 2015). However, guinea pigs, other primates, humans, and a few species of fruit-eating bats cannot synthesize ascorbate because of the dysfunction of the gene encoding $_L$-gulonolactone oxidase (GLO) (Nishikimi et al. 1994). GLO is the enzyme required for the last step in ascorbate synthesis (Cui et al. 2011; Drouin et al. 2011). Therefore, dietary intake is vitally important. It can be acquired through the consumption of many plants, particularly in vegetables such as broccoli and

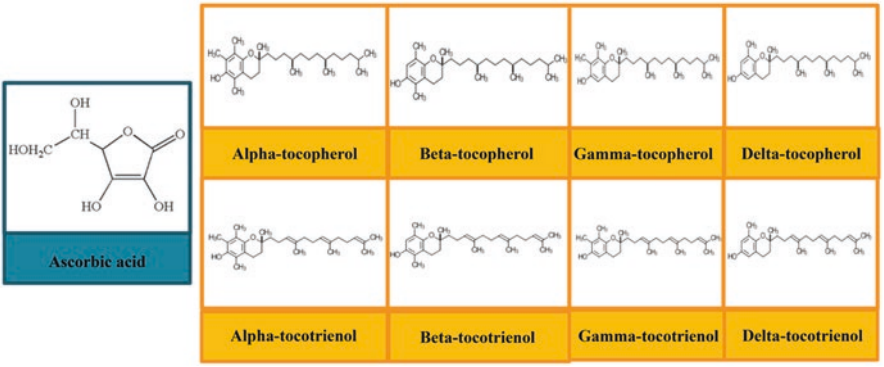

Fig. 7.5 Molecular structures of ascorbic acid and vitamin E congeners, namely tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol) and tocotrienols (α-tocotrienol, β-tocotrienol, γ-tocotrienol, and δ-tocotrienol)

tomatoes, and citrus fruits including orange and lemon (Aditi and Graham 2012). A typical human diet contains both DHA and ascorbate, in which the absorption occurs in the enterocytes of the small intestine (Vanderslice and Higgs 1991). In general, the DHA is absorbed through Na^+-independent facilitative glucose transporters (GLUTs) followed by intracellular reduction (Navale and Paranjape 2016); whereas the ascorbate is accumulated in cells via Na^+-dependent vitamin C transporters (SVCTs) (Wohlrab et al. 2017). At physiological circumstances, the plasma DHA levels are very low ($\leq$2 μM); whereas the plasma glucose concentrations are relatively higher (2–5 mM). Therefore, high intracellular ascorbate levels are mainly due to the uptake of ascorbate by SVCT2 (SLC23A2) and SVCT1 (SLC23A1) (May 2011).

One of the prominent functions of ascorbic acid in animal and plant metabolism is to mediate several enzymatic reactions (Smirnoff 2018). In general, these enzymes are di- or monooxygenases, which contain copper or iron at the active site and require ascorbic acid for maximal activity. Ascorbic acid plays an important role in maintaining the transition metal ion centers of these enzymes in a reduced form (Du et al. 2012). In animals, the Fe-dioxygenases involved in the collagen biosynthesis and require ascorbic acid for maximal activity (Davey et al. 2000). Ascorbic acid is needed for the mediation of adrenal hormone and folate synthesis, wound healing, carnitine biosynthesis, and osteoblasts and fibroblasts activity (Davey et al. 2000). The previous study further revealed that ascorbic acid can suppress the catechol-*O*-methyl transferase, and thereby promoting the bioavailability of adrenaline (Kern and Bernards 1997). This finding suggests that ascorbic acid could play a crucial role in neuroendocrine control. In support of this, the central nervous system and adrenal medulla, the adrenaline synthesis areas, showed a high concentration of ascorbic acid (May 2012).

Ascorbic acid possesses an ability to protect both membrane components of cells and cytosolic from oxidant damage (Ali et al. 2020). In particular, ascorbate serves as a predominant antioxidant to scavenge the free radicals that are produced as

by-products from cellular metabolism (Akram et al. 2017). Indeed, one of the crucial features of ascorbate is the synergistic action with vitamin E (Vineetha et al. 2020). Ascorbic acid may play an indirect role against α-tocopheroxyl radical in cellular membranes (Traber and Stevens 2011). In this regard, ascorbate is critical in modulating vitamin E to suppress lipid oxidation. It has been demonstrated that increased plasma ascorbate levels through supplementation reduced rates of disappearance of vitamin E in smokers (Bruno et al. 2006), suggesting that ascorbate could maintain vitamin E, more likely via "recycling". Ascorbic acid is a powerful antioxidant that exerts the ability to donate a hydrogen atom and produces a relatively stable ascorbyl-free radical (Nweze et al. 2019). Ascorbic acid is thought to be a critical water-soluble antioxidant in decreasing oxidative stress and neutralizing ROS (Peng et al. 2019).

Ascorbic acid has been suggested to reduce oxidative damage as well as decrease the risk of age-related diseases (Halabi et al. 2018; Delrobaei et al. 2019; Shivavedi et al. 2019). High concentrations of intravenous ascorbic acid (10 g/day) have been used as a complementary agent in cancer patients since 1970s (Cameron and Campbell 1974; Cameron and Pauling 1976; Padayatty et al. 2006; Daniel 2011). The study showed that the rate of survival in patients with advanced cancer was improved following supplementation of a high dose of ascorbic acid (Cameron and Campbell 1974; Cameron and Pauling 1976). However, the methodology of several aspects, for instance, data analysis and collection were criticized in these studies, and thereby limited the use of ascorbic acid in cancer patients (van Gorkom et al. 2019). Subsequently, oral supplementation of ascorbic acid was evaluated in cancer patients (Creagan et al. 1979). Intriguingly, based on the evidence from a systematic review, intravenous administration appears to have a better effect compared to oral administration (van Gorkom et al. 2019).

The therapeutic potential of ascorbic acid has been consistently reported in *in vitro* (Pires et al. 2018), *in vivo* (Ribeiro et al. 2009), and clinical studies (Li et al. 2019b). The previous study has demonstrated that ascorbic acid can suppress the viability of colon cancer (C2BBe1) cells, with half-maximal inhibitory concentrations (IC_{50}) of 0.95 mM after 24 h incubation (Pires et al. 2016). In line with this, the proliferation of breast cancer (MCF-7) cell lines was significantly reduced following administration of a high concentration of ascorbic acid (10 mM or 20 mM for 2 h) (Lee et al. 2019). Ascorbic acid has also been evaluated as a component of combination therapy with chemosensitization agents or primary treatment (Hoffer et al. 2015; Baillie et al. 2018). It has been shown that combining high dose of ascorbic acid (5, 10, and 20 mM for 2 h) with tamoxifen (1, 2, and 4 μM for 24 h) or fulvestrant (25 and 50 μM for 24 h) further reduced the viability of MCF-7 cell lines, suggesting that combination of high concentration of ascorbic acid and chemotherapy may have therapeutic potential against breast cancer (Lee et al. 2019). In an animal study, feeding Balb/c nu/nu mice with ascorbic acid (150 mg/kg for 14 days) significantly suppressed the colon tumor growth compared to the control group (Pires et al. 2018) (Table 7.10). In human study, a relatively low plasma ascorbic acid level was found in patients with endometrial cancer (Kuiper et al. 2010). From the study reviewed, high-grade tumors had low amounts of ascorbate

Table 7.10 *In vitro*, *in vivo*, and clinical studies conducted in ascorbic acid supplements and their effects on cancer

Cell lines/animal models/ subjects	Treatment	Findings	References
Advanced cancer patients	10 g/day	↑ The rate of survival	Cameron and Campbell (1974); Cameron and Pauling (1976)
Colon cancer cells (C2BBe1)	0.95 mM for 24 h	↓ Cell proliferation	Pires et al. (2016)
Different stages of cancers (breast, nasopharynx carcinoma, lung, ovarian, and liver)	25–100 g/day	Improved the quality of life and reduce the risk of metastasis	Raymond et al. (2016)
Stage IV poorly-differentiated pancreatic ductal adenocarcinoma male patient	75–125 g/infusion for 2–3 times/week	Ameliorates the progression of the disease and improved the survival	Drisko et al. (2018)
Balb/c nu/nu mice	150 mg/kg for 14 days	↓ Colon tumor growth	Pires et al. (2018)
Breast cancer cells (MCF-7)	10 mM or 20 mM for 2 h	↓ Cell viability	Lee et al. (2019)

concentrations (Kuiper et al. 2010). Importantly, reduced plasma ascorbic acid level was linked to a high concentration of the inflammatory marker including CRP (Halabi et al. 2018). Ascorbic acid deficiency is commonly observed in 30% of patients with advanced cancer (Mayland et al. 2005). In stage IV poorly-differentiated pancreatic ductal adenocarcinoma male patient aged 68 years old, high concentration of ascorbic acid (75–125 g/infusion for 2–3 times/week) ameliorates the progression of the disease and improved the survival of the patients (about 4 years after diagnosis) (Drisko et al. 2018). A study reported by Raymond et al. (2016) evaluated intravenous ascorbic acid (25–100 g/day) in relation to several types of cancers of different stages including breast, nasopharynx carcinoma, lung, ovarian, and liver. The study showed that intravenous ascorbic acid therapy improved the quality of life and thereby may prolong their life expectancy (Raymond et al. 2016). The study further revealed that intravenous ascorbic acid may reduce the risk of metastasis and stabilize cancer (Raymond et al. 2016). In the context of dietary ascorbic acid from foods, the data from systematic review and meta-analysis involving 17 studies suggested that dietary intake of citrus fruits, one of the excellent sources of ascorbic acid, reduced the oral cavity and pharyngeal cancer risk by 50% (Cirmi et al. 2018) (Table 7.11). In support of this, 10 case-control studies involving 18,207 participants have shown that intake of ascorbic acid derived from a variety of vegetables and fruits such as pears/apples, green salad, tomatoes, kiwi, citrus fruits, potatoes, cabbage, mandarin orange, Japanese persimmon, and spinach (mean intake of ascorbic acid = 133.40 mg/day) was negatively associated with head and neck cancer (Favero et al. 1997; Imaeda et al. 1999; Edefonti et al. 2015)

Table 7.11 Effects of dietary consumption of foods rich in ascorbic acid on cancers in human studies

Types of cancers	Dietary food intake	Findings	References
Pancreatic cancer	Ascorbic acid from diet (22.9–226 mg/day)	↓ Risk of pancreatic cancer	Hua et al. (2016)
Pancreatic cancer	Ascorbic acid from diet (51.3–678.55 mg/day)	No effect	Hua et al. (2016)
Oral cavity and pharyngeal cancer	Citrus fruits	↓ Oral cavity and pharyngeal cancer risk by 50%	Cirmi et al. (2018)
Head and neck cancer	Pears/apples, green salad, tomatoes, kiwi, citrus fruits, potatoes, cabbage, mandarin orange, Japanese persimmon, and spinach (mean intake of vitamin C = 133.40 mg/day)	↓ Risk of head and neck cancer	Favero et al. (1997); Imaeda et al. (1999); Edefonti et al. (2015)

(Table 7.11). Likewise, the meta-analysis of case-control studies conducted between 1988 and 2013 involving 10,115 controls and 3818 pancreatic cancer had revealed that ascorbic acid from the diet (22.9–226 mg/day) was inversely associated with the risk of pancreatic cancer (Hua et al. 2016) (Table 7.11). However, Hua et al. (2016) did not identify an association of ascorbic acid obtained from the diet (51.3–678.55 mg/day) and pancreatic cancer in a follow-up study conducted from 2002 to 2013 involving a total of 278,000 subjects and 1140 cancer participants (Table 7.11). Compared to those who consume ascorbic acid from supplements (60–450 mg/day), individuals who consume ascorbic acid-rich diet have relatively strong protection against pancreatic cancer (Hua et al. 2016). The preventive effect of ascorbic acid on cancers could be attributed to its antioxidant and anti-inflammatory actions. Yet, the anticancer ability of ascorbic acid is modulated via a few mechanisms, for instance, inducing apoptosis, mediating growth factor signaling, and regulating cell cycle and phase II detoxifying enzymes (Kim et al. 2015; Piersma et al. 2017; Gao et al. 2019; Zhou et al. 2020a).

Intakes of vegetables and fruits, especially rich in ascorbic acid, are thought to have a protective effect on cardiovascular health (Tan et al. 2018) (Table 7.12). Data from a meta-analysis of prospective studies have shown that a diet high in ascorbic acid (45–375.8 mg/day) is negatively associated with the risk of stroke (Chen et al. 2013). From the study reviewed, it showed that high circulating ascorbic acid concentration (3.6–73.36 μmol/L) may reduce the risk of stroke (Chen et al. 2013). Ascorbic acid prevents stroke via a few mechanisms including protect the membrane from peroxidation, suppress the growth of smooth muscle, and decrease the oxidation of LDL activity (Siow et al. 1998). Importantly, systemic inflammation is implicated in the pathogenesis of stroke (Dziedzic 2015). Ascorbic acid has been suggested to have anti-inflammatory activity (Diomede et al. 2020). In this regard, ascorbic acid may delay the development of stroke through pressure-lowering

Table 7.12 Clinical studies conducted in ascorbic acid supplements and foods rich in ascorbic acid and their effects on cardiovascular health

Cardiovascular health	Source of ascorbic acid	Findings	References
Coronary heart disease	Ascorbic acid-rich vegetables and fruits (>30 mg ascorbic acid/serving)	Protect against coronary heart disease	Joshipura et al. (2001)
Healthy young adults	Ascorbic acid (≥150 mg/day) from fruits and vegetables intakes (including tangerine/orange, kiwi, avocado, papaya, mango, melon, watermelon, nectarine/apricot/peach, grape-fruit, strawberry, pear/apple, banana, pineapple, fig, guava, plum, cherry, cucumber/zucchini/aubergines, peppers, green beans, pumpkin/carrot, tomatoes, cabbage, broccoli/cauliflower, chicory/lettuce, dark-green leaves/spinach, onion, 'gazpacho', beetroot, and asparagus)	↑ Glutathione peroxidase activity and total antioxidant capacity ↓ Plasma ox-LDL levels	Hermsdorff et al. (2012)
Adults	Ascorbic acid (500–4000 mg/day and 500–2000 mg/day)	↓ Blood pressure and improve endothelial function	Juraschek et al. (2012); Ashor et al. (2014)
Stroke	Diet high in ascorbic acid (45–375.8 mg/day)	↓ Risk of stroke	Chen et al. (2013)
Stroke	Circulating ascorbic acid concentration (3.6–73.36 μmol/L)	↓ Risk of stroke	Chen et al. (2013)
Hypertensive and/or diabetic obese adults	Ascorbic acid supplements (500–1000 mg/day)	No significant effects on several cardiovascular endpoints	Sesso et al. (2008); Ellulu et al. (2015); Buijsse et al. (2015)
Adults aged 18 years or older	Increased 50 mg/day of dietary ascorbic acid intake	↓ 8% of CVD mortality risk	Jayedi et al. (2019)
Adults aged 18 years or older	Increased 20 μmol/L in circulating ascorbic acid levels	↓ 13% risk of CVD mortality	Jayedi et al. (2019)

CVD cardiovascular disease, *ox-LDL* oxidized-low density lipoprotein

activity (Uesugi et al. 2017). Based on the clinical evidence, ascorbic acid supplementation is not likely to prevent stroke (Myung et al. 2013). Increasing consumption of ascorbic acid-rich foods and adhering to healthy lifestyles and dietary habits may markedly decrease the burden of stroke and other CVD (Chen et al. 2013). The previous study stated that circulating ascorbic acid concentrations may act as a good predictor of diet status and stroke risk (Chen et al. 2013). Similarly, the prospective cohort study involving 42,148 men aged 40 to 75 years old and 84,251 women aged 34 to 59 years old and followed up for 8 and 14 years, respectively, on ascorbic acid-rich vegetables and fruits (>30 mg ascorbic acid/serving) in relation to the risk of coronary heart disease (Joshipura et al. 2001). The study showed that consumption of ascorbic acid-rich vegetables and fruits may protect against the development of

coronary heart disease (Joshipura et al. 2001). Intriguingly, increased 1 serving/day of vegetables and fruits reduced the risk of coronary heart disease by 4%, suggesting that ascorbic acid-rich vegetables and fruits and green leafy vegetables played a pivotal cardioprotective role in total vegetables and fruits (Joshipura et al. 2001). In support of this, the cross-sectional study has demonstrated that ascorbic acid (≥150 mg/day) from fruits and vegetables intake (including tangerine/orange, kiwi, avocado, papaya, mango, melon, watermelon, nectarine/apricot/peach, grapefruit, strawberry, pear/apple, banana, pineapple, fig, guava, plum, cherry, cucumber/zucchini/aubergines, peppers, green beans, pumpkin/carrot, tomatoes, cabbage, broccoli/cauliflower, chicory/lettuce, dark-green leaves/spinach, onion, 'gazpacho', beetroot, and asparagus) significantly increased GPx activity and total antioxidant capacity and reduced plasma ox-LDL levels in healthy young adults, suggesting that ascorbic acid has the potential to regulate antioxidant-mediated mechanism and combat oxidative stress (Hermsdorff et al. 2012). Hypertension and CVD are often linked to low GPx levels (Jin et al. 2011), indicating that GPx can prevent free radical production in the redox homeostatic balance of cellular metabolism. In a further study focused on the risk of total cardiovascular mortality outcomes, a dose-response meta-analysis of 15 prospective observational studies showed that a relatively low risk (8%) for CVD mortality for those with increased 50 mg/day of dietary ascorbic acid intake (Jayedi et al. 2019). From the study reviewed, it showed that increased 20 μmol/L in circulating ascorbic acid levels is linked to the 13% lower risk of CVD mortality (Jayedi et al. 2019). Importantly, a dose-response meta-analysis suggested that a possible threshold of ascorbic acid intake of about 200 mg/day (Jayedi et al. 2019). Some research has also emerged to suggest that the optimal dietary intake of ascorbic acid is about 200 mg/day; the concentration in which the blood cells are completely saturated and the plasma is relatively saturated with ascorbic acid (Frei et al. 2012). Mangels et al. (1993) exploring the bioavailability of synthetic ascorbic acid and food rich in ascorbic acid. Interestingly, the bioavailability of ascorbic acid from cooked broccoli, orange juice, and oranges is similar to ascorbic acid supplements (Mangels et al. 1993). The data from clinical trials (Sesso et al. 2008; Ellulu et al. 2015) and observational studies (Buijsse et al. 2015) have shown that supplementation of ascorbic acid (500–1000 mg/day) did not lead to any significant effects on several cardiovascular endpoints. By contrast, studies from meta-analyses revealed that a high concentration of ascorbic acid (500–4000 mg/day and 500–2000 mg/day) can reduce blood pressure (Juraschek et al. 2012) and improve endothelial function (Ashor et al. 2014), respectively.

Research evidence has demonstrated the potential protective function of ascorbic acid in diabetes (Mason et al. 2019) (Table 7.13). Ascorbic acid deficiency (<0.3 mg/dL) is linked to type 2 diabetes mellitus (Praveen et al. 2020). It has been shown that individuals with ascorbic acid deficiency have high serum MDA levels, suggesting that increased oxidative stress (Praveen et al. 2020). In a further study focused on diabetes outcomes, Praveen et al. (2020) showed that high serum ascorbic acid levels are negatively linked to glycated hemoglobin (HbA1c), suggesting that ascorbic acid may be beneficial in managing glycemic control and prevent micro- and macrovascular complications. These complications contribute to the mortality and

Table 7.13 Clinical studies conducted in ascorbic acid supplements and foods rich in ascorbic acid and their effects on diabetes mellitus

Sources	Dosages	Findings	References
Ascorbic acid and vitamin E	Ascorbic acid (1250 mg) and vitamin E (680 IU) for 4 weeks	Inhibited albuminuria	Gaede et al. (2001)
Sour orange juice	240 mL/day for 4 weeks	↓ Fasting blood glucose levels	Ravanshad et al. (2006)
Fruits	86.2–165.5 mg/day	↓ Risk of diabetic retinopathy	Tanaka et al. (2013)
Watermelon, bananas, berries (grapes, blueberries, and strawberries), drupes (Japanese apricots, cherries, and peaches), citrus fruits (lemon, grapefruit, and orange), and pome fruits (Japanese persimmons, Japanese pears, and apples), and other melons	22.6–253 g/day	↓ Incidence of diabetic retinopathy	Tanaka et al. (2013)

morbidity of diabetes mellitus patients, in which all these factors are linked to oxidative stress (Ullah et al. 2016). Importantly, patients with diabetic nephropathy show reduced levels of ascorbic acid (Varma et al. 2014; Chou and Tseng 2017). The exclusion of ascorbic acid from the tubular epithelial cells via the competition of dehydroascorbate and glucose, and thereby deprive the cells from antioxidant capacity and ultimately results in the accumulation of ROS in diabetes (Chen et al. 2005). The deficiency of ascorbic acid stimulates the transforming growth factor beta (TGF-β) signaling pathway, and thereby aggravates the diabetic mesangial cellular expansion and deposits of extracellular matrix (Ji et al. 2017). Dietary ascorbic acid has demonstrated a positive impact on diabetes (Mason et al. 2019). The consumption of sour orange juice (240 mL/day for 4 weeks) significantly increased the ascorbic acid intake by 24% (Ravanshad et al. 2006). The study further revealed that the fasting blood glucose levels were significantly reduced after intakes of sour orange juice, suggesting that short-term dietary consumption of sour orange juice may reduce the fasting blood glucose levels (Ravanshad et al. 2006). Dietary ascorbic acid not only decreases blood glucose levels but also declines the risk of diabetic retinopathy (May 2016). A follow-up study for 8 years including 978 patients with type 2 diabetes aged 40–70 years old had revealed that ascorbic acid in fruits (86.2–165.5 mg/day) decreased the risk of diabetic retinopathy (Tanaka et al. 2013). Tanaka et al. (2013) further demonstrated that increased consumption of fruits (22.6–253 g/day) such as watermelon, bananas, berries (grapes, blueberries, and strawberries), drupes (Japanese apricots, cherries, and peaches), citrus fruits (lemon, grapefruit, and orange), and pome fruits (Japanese persimmons, Japanese pears, and apples), and other melons is negatively linked to the incidence of diabetic retinopathy. Such protection has been accredited to antioxidant vitamins including ascorbic acid. High fruits and vegetables consumption are known to trigger the elevation of

plasma ascorbic acid levels (Djuric et al. 2006). Nonetheless, Lee et al. (2010) did not identify an association between ascorbic acid and diabetic retinopathy. In support of this, a systematic review involving 4094 participants found that no association between dietary intake of ascorbic acid and diabetic retinopathy (Lee et al. 2010). While, a systematic review including 3 randomized controlled trials, 15 cross-sectional, 4 case-control, and 9 prospective studies performed by Wong et al. (2018a) suggest that the relationships of ascorbic acid intakes and diabetic retinopathy are remained unclear, suggesting that further studies are required to elucidate these relationships. In addition to the effects reported on diabetic retinopathy, supplementation of ascorbic acid has also shown a beneficial effect on diabetic nephropathy (Hirsch et al. 1998). Diabetic nephropathy is a microvascular complication of diabetes mellitus that contributes to end-stage renal disease (Singh et al. 2011; Rondeva and Wolf 2014). For instance, ascorbic acid (1250 mg) and vitamin E (680 IU) for 4 weeks were significantly inhibited albuminuria in patients with type 2 diabetes with macro- or microalbuminuria (Gaede et al. 2001).

Oxidative stress is implicated in the etiology of neurodegenerative disease such as Parkinson's disease (Butterfield and Halliwell 2019). The plasma ascorbate levels were linked to cognition in the general population. Compared to cognitively intact individuals, the cognitively impaired group had relatively low amounts of ascorbate concentrations (Travica et al. 2017). In general, brain ascorbate levels are maintained at higher levels compared to other organs (Harrison and May 2009). Research evidence indicates that patients with Parkinson's disease showed high oxidative stress markers and low plasma ascorbate levels compared to healthy individuals (Sudha et al. 2003; Medeiros et al. 2016). A study including 215 participants aged 50–90 years old had revealed a significant role of ascorbate levels in Parkinson's disease. It has been shown that ascorbate levels (>23 μmol/L) were positively related to the cognitive function in Parkinson's disease (Spencer et al. 2020). This favorable effect is more likely due to the other non-antioxidant acts as ascorbate, which may contribute to the cognitive function (Spencer et al. 2020). Ascorbic acid has been shown to prevent Alzheimer's disease-induced by oxidative stress (Monacelli et al. 2017) (Table 7.14). The implication of ascorbic acid in relation to the pathophysiology of dementia and Alzheimer's disease has been widely demonstrated in both *in vivo* and *in vivo* studies. Ascorbic acid delays disease progression through several mechanisms including reduce neuronal cell death, decrease oxidative stress, and

Table 7.14 Clinical studies conducted in foods rich in ascorbic acid and their effects on neurological disorders

Sources	Dosages	Findings	References
Ascorbic acid from cabbage, broccoli, sprouts, kiwi, and citrus fruits	121.6 mg/day for 6 years	↓ Risk of Alzheimer's disease	Engelhart et al. (2002)
Ascorbic acid-rich fruits and vegetables	90.3–238.4 g/day for 13 years	Improved verbal memory performance	Péneau et al. (2011)
Ascorbic acid derived from oranges and orange juice	95–213 g/day for a mean of 17 years	Not associated with the cognitive decline	Devore et al. (2013)

inhibit proinflammatory cytokines (Zhang et al. 2018c). A follow-up study for 6 years including 5395 participants had revealed a significant role of ascorbic acid in Alzheimer's disease (Engelhart et al. 2002). It has been shown that for individuals aged ≥55 years old, dietary intake of ascorbic acid (121.6 mg/day) from cabbage, broccoli, sprouts, kiwi, and citrus fruits may reduce the risk of Alzheimer's disease (Engelhart et al. 2002). In support of this, a prospective study analyzed of 2533 participants aged 45–60 years has demonstrated that dietary intake of ascorbic acid-rich fruits and vegetables (90.3–238.4 g/day) for 13 years shows a better verbal memory performance (Péneau et al. 2011). This finding indicates that verbal memory performance could be improved by increasing fruits and vegetables consumption (Péneau et al. 2011). Intriguingly, supplementation of ascorbic acid (124–761 g/day) for a mean of 17 years reduced cognitive decline in the elderly (Devore et al. 2013). Although research evidence indicates that ascorbic acid shows a better cognitive function, not all experimental studies demonstrated such an association. Devore et al. (2013) did not identify an association between dietary consumption of ascorbic acid and cognitive decline. The study involving 16,010 participants aged ≥70 years old from 1995 to 2001 revealed that dietary consumption of ascorbic acid (95–213 g/day) derived from oranges and orange juice for a mean of 17 years was not linked to the cognitive decline (Devore et al. 2013). Together, the research evidence indicates that ascorbic acid has significant beneficial outcomes in diseases suffered by the elderly. Ascorbic acid should be included in the diet of the elderly through the consumption of foods rich in ascorbic acid. Indeed, the potential implications of ascorbic acid on age-related diseases are nonetheless worthy of further elucidation to explore the pathophysiology of age-related diseases.

7.7 Vitamin E

Vitamin E is a lipid-soluble and plant-derived compound comprised of eight structurally related lipophilic chromanol congeners with a side chain located at the C2 position (Niki and Abe 2019). Vitamin E usually found in fat-rich food, for instance, seeds and edible oils, or present in fortified food (Rizvi et al. 2014), including α-, β-, γ-, and δ-tocopherols and four corresponding tocotrienols (Shahidi and de Camargo 2016) (Fig. 7.5). The four tocopherols possess a saturated phytyl side chain; whereas four tocotrienols exert an unsaturated isoprenyl side chain with three double bonds at C11′, C7′, and C3′ (Shahidi and de Camargo 2016). The double bonds of tocotrienols' side chains at both C7′ and C3′ containing *trans*-configuration. Both α-, β-, γ-, and δ-tocotrienols and tocopherols are classified based on the position and the number of methyl substitution in the chromanol ring (Ahsan et al. 2015). The δ-forms of tocotrienols and tocopherols possess one methyl group and γ- and β-forms exert two methyl groups; whereas the α-forms have three methyl groups at C8, C7, and C5-position in their chromanol ring (Niki and Abe 2019). Of all isoforms of vitamin E, γ-tocopherol is the predominant form of vitamin E found in the diet; whereas α-tocopherol is the most common form of vitamin E in the

mammalian tissues (Jiang et al. 2001; Jiang 2014). Vitamin E has been recognized as one of the crucial free radical scavenging antioxidants in humans to protect the biological molecules from detrimental oxidative modifications (Niki and Abe 2019).

Vitamin E exerts a unique anti-atherosclerotic property (Elbeltagy et al. 2019). Much information indicates that vitamin E can modulate the activity of several protein kinases such as protein kinase C and protect against platelet aggregation, lipid deposition in the aorta, and inflammation (Khadangi and Azzi 2019). A systematic review and dose-response meta-analysis of prospective observational studies comprising of 7777 cases and 228,531 participants showed an inverse association of CVD mortality risk for 10 μmol/L increment in circulating α-tocopherol concentration (Jayedi et al. 2019). However, in a further study focused on the risk of CVD mortality outcomes, Jayedi et al. (2019) found that every 5 mg/day increment in dietary vitamin E intake was not linked to the risk of CVD mortality. These findings suggested that the circulating α-tocopherol may have a better predictive value in relation to the risk of total CVD mortality compared to the dietary vitamin E intakes (Jayedi et al. 2019). A significant decrease in ATP-binding membrane cassette transporter A1 (*ABCA1*) DNA methylation levels among Japanese women was found to be related to the high dietary vitamin E intake (6.88–9.43 mg/day) (Fujii et al. 2019). Research evidence indicates that the antioxidant property of vitamin E is involved in the mediation of transcriptional activity via DNA methyltransferase-dependent pathway (Remely et al. 2017). In this regard, it is plausible that the negative association of *ABCA1* DNA methylation and dietary intake of vitamin E modulates DNA methyltransferase activity (Fujii et al. 2019). ABCA1 is a predominant transporter that modulates the formation of HDL particles via interaction with apolipoprotein A1 (apoA1) (Fujii et al. 2019). The previous study stated that high levels of ABCA1 DNA methylation are negatively linked to HDL-cholesterol levels and subsequently increased the risk of coronary heart disease in humans (Guay et al. 2012, 2014). In addition, dietary vitamin E from vegetable oils, nuts, cereal grains, and seeds (median intake = 12.9 IU/day during 4 years of follow-up) has also been reported to decrease the risk of coronary heart disease among men who did not consume vitamin supplements (Rimm et al. 1993). Table 7.15 summarizes the *in vitro*, animal, and clinical studies of vitamin E on age-related diseases.

Research evidence has demonstrated that a vitamin E-rich diet has the potential to protect against neurodegenerative disease (Frank et al. 2012; Boccardi et al. 2016). In a human study, Engelhart et al. (2002) followed 5395 participants aged 55 years and above for 6 years had found that high consumption of vitamin E-rich foods (13.8 mg/day) such as egg yolk, milk, nuts, and grains, reduced the risk of Alzheimer's disease. Inflammation and oxidative stress are implicated in age-related cognitive impairment (Costa d'Avila et al. 2018). A single-blinded and randomized-controlled trial among healthy and middle-aged/old adults showed that intakes of 3 oz/day (84 g) almond for 6 months significantly increased serum α-tocopherol level by 8% compared to the baseline (Rakic et al. 2021). Although the study reported by Rakic et al. (2021) did not find an association of serum α-tocopherol concentration with the improved cognition performance, the pivotal role played by α-tocopherol on brain function should not be neglected. Alpha-tocopherol acts as a

Table 7.15 *In vitro*, animal, and clinical studies of vitamin E on age-related diseases

Age-related diseases	Study conditions	Source of vitamin E	Durations	Outcomes	References
CVD	Systematic review and dose-response meta-analysis of prospective observational studies comprising of 7777 cases and 228,531 adults aged 18 years and above	Dietary vitamin E	Every 5 mg/day increment	Not associated with the CVD mortality risk	Jayedi et al. (2019)
CVD	Systematic review and dose-response meta-analysis of prospective observational studies comprising of 6542 cases and 34,285 participants	Circulating α-tocopherol	Every 10 μmol/L increment	↓ CVD mortality	Jayedi et al. (2019)
CVD	Cross-sectional study involving 225 participants (117 women and 108 men) aged 39 years old and above	Dietary vitamin E	6.88–9.43 mg/day	↓ ABCA1 DNA methylation levels	Fujii et al. (2019)
Coronary disease	39,910 U.S. male health professionals aged 40 to 75 years old and follow-up for 4 years	Dietary vitamin E from vegetable oils, nuts, cereal grains, and seeds	Median intake = 12.9 IU/day	↓ Coronary disease risk in men	Rimm et al. (1993)
Alzheimer's disease	Prospective cohort study including 5395 participants aged 55 years and above and follow-up for an average of 6 years	Vitamin E-rich foods such as egg yolk, milk, nuts, and grains	13.8 mg/day	↓ Risk of Alzheimer's disease	Engelhart et al. (2002)
Age-related cognitive impairment	Single-blinded, controlled, randomized-trial including 60 men and postmenopausal women aged 50–75 years	Almond	3 oz./day or 84 g for 6 months	↑ Serum α-tocopherol level by 8%	Rakic et al. (2021)
Neurodegenerative disease	Systematic review of 10 animal studies	Tocotrienol-rich fraction from palm oil	100–200 mg/kg per day for 10 weeks-8 months orally	Improved cognitive function	Ismail et al. (2020)
Osteoporosis	MC3T3-E1 cells	Annatto-derived tocotrienol	0.001–1 μg/mL	↓ RhoA activation and downregulating HMGR transcriptional activity	Hasan et al. (2020)

Osteoporosis	Male Sprague-Dawley rats	Annatto-derived tocotrienol	60 and 100 mg/kg	Enhances bone calcium content and femoral biomechanical strength	Mohamad et al. (2018)
Osteoporosis	Male Sprague-Dawley rats	Palm tocotrienol	60 mg/kg/day for 2 months	Preserved bone strength and structure and maintained serum resorption levels	Elvy Suhana et al. (2018)
Osteoporosis	Male Wistar rats	Palm vitamin E	60 or 100 mg/kg for 12 weeks	Improved trabecular thickness, bone volume, and osteoblast surface	Wong et al. (2018b)
Prostate cancer	PC-3 cell line	Annatto tocotrienol	20 μg/mL for 24 h	↓ Proliferation of PC-3	Sugahara et al. (2015)
Lung cancer	Dose-response meta-analysis involving 9 prospective cohort studies including 431,359 controls and 4164 cases	Dietary vitamin E mainly from soybean oil, soybeans, eggs, and leafy greens	Every 2 mg/day increment	↓ 5% of lung cancer risk	Zhu et al. (2017)

ABCA1 ATP-binding membrane cassette transporter A1, *CVD* cardiovascular disease, *HMGR* HMG-CoA reductase, *MC3T3-E1* murine pre-osteoblastic cells, *PC-3* prostate cancer cell lines

protector of the integrity of polyunsaturated fatty acid as well as modulating the cell membrane function and morphology, suggesting a critical in maintaining adequate α-tocopherol concentration in a brain (Traber and Atkinson 2007). In support of this, a systematic review revealed that feeding healthy animals with a tocotrienol-rich fraction from palm oil (100–200 mg/kg per day for 10 weeks–8 months orally) had better cognitive function (Ismail et al. 2020). The study further demonstrated that tocotrienol-rich fraction (25, 50, or 100 mg/kg for 10 weeks) possesses anti-inflammatory and antioxidant activities, improved cognition performance by ameliorating the oxidative stress and decreasing neuroinflammation in diabetes-induced rats (Ismail et al. 2020). This finding is further supported by Kuhad et al. (2009) and Tiwari et al. (2009) who found that α-tocotrienol and tocotrienol-rich fraction had similar antioxidant activity and improved cognitive function in diabetes-induced rats, implied that α-tocotrienol is the isomer that may responsible for the antioxidant activities and better cognitive function of the tocotrienol-rich fraction. The previous study also found that a mutual underlying pathophysiological event between neurological disorders and diabetes mellitus (Nasrolahi et al. 2019) is likely due to the homeostatic imbalance of insulin-glucagon in diabetes mellitus, and thereby triggers amyloid deposition in the brain and pancreatic islets of Langerhans (Morsi et al. 2019). Feeding diabetic rats with tocotrienol-rich fraction enhanced the cholinergic function by decreasing the cerebrocortical concentration of acetylcholinesterase (Kuhad et al. 2009). Acetylcholinesterase is the enzyme that catalyzes the breakdown of acetylcholine neurotransmitter, and thereby leads to the development of neurodegeneration and dementia (Bohnen et al. 2018).

In addition to the age-related diseases mentioned above, the deficiency of vitamin E is linked to the diseases closely linked to aging, for instance, osteoporosis (Mata-Granados et al. 2013). *In vitro* study showed that annatto-derived tocotrienol (0.001–1 μg/mL) inhibits the mevalonate pathway by suppressing the RhoA activation and downregulating 3-hydroxy-3-methyl-glutarylcoenzyme-A (HMG-CoA) reductase (HMGR) gene expression in murine pre-osteoblastic (MC3T3-E1) cells, suggesting that annatto-derived tocotrienol may modulate the osteoblast mineralization (Hasan et al. 2020). The inhibition of the mevalonate pathway by annatto-derived tocotrienol indicates that the annatto may serve as a potent bone anabolic agent. Annatto-derived tocotrienol is found in the seeds of achiote plant native to tropical America, containing 10% γ- and 90% δ-tocotrienol (Raddatz-Mota et al. 2017). Consistent with the study reported by Hasan et al. (2020), Mohamad et al. (2018) also found that supplementation of annatto-derived tocotrienol (60 and 100 mg/kg) significantly decreased the degeneration of cortical and trabecular bone thickness in buserelin-induced rats. From the study reviewed, it showed that annatto-derived tocotrienol (60 and 100 mg/kg for 3 months) enhances the bone calcium content and femoral biomechanical strength, suggests that it may serve as a potential anti-osteoporotic agent for men who received androgen deprivation therapy (Mohamad et al. 2018). Further, a beneficial role of palm tocotrienols has also been shown on osteoporosis. An animal study showed that palm tocotrienol (60 mg/kg/day for 2 months) preserved bone strength and structure and maintained serum resorption levels in rats, implied that palm tocotrienol has potential against

glucocorticoid-induced osteoporosis by modulating osteoclast and osteoblast at the transcriptional level (Elvy Suhana et al. 2018). Likewise, palm vitamin E (60 or 100 mg/kg for 12 weeks) also increased trabecular thickness, bone volume, and osteoblast surface in high-carbohydrate high-fat-treated rats (Wong et al. 2018b).

Dietary intake of vitamin E not only can modulate CVD and neurological disorders, it also inhibits several cancers. Annatto tocotrienol (20 μg/mL for 24 h) was shown to inhibit the proliferation of PC-3 prostate cancer cell lines via the suppression of STAT3 and Src (Sugahara et al. 2015). In support of this, a study by Tan and Norhaizan (2021) has revealed that prostate cancer and oxidative stress could be prevented by dietary components rich in antioxidants. While for lung cancer, a dose-response meta-analysis has demonstrated the risk of lung cancer was decreased by 5% for every 2 mg/day increment of dietary vitamin E intake (Zhu et al. 2017). Vitamin E prevents cancer via induction of apoptosis, inhibition of invasiveness, and mediate immune response (Jiang 2017). These data suggest that dietary vitamin E as natural cancer protector. Taken together, the evidence demonstrated that regular intakes of food rich in tocopherols and tocotrienols may potentially decrease the risk of age-related diseases. However, further studies are warranted to explore the overall long-term effects in comparative randomized clinical trials.

7.8 Ubiquinone

Ubiquinone or known as coenzyme Q10 is an endogenously synthesized and unique fat-soluble vitamin-like antioxidant that is produced in the body (Laredj et al. 2014). Ubiquinone was first isolated from beef heart mitochondria in 1957. The ubiquinone is found in organs with high rates of metabolism including kidney, liver, brain, and heart (Parrado-Fernández et al. 2011). Of all the food sources, meat and fish are the richest sources of dietary ubiquinone (Pravst et al. 2010). Ubiquinone is comprised of a polyisoprenoid side chain and benzoquinone ring containing 6 to 10 subunits with species-specific length and confers stability to the molecule inside the phospholipid bilayer (Hernández-Camacho et al. 2018) (Fig. 7.6). Ubiquinone is a ubiquitous component in the mitochondrial ETC placed in the inner mitochondrial membrane, in which it transfers electrons to complex III from complexes II and I to provide energy to the intermembrane space for proton translocation (López-Lluch et al. 2010). Ubiquinone is a potent antioxidant in the mitochondria that involve in energy synthesis via ETC (Saini 2011). It can neutralize ROS and protect plasma lipoproteins and cell membranes (Noh et al. 2013). It has been suggested that ubiquinone exerts the potential to protect against CVD via reduction of lipid peroxidation of LDL-cholesterol (Dludla et al. 2020). However, the concentration of ubiquinone is decreased with advancing age and thereby increased the risk to develop the symptoms associated with aging (Niklowitz et al. 2016). In this regard, decreasing ubiquinone concentration during aging could be one of the major contributors to the development of age-related diseases (de Barcelos and Haas 2019). It has been proposed that NAD(P)H:quinone oxidoreductase 1 (NQO1) may serve as

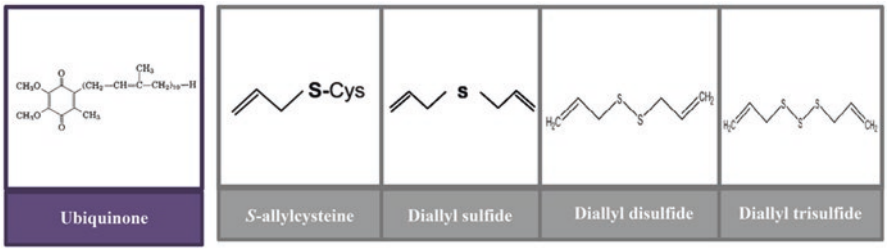

Fig. 7.6 Molecular structures of ubiquinone and organosulfur compounds (*S*-allylcysteine, diallyl sulfide, diallyl disulfide, and diallyl trisulfide)

a redox-sensitive switch to mediate the cell response in relation to the alteration of the redox status (Ross and Siegel 2017).

Emerging research evidence indicates that ubiquinone is beneficial toward neuroinflammation (Nyariki et al. 2019; Yang et al. 2020c) (Table 7.16). A study by Yamagishi et al. (2014a) followed nearly 6000 participants aged 40–69 years for 5 years revealed that serum ubiquinone levels were inversely associated with the risk of disabling dementia in the Japanese population, implied that higher serum ubiquinone concentration may have a potential effect in preventing dementia. The preventive ability of ubiquinone against dementia is more likely due to the antioxidant effect. Yet, ubiquinone prevents dementia progression via a few mechanisms, for instance, improved behavioral performance and decreased deposition of amyloid-β and brain oxidative stress (Dumont et al. 2011; Yang et al. 2016). Indeed, the rats with damaged cerebral cortices and hippocampi showed a detrimental impact on the markers of oxidative damage (Onodera et al. 2003). Matthews et al. (1998) showed that dietary intake of ubiquinone of 200 mg/kg/day for 2 months elevated the ubiquinone concentration in brain mitochondria of rats. Supplementation of 0–100 μM ubiquinone for 48 h protects the detrimental effects of Aβ in a dose-dependent manner, primarily by suppressing oxidative stress through stimulation of the PI3K/Akt pathway in the rat cortical neurons (Choi et al. 2012). An animal study also found that ubiquinone can reduce the total oxidant levels and serum MDA levels as well as increased total antioxidant capacity levels (Komaki et al. 2019). This study suggests that ubiquinone may offer neuroprotection against Aβ-induced neurotoxicity on hippocampal synaptic plasticity through antioxidant activity (Komaki et al. 2019). In human study, ubiquinone concentrations were relatively low in both Parkinson and Alzheimer's disease patients (Mischley et al. 2012; Manzar et al. 2020). In line with this, Yamagishi et al. (2014b) also found that individuals with low ubiquinone levels in the serum have a relatively high risk of dementia. Increased oxidative stress and mitochondrial impairment are thought to be involved in the pathogenesis of neurological disorder (Geldenhuys et al. 2017).

It has been suggested that the synthesis of ubiquinone is changed throughout the entire life of organisms, and is significantly decreased in the initial stages of aging (Alho and Lonnrot 2000; Crane 2001). In mice, reduced mitochondrial ubiquinone concentration of skeletal muscle and liver homogenates (Onur et al. 2014) was

Table 7.16 Animal and clinical studies of ubiquinone on age-related diseases

Age-related diseases	Study conditions	Source of ubiquinone	Durations	Outcomes	References
Neurodegenerative disease	Male Sprague-Dawley rats	Dietary ubiquinone	200 mg/kg for 2 months	↑ Ubiquinone concentration in brain mitochondria	Matthews et al. (1998)
Disabling dementia	Case-control study involving about 6000 Japanese aged 40–69 years and follow-up for 5 years	Serum ubiquinone	–	↓ Risk of disabling dementia	Yamagishi et al. (2014a)
Dementia	Japanese population	Serum ubiquinone	–	Negative associated with the risk of dementia	Yamagishi et al. (2014b)
Neurodegenerative disease	Rat cortical neurons	Ubiquinone supplement	0–100 μM ubiquinone for 48 h	Protects the detrimental effects of Aβ in a dose-dependent manner	Choi et al. (2012)
Oral cancer	Cross-sectional study involving patients more than 20 years old and under 80 years old with oral cancer (mean age = 54 years old)	Serum/plasma ubiquinone	Median ubiquinone = 280 nmol/L	Negative associated with oral cancer	Chan et al. (2020)
Hepatocellular carcinoma	A total of 71 primary hepatocellular carcinoma patients (mean age = 59 ± 11 years old)	Plasma ubiquinone	After surgery: 280 nmol/L	Negative associated with the hepatocellular carcinoma, especially in patients after surgery	Liu et al. (2017b)
Lung cancer	Prospective case-control study involving 596 participants, including 395 control subjects and 201 incident lung cancer cases	Plasma ubiquinone	–	Inverse association between ubiquinone and risk of lung cancer among current smokers	Shidal et al. (2021)

(continued)

Age-related diseases	Study conditions	Source of ubiquinone	Durations	Outcomes	References
Coronary artery disease	Systematic review and meta-analysis of 13 placebo-controlled and double-blind randomized controlled trials (364 individuals from intervention group and 349 participants in control group)	Ubiquinone supplements	60–300 mg/day of ubiquinone for 4 to 48 weeks	Reduced diene and MDA concentration, and increased catalase and SOD levels	Jorat et al. (2019)
Coronary artery disease	A randomized, placebo-controlled trial including 51 patients who were identified with cardiac catheterization with at least 50% stenosis of one major coronary artery and having statins for at least 1 month (24 subjects in placebo and 27 participants from ubiquinone group)	Ubiquinone supplement	300 mg/day for 12 weeks	Decreased TNF-α and increased GPx, catalase, and SOD activities	Lee et al. (2013)
CVD	Systematic review and meta-analysis of randomized controlled trials including 12 studies with a total of 650 diabetic patients	Ubiquinone supplement	20–200 mg/day between 8 weeks and 6 months	Reduced LDL-C and total cholesterol level in diabetic patients	Dludla et al. (2020)
Heart failure	Systematic review of 11 randomized controlled trials including 1573 participants	Ubiquinone supplement	Varied from 2 to 10 mg/kg/day in 2 or 3 divided concentration for 6 months to 400 mg/day for 3 months	Reduce the risk of mortality from all causes and hospitalization related to heart failure	Al Saadi et al. (2021)
Chronic heart failure	Meta-analysis involving 2149 patients with chronic heart failure	Ubiquinone supplement	100–200 mg/day for 3–12 months	Enhanced exercise capacity and reduced mortality	Lei and Liu (2017)

CVD cardiovascular disease, *GPx* glutathione peroxidase, *LDL-C* low-density lipoprotein cholesterol, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TNF-α* tumor necrosis factor-α

observed during aging, but not in the heart, brain, and kidney (Lass et al. 1999). However, Onur et al. (2014) found that *C. elegans*, in which ubiquinone concentration in the elderly is increased with age. Importantly, decreased circulating ubiquinone levels were found in the elderly, in which the redox status of ubiquinone significantly shifted to the oxidized form (Niklowitz et al. 2016). A study by Nagase et al. (2018) evaluated ubiquinone deficiency and increased oxidative stress among Japanese centenarians. The data showed that the percentages of the oxidized form of ubiquinone were significantly increased in centenarians compared to individuals aged 76 years, implied that an elevation of oxidative stress in centenarians (Nagase et al. 2018). The study further revealed that total serum ubiquinone level in centenarians was significantly decreased compared to individuals aged 76 years old (Nagase et al. 2018). Reduced ubiquinone levels in old age were related to the loss of antioxidant capacity in cell organelles, human tissues, or serum/plasma levels (Niklowitz et al. 2016).

Research evidence has indicated that ubiquinone deficiency is associated with cancer (Trueba et al. 2004; Cooney et al. 2011). A cross-sectional study has shown that patients with oral cancer had low ubiquinone levels, and higher ubiquinone status was significantly related to the reduced risk of metabolic syndrome, lipid profiles, and waist circumference (Chan et al. 2020). The study also found that the median ubiquinone concentration in patients with oral cancer was 280 nmol/L, which is lower than that of the healthy adults (500–1700 nmol/L) (Molyneux et al. 2008). In line with this, patients with hepatocellular carcinoma had significantly lower ubiquinone levels (280 nmol/L) after surgery (Liu et al. 2017b). The ubiquinone deficiency observed in patients with oral cancer is likely due to the high oxidative stress (Korde et al. 2011). Interestingly, the previous study stated that ubiquinone concentration was negatively linked to the risk of metabolic syndrome and increased HDL-C levels (Chan et al. 2020). These findings imply that intake of ubiquinone not only decreases oxidative stress, they also modulate lipid metabolism (Chan et al. 2020), suggesting the enormous functional potential of ubiquinone. A prospective case-control study involving 596 participants, including 395 control subjects and 201 incident lung cancer cases demonstrated an inverse association between ubiquinone and risk of lung cancer, particularly in current smokers (Shidal et al. 2021), implied that elevation of ubiquinone may provide an antioxidant reservoir that is capable in scavenging ROS produced by cigarette smoke in lung tissues (Shidal et al. 2021). This finding suggests that ubiquinone is implicated in the pathogenesis of lung cancer and may be related to the disease progression (Shidal et al. 2021).

Besides its effects on neurological disorders and cancer, the previous study has also demonstrated the role of ubiquinone on the incidence of CVD (Table 7.16). Oxidative stress via increased ROS production can affect the availability of endothelial NO, and thereby compromise vascular function (Lubos et al. 2008). The increased arterial atherosclerotic buildup is linked to endothelial dysfunction and thereby elevated the risk of heart failure (Boudina and Abel 2010; Akoumi et al. 2017; Borghetti et al. 2018; American Heart Association 2019). Data from systematic review and meta-analysis of randomized controlled trials including 12 studies with a total of 650 diabetic patients showed that the LDL-C and TC levels were

significantly decreased in diabetic patients supplemented with ubiquinone (20–200 mg/day between 8 weeks and 6 months) compared to those who consume placebo (Dludla et al. 2020), suggesting that ubiquinone may potentially reduce the risk of CVD in diabetic patients by alleviating the oxidative stress and enhancing endothelial function. In particular, heart muscle is relatively prone to ubiquinone deficiency and utilizes more energy compared to other tissues (Hargreaves et al. 2020). The weakening of the heart muscle may result in the swelling of the liver, lower feet and legs, the lining of the intestine, and lung. Heart failure is characterized by a loss of contractile function due to the depletion of energy in mitochondria associated with ubiquinone deficiency (Sharma et al. 2016). The systematic review of 11 randomized controlled trials including 1573 participants evaluated the efficacy and safety of ubiquinone in heart failure (Al Saadi et al. 2021). The study showed that ubiquinone (varied from 2 to 10 mg/kg/day in 2 or 3 divided concentration for 6 months to 400 mg/day for 3 months) may reduce the risk of mortality from all causes and hospitalization related to heart failure (Al Saadi et al. 2021). Emerging research indicates that heart failure patients suffer a deficiency of ubiquinone levels coupled with an elevation of ROS within the heart (Al Saadi et al. 2021). Removal of ROS by ubiquinone can facilitate the mediation of redox status in the heart (Ulla et al. 2017). Ubiquinone may also stabilize myocardial calcium-dependent ion channels and thereby prevent the depletion of metabolites essential for the synthesis of ATP. Likewise, a meta-analysis involving 2149 patients with chronic heart failure demonstrated that intake of 100–200 mg/day ubiquinone for 3–12 months significantly enhanced exercise capacity and reduced mortality compared to those who consume placebo (Lei and Liu 2017). Importantly, Di Lorenzo et al. (2020) showed that ubiquinone may confer prognostic advantage and did not lead to any adverse outcomes in heart failure patients. These observations imply that ubiquinone could be beneficial to patients with heart failure despite may not serve as a primary treatment, suggesting that ubiquinone may be considered as an adjunct to conventional treatment.

In a further study focused on inflammation outcomes, Jorat et al. (2019) evaluated ubiquinone in relation to inflammatory markers and proinflammatory cytokine in coronary artery disease patients. A recent systematic review and meta-analysis of placebo-controlled and double-blind randomized controlled trials involving 364 individuals from the intervention group and 349 participants in the control group demonstrated that supplementation 60–300 mg/day of ubiquinone for 4 to 48 weeks reduced diene and MDA concentration, and increased catalase and SOD levels in coronary artery disease patients (Jorat et al. 2019). From the study reviewed, Jorat et al. (2019) found that supplementation of ubiquinone did not show any improvement in GPx, IL-6, TNF-α, and CRP concentration among coronary artery disease patients. However, a randomized, placebo-controlled trial conducted by Lee et al. (2013) demonstrated that administration of 300 mg/day of ubiquinone supplement for 12 weeks reduced TNF-α concentration and increased GPx, catalase, and SOD levels in patients who had coronary artery disease during statins therapy. The findings on these CVD-related outcomes are inconclusive due to some limitations of clinical trials that have accessed these crucial CVD-related outcomes, including (1)

short duration of treatment; (2) different concentration of ubiquinone used; (3) the characteristics of study population; (4) small sample size; and (5) the differences in study design. Taken together, aging is linked to increased oxidative stress and reduced ubiquinone levels in mitochondria. Ubiquinone not only modulates inflammatory mediators, it has also shown its efficacy in heart failure. Despite many studies have demonstrated the promising finding of ubiquinone intake on several age-related diseases and oxidative stress markers, the efficacy of ubiquinone on clinical trials remains obscure. Further, research evidence available on the reduced risk of age-related diseases via ubiquinone-rich containing food is limited. Therefore, the clinical benefits of food rich in ubiquinone in relation to age-related diseases required further elucidation in long-term randomized clinical trials.

Mitochondria-targeted antioxidants have been identified to play a crucial role in ameliorating the mitochondrial oxidative damage caused by ROS production that is linked to various diseases (Nazarov et al. 2017). The mitochondria-targeted antioxidants provide greater protection towards oxidative damage is likely due to their abilities to cross the mitochondria phospholipid bilayer and thereby eliminating ROS (Jiang et al. 2020). In particular, mitochondria-targeted antioxidants contain a broad spectrum of compounds that contain an antioxidant group associated with the mitochondria-targeted moiety including triphenylphosphonium (TPP) cation (Nazarov et al. 2017). Emerging evidence indicates that mitochondria-targeted antioxidants are widely used to evaluate the impact of mitochondria on different pathological processes involve oxidative stress (Murphy and Smith 2007). It has been shown that mitochondria-targeted lipophilic ubiquinone (MitoQ) had greater protection towards oxidative damage in the mitochondria compared to untargeted antioxidants (Hao et al. 2018). In general, a broad spectrum of antioxidants could be targeted to mitochondria through TPP-conjugated ubiquinone. Substantial studies revealed that ubiquinol moiety of MitoQ can protect against peroxynitrite and react with superoxide (Maiti et al. 2018). A human study has demonstrated that MitoQ can protect against mitochondrial ROS produced in vascular tissues (Chen et al. 2020). Rossman et al. (2018) evaluated the efficacy and safety of MitoQ in healthy older adults aged 60–79 years with impaired endothelial function. The data showed that plasma MitoQ was increased after consuming 20 mg/day MitoQ for 6 weeks and was well-tolerated compared to the placebo group (Rossman et al. 2018) (Table 7.17). Notably, intakes of MitoQ significantly increased brachial artery flow-mediated dilation and decreased plasma ox-LDL, a biomarker of oxidative stress, compared to placebo. This improvement is likely due to the alleviation of mitochondrial ROS-related inhibition of endothelial function (Rossman et al. 2018). Based on the evidence, MitoQ may hold promise in treating age-related vascular dysfunction. Compared to those who consume ubiquinone, elderly aged >55 years who consume MitoQ at 200 mg/day for 14 days significantly increased the plasma ubiquinone levels in older men (Zhang et al. 2018d) (Table 7.17). The human study further demonstrated that intake of 200 mg/day of MitoQ for 4 weeks showed a better absorption in adults compared to ubiquinone (Langsjoen and Langsjoen 2014) (Table 7.17). Indeed, the data from two acute pharmacokinetics studies indicate that MitoQ shows better bioavailability compared to ubiquinone (Miles et al.

Table 7.17 Effects of MitoQ treatment on health

Age-related diseases	Study conditions/ experimental model	Source of MitoQ	Durations	Outcomes	References
CVD	Randomized, placebo-controlled, double-blinded, cross-over design study involving 20 healthy older adults (60–79 years old)	MitoQ supplement	20 mg/day for 6 weeks	Increased branchial artery flow-mediated dilation and decreased plasma oxidized LDL	Rossman et al. (2018)
Alzheimer's disease	Transgenic *Caenorhabditis elegans* model of Alzheimer's disease	MitoQ supplement	1 and 5 μM	Delays Aβ-induced paralysis and ameliorates depletion of the mitochondrial cardiolipin levels	Ng et al. (2014)
–	Healthy subjects	MitoQ supplement	200 mg/day for 4 weeks	Shows a better absorption compared to ubiquinone	Langsjoen and Langsjoen (2014)
–	Elderly aged >55 years	MitoQ supplement	200 mg/day for 14 days	Increased the plasma ubiquinone levels	Zhang et al. (2018d)

CVD cardiovascular disease, *LDL* low-density lipoprotein

2004; Evans et al. 2009). Besides its effects on CVD, previous studies have also indicated the role of MitoQ in the mediation of neuroinflammation. In the context of Alzheimer's disease, MitoQ (1 and 5 μM) delays Aβ-induced paralysis in transgenic *Caenorhabditis elegans* model of Alzheimer's disease as well as prolongs the lifespan of transgenic Aβ-overexpressing nematodes, suggesting that MitoQ not only promote healthspan but also increase lifespan (Ng et al. 2014) (Table 7.17). Importantly, loss of cardiolipin may contribute to mitochondrial dysfunction in aging and neurodegenerative disease (Falabella et al. 2021). Another study further demonstrated that treatment of MitoQ (1 and 5 μM) ameliorates depletion of the mitochondrial cardiolipin levels, indicates that MitoQ may protect the mitochondrial matrix (Ng et al. 2014). Collectively, the findings showed that MitoQ may decrease the mitochondrial dysfunction related to age-related diseases.

7.9 Organosulfur Compounds

Organosulfur compounds (Fig. 7.6) are predominantly found in vegetables species belonging to *Brassica* (Cruciferous) and *Allium* genus, for instance, cauliflower, cabbage, broccoli, garlic, and onion (Ruhee et al. 2020). The vegetables of the *Allium* genus possess a typical pungent aroma and flavor, due to the presence of volatile or oil-soluble sulfur compounds (Itakura et al. 2001). While the less odorous organosulfur compounds such as S-allyl mercapto cysteine (SAMC) and S-allyl cysteine (SAC) found in aqueous extract of garlic are water-soluble in nature and usually present in vegetables of the *Allium* genus (Wang et al. 2016b). Organosulfur compounds are liberated when the garlic is crushed or cut into pieces (Garrow et al. 2001). In onion, several intermediary sulfur compounds, for instance, tri-, di-, and monosulfides, thiosulfonates, and thiosulfinates are identified, which contributes to the strong flavor (Liguori et al. 2017). Dietary organic sulfur compounds from *Allium* species such as propyl disulfide, dimethyl disulfide, and diallyl disulfide have vasodilating, anti-inflammatory in addition to prevent several chronic diseases (Chu et al. 2017) (Table 7.18). Indeed, Fe-S clusters play a crucial role in the origin of life including RNA, acetyl-CoA, and DNA (Fuss et al. 2015). Glucosinolates are one of the naturally occurring compounds found in the *Brassica* genus, which are known as the precursors of isothiocyanates (Ruhee et al. 2020). In general, the hydrolysis of glucosinolates into thiocyanates and isothiocyanates is caused by insects and food preparation (Cabello-Hurtado et al. 2012).

Emerging research evidence indicates that organosulfur compounds exert many health benefits including anticancer properties (Alkreathy 2020). The preclinical data has demonstrated that Alliaceous vegetables containing organosulfur compounds can protect against carcinogenesis via several mechanisms such as induction of xenobiotic-metabolizing enzymes, scavenging free radicals, inhibiting the metabolism of nitrosamines and hydrocarbons, modulating cell cycle arrest, alleviating the detoxification of carcinogens, decreasing bioactivation of carcinogens, induction of apoptosis, and mediation of redox modification (Somade et al. 2018). The previous studies suggest that high broccoli sprout, garlic, and onion consumption provides greater protection in cancer risk (Zhang et al. 2020a), including breast (Desai et al. 2020), prostate (Beaver et al. 2018), and colorectal (Zhou et al. 2020b). A meta-analysis involving 12,558 cases included a study from inception to May 2019 demonstrated that intake of garlic was negatively linked to colorectal cancer (Zhou et al. 2020b). Of all phytochemicals from the *Allium* genus, organosulfur compounds were shown a greater protective effect on metabolic disorders (Ahmad et al. 2019). Much information indicates that most of the organosulfur compounds from garlic possess anticancer activity. S-allylmercaptocysteine and S-allyl-L-cysteine are abundant organosulfur compounds identified in aged garlic extract (Yan et al. 2013). In neuroblastoma cancer cells, aged garlic extract (2 mg/mL) and its derived compounds, S-allyl-L-cysteine (50 mM for 48 h) triggered apoptosis by inducing mitochondrial permeability transition (Kanamori et al. 2020). The protective effect of S-allyl-L-cysteine against neuroblastoma cancer cells could be

Table 7.18 Effects of organosulfur compounds on age-related diseases in *in vitro*, *in vivo*, and human studies

Age-related diseases	Experimental model	Source of organosulfur compounds	Durations	Outcomes	References
Hypertension	SVEC4-10	Dimethyl disulfide and diallyl disulfide from *Allium* species	500 μM for 4 h	Positively triggered PGI_2 production	Chu et al. (2017)
Breast cancer	Transgenic mouse models including SV40 and Her2/neu mice	AIN-93G diet containing 26% of sulforaphane-based broccoli sprout	Began from conception and continued throughout pregnancy until the weaning period	Exhibited a maximal preventive against breast cancer development compared to postnatal early life treatment	Li et al. (2018b)
Prostate cancer	Phase II study involving 20 patients with recurrent prostate cancer	Sulforaphane-rich broccoli sprout extracts	200 μmoles/day for 20 weeks	Did not lead to ≥50% PSA declines	Alumkal et al. (2015)
Prostate cancer	TRAMP mice	AIN-93G diet containing 15% broccoli sprout powder	9–25 weeks	Decreased the prostate cancer incidence	Beaver et al. (2018)
Prostate cancer	Randomized, double-blinded 3-arm parallel intervention study involving 49 localized prostate cancer patients on active surveillance	Glucoraphanin-rich broccoli soup	300 mL/week for 12 months	Inversely related to the risk of prostate cancer progression	Traka et al. (2019)
Neuroblastoma cancer	SJ-N-KP and IMR5 cell lines	Aged garlic extract and its derived compounds, S-allyl-L-cysteine	Aged garlic extract (2 mg/mL) and its derived compounds, S-allyl-L-cysteine (50 mM for 48 h)	Triggered apoptosis by inducing mitochondrial permeability transition	Kanamori et al. (2020)
CVD	A systematic review of 10 randomized clinical trials between 2004 and 2018	Garlic or aged garlic extract	400–2400 mg/day varied from 15 days to 3 months	Improved vascular function	Emamat et al. (2020)

CVD	36 Male Wistar albino rats, the metabolic syndrome rats were fed with high-fat diet for 4 weeks followed by intraperitoneal single streptozotocin injection in a dose of 25 mg/kg	Diallyl trisulfide derived from garlic	40 mg/kg every second day for 3 weeks	Increased HDL-C and reduced LDL-C and TG levels	Jeremic et al. (2020)
Type 2 diabetes mellitus	Adults from Tehran Lipid and Glucose Study (2006–2008 to 2009–2011)	*Allium* vegetables (raw onion and garlic)	≥142 g/week	Reduced incidence of hyperinsulinemia and insulin resistance	Mirmiran et al. (2019)
Type 2 diabetes mellitus	8-week-old female BALB/c mice	Diallyl disulfide	30 mg/kg body weight/day for 23 days	Decreased urinary 8-OHDG and proteinuria levels, alleviated doxorubicin-induced renal injury, and increased catalase activities in renal cortical tissues	Lin et al. (2019)
Neurodegenerative disorders	Male ICR mice	Sulforaphane-enriched broccoli sprouts	200 mg/kg for 2 weeks, 7 times/week	Suppress neuronal apoptosis and modulate scopolamine-induced memory impairment	Subedi et al. (2019)
Neuroinflammation	Streptozotocin-induced diabetic rats	Garlic	0.5 g/kg of for 10 days	Increased GPx and SOD activities in brain	Rahmani et al. (2020)

AIN-93G American Institute of Nutrition, *CVD* cardiovascular disease, *GPx* glutathione peroxidase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PGI_2* prostacyclin, *PSA* prostate-specific antigen, *SOD* superoxide dismutase, *SVEC4-10* endothelial cells, *TG* triglycerides, *TRAMP* transgenic adenocarcinoma of the mouse prostate, *8-OHDG* 8-hydroxy-2′-deoxyguanosine

attributed to its antioxidant properties, and thereby protecting the cells from protein oxidation and lipid peroxidation (Kanamori et al. 2020). The data from animal study also found that feeding mice with a diet containing 15% broccoli sprout or 400 mg sulforaphane/kg diet for 9–25 weeks decreased the prostate cancer incidence and HDAC3 protein expression in the anterior lobes and ventral of the prostate epithelial cells (Beaver et al. 2018). HDAC3 is predominantly expressed in patients with prostate cancer and an increase of class-I HDAC is thought to be associated with the initial stage of prostate carcinogenesis (Weichert et al. 2008). Sulforaphane, a natural dietary isothiocyanate abundantly found in cruciferous vegetables (Dacosta and Bao 2017). A study has shown that sulforaphane at 10 or 20 μM can effectively decrease NO, iNOS, and proinflammatory cytokines expression via stimulation of Nrf2/HO-1 signaling pathways in LPS-induced RAW 264.7 cells (Ruhee et al. 2019). Compared to postnatal early-life treatment, administration a diet containing 26% of sulforaphane-based broccoli sprout during maternal/prenatal (began from conception and continued throughout pregnancy until the weaning period) exhibited a maximal preventive against breast cancer development, suggesting that feeding mice with sulforaphane-based broccoli sprout diet during prenatal/maternal may affect the gene expression through transplacental epigenetic modulation and thereby delay breast tumor development in later life (Li et al. 2018b). The preventive ability of sulforaphane-based broccoli sprout in prenatal/maternal transgenic mice is mediated by multiple cellular pathways including modulation of epigenetic pathways, apoptosis, cell cycle, DNA repair, and regulation of transcription activity (Li et al. 2018b). While for prostate cancer, Traka et al. (2019) found that dietary intake of 300 mL/week of glucoraphanin-rich broccoli soup for 12 months was inversely linked to the risk of prostate cancer progression by modulating the transcriptional activity in the prostate of men on active surveillance. Intriguingly, Alumkal et al. (2015) did not identify a beneficial role of sulforaphane-rich broccoli sprout extracts against prostate cancer. The men with high levels of PSA in serum were associated with a higher incidence of prostate cancer (Catalona et al. 1991). Alumkal et al. (2015) found that the consumption of 200 μmoles/day sulforaphane-rich broccoli sprout extracts for 20 weeks did not lead to ≥50% PSA declines in men with recurrent prostate cancer.

In a study focused on inflammation outcomes, Chu et al. (2017) explored the anti-inflammatory effects of propyl disulfide, dimethyl disulfide, and diallyl disulfide from *Allium* species in LPS-treated RAW 264.7 cells. The data showed that propyl disulfide, dimethyl disulfide, and diallyl disulfide (50–500 μM for 6 h) from *Allium* species significantly suppressed the prostaglandin E_2 (PGE_2) production in LPS-induced RAW 264.7 cells. Dietary propyl disulfide, dimethyl disulfide, and diallyl disulfide (500 μM for 6 h) was found to inhibit COX-2 and iNOS expression in activated RAW 264.7 cells, implied that these dietary organosulfur compounds can prevent the LPS-induced inflammatory response in RAW 264.7 cells (Chu et al. 2017).

Besides its effects on cancer and inflammation, a recent systematic review suggests that consumption of 400–2400 mg/day garlic or aged garlic extract between 15 days and 3 months has the potential to improve vascular function, especially for

those individuals with cardiovascular risk factor (Emamat et al. 2020). Indeed, a wide range of organosulfur compounds was found in different garlic products with possibly mediate different physiological actions. Raw garlic is rich in γ-glutamylcysteines, which thereby convert to alliin (Amagase et al. 2001). When garlic is crushed, cut, or ingested, allinase enzyme is stimulated and thereby converts alliin to allicin. Subsequently, allicin is decomposed to other organosulfur compounds including ajoene (Amagase et al. 2001). Diallyl trisulfide, a secondary metabolite of allicin, is a volatile organosulfur compound produced by crushed garlic (Abe et al. 2020). A recent finding has suggested that diallyl trisulfide can effectively suppress platelet aggregation by regulating the reaction of sulfhydryl groups (Hosono et al. 2020). Jeremic et al. (2020) further demonstrated that feeding metabolic syndrome rats with 40 mg/kg of diallyl trisulfide derived from garlic every second day for 3 weeks increased HDL-C and reduced LDL-C and TG levels. The protective effect of diallyl trisulfide could be attributed to the suppression of endogenous cholesterol synthesis (Aouadi et al. 2000). The previous study has revealed that intake of garlic is associated with the inhibition of hepatic fatty acid synthesis primarily by regulating the critical enzymes and thereby decreasing plasma TG levels and lipid accumulation in the liver (Thomson et al. 2006). Jeremic et al. (2020) further demonstrated that diallyl trisulfide protects the heart against *ex-vivo* treated I/R injury in metabolic syndrome rats by alleviating the inflammation, apoptosis, and oxidative stress in the heart. This finding suggests that diallyl trisulfide has the potential to prevent cardiovascular complications and metabolic disorders (Jeremic et al. 2020). Prostacyclin (PGI_2) is a vasoactive substance derived from the endothelium that plays a crucial role in alleviating hypertension (Mitchell et al. 2014). An *in vitro* study has revealed that dietary dimethyl disulfide and diallyl disulfide (500 μM for 4 h) was positively triggered PGI_2 production in an endothelial cell line (SVEC4-10) (Chu et al. 2017). The data also demonstrated the upregulation of COX-2 expression in SVEC4-10 cells after administration of 500 μM of dimethyl disulfide or diallyl disulfide from *Allium* species for 4 h, suggesting that these organosulfur compounds can stimulate the COX-2 levels in SVEC4-10 cells (Chu et al. 2017). Indeed, COX-2 plays a critical role in the biosynthesis of PGI_2 from arachidonic acid (Nørregaard et al. 2015). In this regard, the upregulation of PGI_2 expression after treatment of dimethyl disulfide or diallyl disulfide from *Allium* species in SVEC4-10 cells could be facilitated by the increase of COX-2 levels (Chu et al. 2017), suggesting that dimethyl disulfide or diallyl disulfide may potentially act as a vasodilative mediator.

Organosulfur compounds not only reduce cancer and CVD, they also suppress hyperglycemia and insulin resistance (Melino et al. 2019). Dysfunctions of β-cell mass and progressive decrease in β-cell function are linked to the development of diabetes (Russo et al. 2014; Miranda-Osorio et al. 2016). Consumption of organosulfur compounds-rich diet was negatively linked to diabetes mellitus (Ülger and Çakiroglu 2020). A longitudinal follow-up study by Mirmiran et al. (2019) evaluated *Allium* vegetables (raw onion and garlic) in relation to hyperinsulinemia, β-cell dysfunction, and insulin resistance among adults. The study showed that high consumption of raw onion and garlic (≥142 g/week) significantly reduced the risk of

hyperinsulinemia and insulin resistance compared to low intake of raw onion and garlic (˂8.0 g/week). This finding suggests that a high intake of *Allium* vegetables may improve insulin homeostasis. However, intake of *Allium* vegetable (raw onion and garlic) was not associated with a better β-cell function (Mirmiran et al. 2019). The previous study stated that diabetic rats had relatively high amounts of DNA damage and low total antioxidant capacity and GSH levels compared to non-diabetic rats (Suresh et al. 2017). Feeding doxorubicin-induced nephrotoxicity mice with diallyl disulfide, one of the crucial components in garlic, at a dose of 30 mg/kg body weight/day for 23 days, decreased urinary 8-hydroxy-2′-deoxyguanosine (8-OHDG) and proteinuria levels, alleviated doxorubicin-induced renal injury, and increased catalase activities in renal cortical tissues, suggesting that garlic could prevent oxidative stress (Lin et al. 2019).

The previous studies demonstrated the beneficial effects of garlic and its organosulfur compounds in neurodegenerative diseases (Sripanidkulchai 2019; Bigham et al. 2021). An animal study showed that administration of 0.5 g/kg of garlic for 10 days increased GPx and SOD activities in the brain of streptozotocin-induced diabetic rats (Rahmani et al. 2020). The study further revealed that garlic (0.5 g/kg for 10 days) can improve depressive- and anxiety-like behaviors in diabetic rats possibly by ameliorating brain oxidative stress (Rahmani et al. 2020), demonstrating the enormous functional potential of organosulfur compounds. Moreover, research evidence indicates that sulforaphane-enriched broccoli sprouts (200 mg/kg for 2 weeks, 7 times/week) are of benefit in the suppression of neuronal apoptosis and modulation of scopolamine-induced memory impairment in mice, particularly via the mediation of caspase-3 and Nrf2 signaling pathways (Subedi et al. 2019). These findings suggest that sulforaphane-enriched broccoli sprouts may protect against neuroinflammation. Taken together, regular consumption of food rich in organosulfur compounds can decrease age-related diseases in addition to offer healthy aging in terms of nutrition.

7.10 Ergothioneine

Ergothioneine is a naturally occurring amino acids that are produced in certain fungi, cyanobacteria, and actinobacteria (Fahey 2001; Hseu et al. 2020). It is a thiourea derivative of histidine with a sulfur atom on its imidazole ring (Hseu et al. 2020) (Fig. 7.7). Ergothioneine serves as a powerful scavenger of hydroxyl radicals (•OH) (Mishra et al. 2018). Due to its excellent antioxidant activity, ergothioneine plays a prominent role in preventing various chronic diseases (Han et al. 2021). Ergothioneine is ubiquitously present in plants, animals, and bacteria and is thought to protect against ultraviolet radiation (Hseu et al. 2020). It also accumulates in various parts of the human body, for instance, skin, eyes, seminal fluids, kidney, erythrocytes, liver, and bone marrow (Markova et al. 2009; Cheah and Halliwell 2012). Oyster mushroom and bolete are the richest sources of dietary ergothioneine (Ey et al. 2007; Nakamichi et al. 2016). In particular, mushroom is capable in the

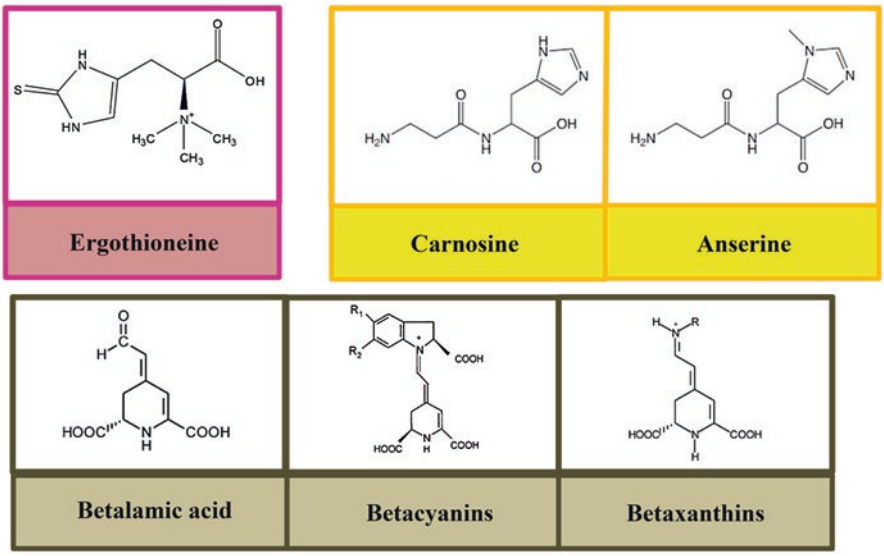

Fig. 7.7 Molecular structures of ergothioneine, betalamic acid, betacyanins, betaxanthins, carnosine, and anserine

biosynthesis of ergothioneine along with other fungi (Cheah and Halliwell 2012; Weigand-Heller et al. 2012; Kalaras et al. 2017). Ergothioneine can also be obtained from the diet such as kidney beans, oat bran, black beans, kidney, and liver (Hseu et al. 2020). Despite ergothioneine is found in many cells, plasma membranes seem to be intrinsically impermeable to ergothioneine, and thus the mode of action for accumulation and uptake in cells must exist (Cheah and Halliwell 2012). The previous study stated that ergothioneine is preferentially produced in secretions, cells, and organs predisposed to high amounts of inflammation and oxidative stress such as kidney and liver (Cheah and Halliwell 2012).

It has been suggested that ergothioneine was effective in protecting the cells from photoaging (Bazela et al. 2014). Data from *in vitro* study showed that ergothioneine (0.125–0.5 μM for 24 h) upregulated type I procollagen levels in UVA-exposed human skin fibroblast (HSF) cells in a concentration-dependent manner, suggesting that ergothioneine may protect the HSF cells from UVA radiation-induced skin aging and collagen degradation (Hseu et al. 2020). Table 7.19 summarizes the effects of ergothioneine on age-related diseases in *in vitro* and human studies.

Many studies revealed that mushroom exerts beneficial effects to the brain (Borodina et al. 2020; Zhang et al. 2017b; Feng et al. 2019b) as well as reduced the incidence of age-related diseases such as diabetes (Calvo et al. 2016; Okada et al. 2019; Hodge and Calvo 2019) and prostate cancer (Zhang et al. 2020b). Compared to those who rarely consume mushrooms, elderly who consume mushroom more than 2 portions/week have a significantly lower incidence of mild cognitive impairment (Feng et al. 2019b). This neuroprotective effect could be mainly ascribed to

Table 7.19 *In vitro* and human studies conducted in ergothioneine and their effects on age-related diseases

Age-related diseases	Experimental model	Outcomes	References
Skin aging	HSF cells treated with ergothioneine at a dose of 0.125–0.5 μM for 24 h	Upregulated type I procollagen levels in UVA-exposed human skin fibroblast	Hseu et al. (2020)
Mild cognitive impairment	Elderly who consume mushroom more than 2 portions/week	Reduced incidence of mild cognitive impairment	Feng et al. (2019b)
Cognitive impairment	Blood ergothioneine levels	Low blood ergothioneine levels in subjects with cognitive impairment	Cheah et al. (2016)
Parkinson's disease	Blood ergothioneine levels	Patients with Parkinson's disease had lower blood ergothioneine levels	Hatano et al. (2016)
CVD	3236 participants free from stroke, coronary artery disease, and type 2 diabetes mellitus aged 57.4 years and follow-up for 21.4 years	Ergothioneine metabolic level decreased the risk of overall mortality, cardiovascular mortality, and coronary disease	Smith et al. (2020)
Frailty	Elderly	Low in ergothioneine metabolic levels	Kameda et al. (2020)

CVD cardiovascular disease, *HSF* human skin fibroblast, *UVA* Ultraviolet A

their ergothioneine composition (Borodina et al. 2020). Research evidence has also revealed a potential protective function of ergothioneine in neurological disorders (Cheah et al. 2019). Ergothioneine supplementation was found to reduce neuronal injury (Yang et al. 2012) and protect rat phaeochromocytoma cells against Aβ-induced apoptotic death (Jang et al. 2004). In human study, individuals with cognitive impairment had lower blood ergothioneine levels compared to individuals with no cognitive impairment (Cheah et al. 2016). Likewise, the previous study also revealed that Parkinson's disease patients had relatively lower blood ergothioneine levels compared to control (Hatano et al. 2016). These findings indicate that ergothioneine transporter is present in the brain, in which the ergothioneine can pass through the blood-brain barrier (Tang et al. 2018), suggesting that low ergothioneine levels may predispose individuals to neurodegenerative disease.

Notably, intake of ergothioneine was associated with longevity (Beelman et al. 2019). A recent study suggested that ergothioneine can serve as a "longevity vitamin" based on the Triage Theory. This theory speculates that the human body utilizes specific micronutrients as it was in a triage phenomenon where the priority is given to its role on survival and reproduction (Ames 2018). When the ergothioneine supply is low, the functions that support long-term health can be compromised, and thereby may result in a decrease in life expectancy (Beelman et al. 2020). Similarly, Paul and Snyder (2010) revealed that ergothioneine is a crucial physiological cytoprotectant and could be served as a vitamin.

In addition to the effects observed above, a follow-up study for 21.4 years including 3236 participants free from stroke, coronary artery disease, and type 2 diabetes mellitus aged 57.4 years had revealed that ergothioneine metabolic level was associated with the lower risk of overall mortality, cardiovascular mortality, and coronary disease (Smith et al. 2020). This finding indicates that high ergothioneine levels may have a reactionary manner to protect from oxidative stress, and is thought to be a crucial factor in the pathogenesis of CVD (Higashi et al. 2009). The study further revealed a correlation between ergothioneine and health-conscious food patterns, particularly vegetable intakes (Smith et al. 2020). A study by Playdon et al. (2017) further supported the association of ergothioneine and higher consumption of seafood and vegetables with a low intake of added sugar and solid fats. Indeed, an interaction between metabolome and healthy dietary intake is particularly interesting because the circulating of specific metabolites have been demonstrated to predict future risk of premature mortality (Cheng et al. 2015), coronary artery disease (Ottosson et al. 2018), and type 2 diabetes mellitus (Wang et al. 2011). In another study, Kameda et al. (2020) evaluated 131 blood metabolites on frailty among the elderly. The data showed that ergothioneine metabolic levels were relatively low in frail individuals compared to non-frail (Kameda et al. 2020). Collectively, more studies are imminently required to explore means to increase ergothioneine in the diet. Given a strong relationship between mushroom intake and blood ergothioneine level (Pallister et al. 2016), the beneficial roles of mushroom are likely due to ergothioneine. Nevertheless, further studies are warranted to support this speculation.

7.11 Betalains

Betalain is a water-soluble pigment consist of nitrogen that is characterized by two structural units, namely red-violet betacyanins and yellow-orange betaxanthins (Fu et al. 2020). Betalains have uniform structural characteristics derived from betalamic acid (Fig. 7.7), with radical R_2 or R_1, in which the substituents can be a radical or hydrogen (Fu et al. 2020). In general, red-violet betacyanins such as neobetanin, isobetanin, prebetanin, and betanin, absorb wavelengths at 538 nanometers; whereas yellow-orange betaxanthins absorb wavelengths at 480 nm (Fu et al. 2020). Betacyanins and betaxanthins (Fig. 7.7) are considered as immonium conjugates of cyclo-3,4-dihydroxyphenylalanine (cyclo-DOPA) with betalamic acid and amino compounds, for instance, amino acids, amines, or their derivatives. Betalains are sensitive toward enzymes, light, pH, heat, and oxygen, which can affect their stability (Ravichandran et al. 2013). Betalain pigments are widely found in red beet and are thought to exert potent immune and intestinal regulatory effect, anti-inflammatory, antibacterial, hepatoprotective, anticarcinogenic, and antioxidant activities (Sanchez-Gonzalez et al. 2013; Tesoriere et al. 2013; Liñero et al. 2017; Bao et al. 2019; Rahimi et al. 2019a). Further, betalains can also protect cells from DNA damage and peroxidation (Winkler et al. 2005; Esatbeyoglu et al. 2014). Due to these health-promoting effects, betalains can be utilized as cosmetics, food

additives, colorants, and drugs in the form of beet powder and beet juice (Janiszewska 2014).

Betalains exert potent antioxidant ability in scavenging free radicals (Mikolajczyk-Bator and Czapski 2017). The potent antioxidant activity of betalains could be due to their molecular structures, in which it exerts its ability to donate hydrogen to reactive species. Betacyanins show a strong antioxidant activity compared to betaxanthins (Stintzing and Carle 2004). Betacyanins and betaxanthins derived from red beetroot demonstrated an antiradical activity by scavenging 2,2′-azino-bis(3-ethylbenzthiazo-line-6-sulfonic acid) (ABTS) radical (Escribano et al. 1998). Indeed, betalains possess unsaturated double bonds and aromatic rings and are potential to quench free radicals (Fu et al. 2020). Due to its antioxidant properties, betalains can effectively decrease the pathogenesis of several diseases (Table 7.20) and prevent LDL oxidation by modulating the redox system, and subsequently creating a good cellular redox environment in modulating the oxidative stress in organisms (Zielinska-Przyjemska et al. 2009; Esatbeyoglu et al. 2014).

Betalains are not only possessed antioxidant properties, they are also exerted anti-inflammatory activity by suppressing the oxidants, hypochlorous acid scavenging, and COX generated by neutrophils during an inflammatory response (Reddy et al. 2005; Allegra et al. 2005). Administration of 50 mg/kg of beetroot betanin for 30 min intraperitoneally prior to ischemia of the superior mesenteric artery for 1 h, followed by the reperfusion for 1, 4, and 24 h in rats model revealed that betanin protects the lung parenchyma and jejunal mucosa and decreases the inflammatory cell density after intestinal ischemic-reperfusion injury (Toth et al. 2019) (Table 7.20). In human study, Tesoriere et al. (2005) evaluated the betalain pigments in red blood cells of healthy individuals after consuming a diet rich in cactus pear fruit. Betanin was shown in red blood cells isolated at 3 h after consuming a cactus pear fruit meal (Tesoriere et al. 2005). The study further revealed that red blood cells isolated at 3 h after intake of cactus pear fruit significantly delay the onset of an *ex vivo* cumene hydroperoxide-induced hemolysis, suggesting that betalains extracted from cactus pear fruits may combat oxidative stress (Tesoriere et al. 2005) (Table 7.20). Oxidative stress can also stimulate inflammatory response via the NF-κB signaling pathway (Mo et al. 2020). The previous study has demonstrated that administration of 100 mg/kg of betalain-rich beetroot subcutaneously or orally reduced carrageenan-induced paw edema, increased IL-10 levels, and decreased IL-1β levels, TNF-α, and carrageenan-induced superoxide anion, indicating that betalain-rich beetroot possesses anti-inflammatory potential on carrageenan-induced peritonitis and paw edema (Martinez et al. 2015).

Emerging studies have demonstrated that betalains exerted beneficial physiological activities in relation to atherosclerosis and hypertension (Fu et al. 2020). An animal study showed that feeding rats with 150 and 300 mg/kg betalain-rich beetroot juice for 28 days restored cardiac endogenous antioxidants and decreased nitrosative and oxidative stress in isoproterenol-induced myocardial injury rats (Raish et al. 2019). Betalain-rich beetroot juice has also been reported to ameliorate the edema, myonecrosis, and histological damage, upregulate Bcl-2 protein expression, and decrease MMP-9 protein levels (Raish et al. 2019). In this regard, this finding

Table 7.20 Effects of betalains in *in vitro*, *in vivo*, and human studies

Diseases	Experimental model	Source of betalains	Durations	Outcomes	References
Intestinal inflammation	Male specific pathogen-free Charles River Wistar rats	Beetroot betanin	50 mg/kg for 30 min	Decreased inflammatory cell density after intestinal ischemic-reperfusion injury	Toth et al. (2019)
Inflammation	Healthy volunteers	Cactus pear fruit meal	–	Delay the onset of an *ex vivo* cumene hydroperoxide-induced hemolysis	Tesoriere et al. (2005)
Myocardial ischemia	Rats	Betalain-rich beetroot juice	150 and 300 mg/kg for 28 days	Restored cardiac endogenous antioxidants and decreased nitrosative and oxidative stress	Raish et al. (2019)
Osteoarthritis	Osteoarthritis participants	Betalain-rich red beet extract	35–100 mg twice/day for 10 days	Improved discomfort associated with osteoarthritis	Pietrzkowski et al. (2010)
Joint mobility	40 people aged 35–75 years with moderate chronic muscle/joint related pain	Betalain-rich Nopal cactus fruit juice	3 oz/day for 8 weeks	Improved joint range of motion and mobility in lumbar, thoracic, and cervical regions	Jensen (2020)
CVD	Systematic review of 7 human and 9 animal studies	Betalain-rich cacti (cactus pear and dragon fruit)	Animal = varied from 1 to 500 mg/kg body weight between 3 and 60 days; human = varied from 25 mg to 3000 mg between 14 and 56 days	Improved endothelial function, reduced vascular stiffness, and modulated heart rate	Cheok et al. (2020)
Dyslipidemia	Male Wistar rats aged approximately 4 weeks	3% beetroot crisps rich in betalains	4 weeks	Reduced hepatic total cholesterol and serum glucose levels	Wroblewska et al. (2011)
Liver cancer	Rats	Red beetroot juice	8 mL/kg body weight/day for 28 days	Decreased the NDEA-induced DNA damage and liver injury	Krajka-Kuźniak et al. (2012)
Liver cancer	THLE-2 cells	Betalain	2, 10, and 20 μM	Induced Nrf2 activation and downstream phase II detoxification gene expression	Krajka-Kuźniak et al. (2013)

CVD cardiovascular disease, *NDEA* N-nitrosodiethylamine, *Nrf2* nuclear factor erythroid 2-related factor 2, *THLE-2* human liver cell line

implies that betalain-rich beetroot juice alleviates cardiac structural damages and dysfunction by reducing apoptosis, inflammation, and oxidative stress in cardiac tissues (Raish et al. 2019). Consistent with the study reported by Raish et al. (2019), Wroblewska et al. (2011) also found that hepatic total cholesterol and serum glucose concentration were reduced after 4 weeks of 3% beetroot crisps rich in betalains administration in the hyperlipidemia mouse model. A recent systematic review of 7 human and 9 animal studies suggested that dietary intake of betalain-rich cacti (cactus pear and dragon fruit) (animal = varied from 1 to 500 mg/kg body weight between 3 and 60 days; human = varied from 25 mg to 3000 mg between 14 and 56 days) improved endothelial function, reduced vascular stiffness, and modulated heart rate in both populations at risk of CVD and healthy individuals (Cheok et al. 2020), suggesting that betalain-rich cacti may improve vascular health.

In addition, betalains have the potential to protect against osteoarthritis. Betalains from plant extract exert anti-inflammatory activity by inactivating COX and lipoxygenase (Vidal et al. 2014; Rahimi et al. 2019b). In human study, consumption of betalain-rich red beet extract at a dose of 35–100 mg twice/day for 10 days improved discomfort associated with osteoarthritis (Pietrzkowski et al. 2010). It has been suggested that mobility and joint function are negatively affected by inflammation (Chow and Chin 2020). Low-grade inflammation has been implicated in the development of chronic pain in muscles and joints (Christensen et al. 2021). Data from a double-blind, placebo-controlled study involving 40 people aged 35–75 years with moderate chronic muscle/joint-related pain revealed that consumption of 3 oz/day of betalain-rich Nopal cactus fruit juice for 8 weeks improved joint range of motion and mobility in lumbar, thoracic, and cervical regions (Jensen 2020). Notably, patients consuming betalain-rich Nopal cactus fruit juice relied less on pain medication to complete daily activities and improved some daily activities including lying, sitting, and walking, compared to those who consume placebo (Jensen 2020). The protective effects of betalain-rich Nopal cactus fruit juice toward physical and joint mobility functioning are likely due to the anti-inflammatory and antioxidant properties of betalain-rich Nopal cactus fruit juice. However, Jensen (2020) found that betalain-rich Nopal cactus fruit juice failed to show any benefit in improving the mobility of shoulders, knees, and hips in patients with chronic muscle/joint-related pain.

Notably, research evidence indicates that dietary intake of betalain-rich containing food may decrease the risk of cancer. Betalains in red beetroot are of benefit in the activation of Nrf2 transcriptional factor and phase II enzymes to trigger the antioxidant defense activity of endogenous cells (Lechner and Stoner 2019). An animal study demonstrated that feeding rats with 8 mL/kg body weight/day of red beetroot juice for 28 days decreased the N-nitrosodiethylamine (NDEA)-induced DNA damage and liver injury (Krajka-Kuźniak et al. 2012). Moreover, betalain (2, 10, and 20 μM) was found to trigger Nrf2 activation and downstream phase II detoxification gene expression in human liver (THLE-2) cells (Krajka-Kuźniak et al. 2013), indicates that betalain may exert anticarcinogenic and hepatoprotective activity. In colon cancer, Farabegoli et al. (2017) revealed that red beetroot betalains induced cytotoxicity of colon cancer (CaCo-2) cells by increased Bcl2-like protein 4, cleaved caspase-3 and poly ADP-ribosyl polymerase 1 levels, and dampened IL-8

and COX-2 mRNA expression in LPS-induced Caco-2 cells. Taken together, the effects mentioned above indicate that betalains from beetroot have the potential to protect against metabolic ailments and oxidative stress. Based on the evidence, the reported findings are mainly focused on the bioactivities of red beetroot extracts. Most of the nutritional values of red beetroot are also contributed by micronutrients and bioactive compounds such as betaine, ferulic acid, lutein, and betalains (Lechner and Stoner 2019). Thus, further studies are warranted to evaluate the bioactivities of individual betalains in daily betalain-rich diets.

7.12 Carnosine and Anserine

Carnosine was first identified as a dipeptide, β-alanyl-L-histidine in 1918 (Barger and Tutin 1918; Baumann and Ingvaldsen 1918). Carnosine consists of three ionizable groups, namely imidazole ring in histidine, amino group of the β-alanine residue, and carboxylic group (Tanokura et al. 1976) (Fig. 7.7). Under physiological pH, carnosine exists mainly as zwitterionic and exerts a net positive charge (Wu 2020). Dietary carnosine is absorbed through enterocytes of the small intestine across the apical membrane mediated by peptide transporter-1 (PepT1) (Wu 2020). In the enterocytes, a small level of carnosine is hydrolyzed into histidine and β-alanine by carnosinase-2 (Sadikali et al. 1975). Carnosine is actively hydrolyzed into the histidine and β-alanine by carnosinase-1, an enzyme that is released and synthesized from the liver, subsequently taken up by extra-intestinal cells through specific transporters. Indeed, dietary consumption of carnosine can increase its concentration in heart, brain, and skeletal muscle (Boldyrev et al. 2013). Intriguingly, the previous study found that intake of 4 g synthetic carnosine does not influence the plasma concentration in the human body, possibly due to the activity of plasma carnosinase-1 activity, in which it is rapidly hydrolyzed into histidine and β-alanine (Gardner et al. 1991). In general, carnosine is synthesized from histidine and β-alanine which catalyzed by ATP-dependent carnosine synthetase (Wu 2013); both of the amino acids are reused for the synthesis of carnosine by the olfactory bulb of the brain, heart, and skeletal muscle (Harding and O'Fallon 1979; Drozak et al. 2010; Boldyrev et al. 2013). Beta-alanine can be obtained from the diet or via endogenous syntheses from the catabolism of polyamines, pyrimidines, coenzyme A, malonic acid semialdehyde, and aspartate (Wu 2013); whereas histidine can also be found in the diet and the degradation of myosin, actin, hemoglobin, and other proteins in the body (Wu 2020). Compared to those who rarely consumption of meat, adults who consume 150 g chicken broth or beef had a relatively higher urinary carnosine concentration within 7 h after consumption was 15- and 13-fold, respectively (Yeum et al. 2010).

Carnosine contains a functional imidazole ring, which can donate hydrogen to free radicals and convert in the form of non-radical substances (Kohen et al. 1988). There are several physiological roles of carnosine that have been reported, specifically in organs and tissues, including protects against protein oxidation, lipid

peroxidation, and the formation of lipoxidation end products and advanced protein glycation, scavenging peroxyl radicals and ROS, activation of muscle ATPase to provide energy, mediation of homeostasis and metal-ion chelation, and acting as an intracellular pH buffer (Boldyrev et al. 2013; Barca et al. 2019; Nelson et al. 2019).

Following the discovery of carnosine in beef, the researchers attempt to evaluate this compound in other animal species. In 1929, Ackermann et al. (1929) and Tolkatschevskaya (1929) identified a carnosine-like compound, namely methyl carnosine or β-alanyl-1-methyl-L-histidine, in goose skeletal muscle. Subsequently, this compound was named anserine after the taxonomic name for the goose. Similar to carnosine, this peptide is characterized by three ionizable groups, namely imidazole ring in histidine, amino group of the β-alanine residue, and carboxylic group (Bertinaria et al. 2011) (Fig. 7.7). Under physiological pH, anserine exists mainly as zwitterionic and has a net positive charge (Wu 2020). Most of the anserine in the human diet comes from beef (Wu et al. 2016) and fish such as trout, tuna, and salmon (Boldyrev et al. 2013), but it is absent from human tissues, for instance, brain, heart, and skeletal muscle (Mannion et al. 1992). Notably, anserine has a physiological function similar to carnosine (Kohen et al. 1988; Boldyrev et al. 2013; Everaert et al. 2019). Nonetheless, some of the biochemical properties of anserine are different from carnosine. For instance, anserine did not chelate copper and may not modulate the availability of nitric oxide in cells (Boldyrev et al. 2013).

Anserine and carnosine are potent antioxidants (Wu et al. 2003) and are widely found in beef skeletal muscle. In particular, anserine and carnosine are absent from all plant sources such as white rice, wheat flour, sweet potatoes, soybeans, peanuts, and corn grains (Hou et al. 2019). In this regard, vegetarians were shown to have a greater likelihood of deficiencies of anserine and carnosine, especially to those physically active individuals (Rogerson 2017). Substantial studies indicate that anserine and carnosine play a pivotal role in protecting mammalian cells from injury and oxidative stress (Abplanalp et al. 2019; Alkhatib et al. 2020).

Research evidence demonstrated that carnosine's precursors, L-histidine and β-alanine, can easily be taken up into the brain from circulation via amino acid transporters in the blood-brain barrier (Hawkins et al. 2018). Besides carnosine's precursors, carnosine can also cross the blood-brain barrier (Jin et al. 2005). Brain carnosine is vitally important for the proper modulation of brain function and may serve as a neuroprotective molecule, neuromodulator, and endogenous antioxidant (Berezhnoy et al. 2019). Carnosine is believed to have a neuroprotective effect by improving the acetylcholinesterase activity (Ma et al. 2015), strengthening the antioxidant system (Maiese et al. 2007), and decreasing oxidative stress (Colín-Barenque et al. 2018). Data from systematic review and meta-analysis including 454 animals revealed that carnosine exerts neuroprotective efficacy in decreasing infarct size (Davis et al. 2016). The data showed that administration of 1000 mg/kg of carnosine led to a 38.1% reduction in infarct size, suggesting that carnosine may protect against brain ischemia (Davis et al. 2016) (Table 7.21). One potential biological mechanism linking neuroinflammation and carnosine has been described by Wang et al. (2018). Wang et al. (2018) demonstrated that dietary intake of 600 mg/kg beef decoction rich in carnosine for 7 days reduced neurological deficits,

Table 7.21 Effects of carnosine, anserine, and its precursors in *in vivo* and human studies

Age-related diseases	Experimental model	Carnosine/Anserine and its precursors	Concentration/Durations	Outcomes	References
Alzheimer's disease	Aged AβPPswe/PSEN1dE9 Alzheimer's-model mice	Anserine	10 mg for 8 weeks	Inhibited glial inflammatory response, modulated pericyte coverage on endothelial cells in the brain, and improved memory deficits	Kaneko et al. (2017)
Ischemic stroke	Systematic review and meta-analysis including 454 animals	Carnosine	1000 mg/kg	Reduced 38.1% infarct size	Davis et al. (2016)
Neurodegenerative disorder	12 middle-aged subjects (8 men and 4 women)	β-alanine	2.4 g/day for 28 days	Reduced exercise-induced declines in executive functions	Furst et al. (2018)
Neurodegenerative disorder	7 healthy vegetarians (3 women and 4 men) and 19 trained male cyclists	β-alanine	6.4 g/day for 28 days	No effect on brain carnosine/homocarnosine signal in vegetarians and omnivores and the cognitive function after or before exercise in trained cyclists	Solis et al. (2015)
Ischemic stroke	Sprague-Dawley rats	Beef decoction	600 mg/kg for 7 days	Reduced neurological deficits	Wang et al. (2018)
Atherosclerosis	Apolipoprotein E-null mice	Carnosine	60 mg/kg in drinking water for 6 weeks	Reduced atherosclerotic lesion formation in aortic valves	Barski et al. (2013)
Type 2 diabetes mellitus	Randomized, double-blinded, placebo-controlled trial of 100 obese women with metabolic syndrome aged 33–51 years	Histidine	4 g/day for 12 weeks	Reduced insulin resistance	Feng et al. (2013)
Type 2 diabetes mellitus	Male C57BL/KsJm/Leptdb (db/db) mice	Anserine	3 doses of 100 mg/kg every other day intravenously	Decreased proteinuria and blood glucose levels and improved vascular permeability	Peters et al. (2018)

decreased the proinflammatory cytokines including interferon-γ, TNF-α, and IL-6 expression, and increased anti-inflammatory cytokine such as IL-4 levels in rats. In human study, an increase in exercise capacity and reduced exercise-induced declines in executive functions was found in middle-aged individuals supplemented with 2.4 g/day of β-alanine for 28 days (Furst et al. 2018). As mentioned above, β-alanine is one of the carnosine's precursors. A study by Hoffman et al. (2015) further supported the role of β-alanine in the modulation of the thalamus, hypothalamus, amygdala, hippocampus, and cerebral cortex in the rodent model. Improved intracranial carnosine was correlated with better executive functioning (Furst et al. 2018). Nonetheless, Solis et al. (2015) did not identify the association between β-alanine and neurodegenerative disorders. The data showed that intake of 6.4 g/day β-alanine for 28 days did not affect the brain carnosine/homocarnosine signal in vegetarians and omnivores as well as the cognitive function after or before exercise in trained cyclists (Solis et al. 2015). In addition, the neuroprotective effect was also shown in anserine (Schön et al. 2019; Masuoka et al. 2021). The data from animal study revealed that feeding AβPPswe/PSEN1dE9 mice with 10 mg of anserine for 8 weeks inhibited the glial inflammatory response, modulated pericyte coverage on endothelial cells in the brain, and improved memory deficits in aged mice (Kaneko et al. 2017) (Table 7.21). This finding implies that anserine may improve spatial memory and alleviate neurovascular dysfunction in aged animals.

A study by Yeum et al. (2010) evaluated the systemic delivery of anserine, carnosine, and histidine dipeptides in humans after intake of food rich in histidine dipeptides. A significant increase of plasma anserine concentration among healthy women was found to be associated with 150 g chicken or chicken broth from 150 g chicken (Yeum et al. 2010). However, the plasma carnosine levels were not detected after intake of chicken broth from 150 g chicken, 150 g chicken, 150 g beef, or 450 mg pure carnosine (Yeum et al. 2010). The undetectable carnosine in the blood is likely due to the rapid uptake of dipeptides into the tissues or hydrolysis by carnosinase (Yeum et al. 2010). The study further revealed that intake of 150 g beef increased the urinary concentration of carnosine and anserine (Yeum et al. 2010). Similarly, the urinary levels of anserine and carnosine were also increased after consuming chicken broth from 150 g chicken. This finding indicates that dietary histidine-dipeptides are rapidly hydrolyzed by carnosinase in plasma and excreted through urine may serve as a reactive carbonyl species sequestering agent. In another study, Park et al. (2005) found that the serum carnosine levels were increased after 15 min from 0 to 46.0 mM/L of plasma in participants who received beef patties, and reaching the highest after 3.5 h beef consumption. The ability of carnosine to absorb intactly suggests that carnosine could be a crucial dietary intervention to suppress advanced glycation end products (AGEs) formation (Freund et al. 2018). A recent study by Cripps et al. (2017) revealed that carnosine is effective in scavenging the glucolipotoxic free radicals, for instance, RONS. It has been suggested that carnosine can regulate glucose homeostasis by modulating skeletal muscle glucose uptake and increasing insulin secretion (Cripps et al. 2017). Feng et al. (2013) exploring the impact of serum histidine on oxidative stress and insulin resistance in randomized, double-blinded, placebo-controlled trials. The study showed that obese women with

metabolic syndrome who received 4 g/day of histidine for 12 weeks decreased GPx, SOD, IL-6, TNF-α, fat mass, waist circumference, BMI, and HOMA-IR and increased adiponectin and serum histidine, implied that histidine may improve insulin resistance by suppressing proinflammatory cytokine, possibly via NF-κB signaling pathway in adipocytes (Feng et al. 2013) (Table 7.21). Moreover, intravenous injections of male C57BL/KsJm/Leptdb (db/db) mice with anserine (3 doses of 100 mg/kg every other day) decreased proteinuria and blood glucose levels and improved vascular permeability (Peters et al. 2018). Heat shock protein (Hsp70) deficiency is often associated with stress in the target organs of diabetic complications (Bellini et al. 2017). The inability of the diabetic glomeruli to modulate stress response may increase the susceptibility of the diabetic lesion (Barutta et al. 2008). Intriguingly, the *in vitro* study demonstrated that anserine (1 mM) is only effective to stimulate the Hsp70-expression in H_2O_2-stressed human tubular cells (HK-2), but it is not observed in carnosine (Peters et al. 2018).

Besides its effects mentioned above, a beneficial effect of carnosine has also been described on the incidence of CVD. Carnosine inhibits Cu^{2+}-induced LDL oxidation (Decker et al. 2001). Consistent with the study reported by Decker et al. (2001), Barski et al. (2013) also found that carnosine (60 mg/kg in drinking water for 6 weeks) reduced atherosclerotic lesion formation in aortic valves and alleviated the accumulation of protein-4-hydroxynonenal adducts, protein-4-hydroxyhexenal, and protein-acrolein in apolipoprotein E-null mice, possibly by modulating aldehyde removal from atherosclerotic lesions. Further, a systematic review and meta-analysis of randomized controlled trials included 21 studies from inception to January 25, 2019, demonstrated that a relatively low level of TG for those with a greater intake of carnosine supplements compared to the control (Menon et al. 2021). However, no effects were observed in the total cholesterol to HDL-C ratio, HDL-C, LDL-C, heart rate, and blood pressure after consuming carnosine (Menon et al. 2021). Based on the evidence, intakes of carnosine and anserine might be a promising strategy to improve age-related diseases conditions and ameliorate oxidative stress. However, there was limited evidence on the implication of the dietary consumption of carnosine and anserine-rich containing food on age-related diseases. Therefore, the beneficial effects of carnosine and anserine-rich food on pathological changes of mitochondrial oxidative stress related to chronic disease conditions are worth further elucidation in randomized clinical trials.

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Chapter 8
Summary and Future Prospects

Aging is biological and functional changes characterized by a progressive decline of tissue renewal capability and diminish of cellular functions of an organism (Bonomini et al. 2015; Forni et al. 2019). ROS are generated as by-products by many exogenous and endogenous factors, which may induce oxidative damage to lipids, proteins, and DNA, and ultimately lead to cellular dysfunction (Harman 1956). Indeed, age-related pathologies are closely related to an elevation of oxidative stress (Liguori et al. 2018). Dysregulation of the immune response is one of the primary changes that occurred during aging, which may lead to a chronic systemic inflammatory state (Chung et al. 2019). Of all proinflammatory mediators, chemokines and cytokines are the primary contributors to chronic inflammation (Chung et al. 2019). Low-grade chronic systemic inflammation plays a crucial role in the aging process (Guarner and Rubio-Ruiz 2015). It has been demonstrated that aging is linked to the elevation of circulating proinflammatory cytokines and other inflammatory substances in the blood, such as increased levels of IL-6 and TNF-α (Bruunsgaard 2002). The production of enzymes and cytokines becomes dysregulated with increased age and possesses highly pleiotropic activities and subsequently modified the physiology of cells, tissues, and organs in the body. Indeed, many cytokines that are stimulated during aging are involved in the host inflammatory response, an innate immune response that plays a crucial role in the host defense toward infectious agents (Bernstein and Murasko 1998). Inappropriate activation of the chronic inflammatory response may lead to the pathologic condition, which plays a pivotal role in chronic and acute disease conditions (Arida et al. 2018). Substantial studies indicate that aging is linked to several pathological conditions, such as neurodegenerative diseases, cancer, CVD, obesity, and metabolic syndrome (Franceschi et al. 2018; Liguori et al. 2018; Tan et al. 2018a).

Chronic inflammation in the elderly is thought to be caused by cellular senescence, which is characterized by the onset of a multifaceted senescence-associated secretory phenotype (SASP) and an arrest of cell survival (Coppé et al. 2010;

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Furman et al. 2019). A prominent characteristic of this phenotype is upregulated the secretion of other proinflammatory molecules from cells, chemokines, and proinflammatory cytokines (Coppé et al. 2010). Natural products have been suggested to counteract oxidative stress and promoting the healthy longevity of an organism (Chen et al. 2016). Such protection has been ascribed to antioxidants including polyphenols, carotenoids, and vitamins (Tan et al. 2018a). Natural antioxidants, for instance, organosulfur compounds, vitamins, carotenoids, and polyphenols are widely found in vegetables and fruits (Tan et al. 2018a). Natural antioxidants possess many biological activities, for instance, antioxidant activity, antitumor effects, and anti-inflammatory activity as well as inhibit platelet aggregation (Tan et al. 2018a, b).

Although many studies evaluating the generation and the origin of ROS, current antioxidant-based therapies show a lack of specificity for defective cells, tissues, and organelles, and hence may not achieve an effective dose at the target site. Further, antioxidant targets a high concentration of reactive species and is unable to mediate certain reactive oxygen intermediates during the oxidative reaction and thereby resulting in some therapeutic approaches are unfocused. Mitochondria-targeted antioxidants hold great promise and may provide a useful tool for the amelioration of a broad spectrum of human diseases (Jiang et al. 2020; Le Gal et al. 2021). In this regard, further studies are required to enhance the potency of antioxidant-based therapy, specifically via antioxidants-rich containing food. In addition, it is worth elucidating the role of iron-modulated oxidative damage via Fenton reaction to further verify the association of iron production and mitochondrial dysfunction in relation to the development and onset of age-related diseases. Moreover, the literature reported on the interaction between antioxidants and chelating is limited, and further elucidation may facilitate the development of novel biomarkers and potential therapeutic agents targeting certain disease organs and tissues, as well as to investigate the downstream mediators in oxidative signaling.

Oxidative stress is enhanced by other reactive species including singlet oxygen, $\bullet O_2^-$, and H_2O_2 as well as other non-radicals, which are produced continuously in the body and thereby altering basic structural components and cellular activity (Droge 2002; Pizzino et al. 2017). It has been demonstrated that ROS accumulation may contribute to the formation of mutagen compounds and increase oncogene transcription factors, and thereby induce inflammation and proatherogenic activity (Tan et al. 2018b). In fact, longevity is not merely embedded in the genes; intakes of food rich in antioxidants are crucial for the proper modulation of physiological function. The essential role of food rich in antioxidants in scavenging ROS, producing cellular energy, and regulating immune system is well-recognized (Tan et al. 2018a, b). The diverse mechanisms in which the antioxidants are involved imply that antioxidants may protect against the pathogenesis of age-related diseases and oxidative stress. Therefore, the consumption of food rich in antioxidants might be a useful strategy for promoting healthy longevity. Overall, more long-term randomized clinical studies are required to elucidate the implication of antioxidant-rich foods in relation to aging and age-related diseases.

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Conclusion

This book has demonstrated clear evidence of the vital role played by dietary antioxidants in combating age-related diseases and providing optimal health in preclinical and human studies. Antioxidants exert strong potential to suppress oxidative stress and lipid peroxidation. Oxidative stress has been identified as a primary risk factor in the development of age-related diseases such as osteoporosis, vascular diseases, cancer, diabetes, metabolic syndromes, atherosclerosis, dementia, and arthritis. There is discrepant finding supporting the beneficial effects of antioxidants in preventing the progression and onset of age-related diseases, yet most clinical studies are limited to their duration of the study and sample size. Therefore, greater adherence to healthy dietary patterns is encouraging and may link to a lower risk of age-related diseases. Strikingly, some research has emerged to suggest that a combination of antioxidants exert greater beneficial potentials than the individual antioxidant, implied that the phytochemicals work in concert rather than individually. Therefore, an antioxidant might be a useful strategy for lifespan extension as well as healthspan extension. Despite antioxidants may not serve as a drug, they hold a great promise in delaying the development of chronic metabolic ailments. Accordingly, more randomized clinical studies are required to further elucidate the impact of food rich in antioxidants on age-related diseases.

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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