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Review Article

Carbonyl Stress in Aging Process: Role of Vitamins and Phytochemicals as Redox Regulators

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ABSTRACT: There is a growing scientific agreement that the cellular redox regulators such as antioxidants, particularly the natural polyphenolic forms, may help lower the incidence of some pathologies, including metabolic diseases like diabetes and diabesity, cardiovascular and neurodegenerative abnormalities, and certain cancers or even have anti-aging properties. The recent researches indicate that the degree of metabolic modulation and adaptation response of cells to reductants as well as oxidants establish their survival and homeostasis, which is linked with very critical balance in imbalances in cellular redox capacity and signaling, and that might be an answer the questions why some antioxidants or phytochemicals potentially could do more harm than good, or why some proteins lose their function by increase interactions with glyco- and lipo-oxidation mediates in the cells (carbonyl stress). Nonetheless, pursue of healthy aging has led the use of antioxidants as a means to disrupt age-associated physiological dysfunctions, dysregulated metabolic processes or prevention of many age-related diseases. Although it is still early to define their exact clinical benefits for treating age-related disease, a diet rich in polyphenolic or other forms of antioxidants does seem to offer hope in delaying the onset of age-related disorders. It is now clear that any deficiency in antioxidant vitamins, inadequate enzymatic antioxidant defenses can distinctive for many age-related disease, and protein carbonylation can used as an indicator of oxidative stress associated diseases and aging status. This review examines antioxidant compounds and plant polyphenols as redox regulators in health, disease and aging processes with hope that a better understanding of the many mechanisms involved with these distinct compounds, which may lead to better health and novel treatment approaches for age-related diseases.

Key words: Carbonyl stress, aging, phytochemicals, redox regulators, vitamin, diseases

Unmitigated stress as senescent factor

In living systems, the cells are exposed to environmental and endogenous stressors, which are initiated and promoted by physical, chemical, and biological stimuli triggering a series of events in order to counteract, adapt and survive. To maintain homeostasis, the cells are required to rapidly respond in a manner that will allow for redox balance, recycling of antioxidants, clearance of abnormal proteins and remodeling [1]. There are some main pathways of stress response intrinsic to cells including heat shock response, unfolded protein response, autophagy, antioxidant response, inflammatory response and DNA repair response [2]. Any deficit in the ability of the cell to perform these functions would have significant impact on the state of health of the tissues [3]. For instance, brain cells have a particularly high basal level of metabolic activity and use distinct oxidative damage

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repair mechanisms to remove oxidative damage from DNA, and accumulation of this damage in the background of a functional DNA repair response is associated with normal aging, but defective repair in brain cells can contribute to neurological dysfunction [4, 5]. On the other hand, dysfunctional ROS-induced DNA damage response is mediating to early asymptomatic stages of calcific aortic valve disease, and may be reversible by antioxidant enzymes delivery [6]. Similarly, chronic obstructive pulmonary disease reflects the exhausted response of respiratory tract to external oxidants like oxygen, pollutants, toxicants and cigarette smoke and characterized by chronic inflammation and airflow limitations due to the increased systemic oxidative stress [7].

Aging is a multifactorial process that depends on diverse molecular and cellular mechanisms, such as protein availability, genome maintenance and inflammation [8]. Proteins are among the main targets for oxidants due to their high rate constants for several reactions with reactive oxygen species (ROS) and their abundance in biological systems. The interactions of proteins with ROS may result in numerous post-translational, reversible or irreversible modifications, which may lead to a change in the structure and/or function of the oxidized protein. The level and the type of protein damage have an important for the maintenance of viability since most protein damage is non-repairable, and has deleterious consequences on protein structure and function. In addition, damaged and modified proteins can form cross-links and provide a basis for many senescence-associated alterations and may contribute to a range of human pathologies [9, 10]. Protein damage leading to the formation of carbonyl groups derives from direct oxidation of several amino acids side chains but can also derive through protein adducts formation with lipid peroxidation products and dicarbonyl glycating compounds. All these modifications have been implicated during oxidative stress, aging and age-related diseases [11]. The degrading systems as proteolytic systems and the lysosomal system provide a last line of antioxidative protection, removing irreversible damaged proteins and recycling amino acids for the continuous protein synthesis. It is now well known that during aging, both systems are affected and their proteolytic activity declines significantly [9, 12]. On the other hand, during aging, the continuous pressure on the immune system caused by repeated antigen stimulation, leads to an increase in activated cells and secretion of pro-inflammatory cytokines, such as TNFα, IL-6 [13]. These circulating pro-inflammatory factors may keep the immune system in a state of chronic low-level activation, a phenomenon described as "inflammaging" [14]. Eventually, this causes "immunosenescence," that is, an age-related decline in the capacity of adaptive immunity, consisting of more specific responses carried out by B and T cells [15]. Shorter telomere length is also associated with advancing chronological age and also increased disease morbidity and mortality. Emerging studies suggest that redox stress accelerates the erosion of telomeres from very early in life and possibly even influences the initial (newborn) setting of telomere length [16]. Telomeres are shortened by each cell division until a critical length is reached and dysfunction ensues. DNA-repair pathways are then recruited and cells enter senescence, losing their capacity to proliferate. In addition to cell division, factors causing telomere shortening include DNA damage, inflammation, and oxidized protein accumulation [17, 18]

Nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP1) represents an interesting player in several aging mechanisms and is discussed as a longevity assurance factor. There is a large body of evidence showing a positive correlation of poly(ADP-ribosyl)ation capacity and mammalian longevity. [12, 19]. In other side, the treatment with rapamycin, an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) increases mammalian life span via increasing hepatic gluconeogenesis concomitant with increase insulin insensitivity [20], while PI3K-AKT-mTOR-ROS pathway is necessary for CKII inhibition-mediated cellular senescence in colon cancer [21].

Impaired redox homeostasis and diseases development

Aging has been defined as a progressive postmaturational decline in physiological capacity, accompanied by an increased susceptibility to disease and an increased mortality risk. A mounting body of evidence suggests that increased production of ROS-mediated damages is linked to aging processes and to the etiopathogenesis of aging-related diseases, such as cancer, diabetes, atherosclerosis and neurodegenerative diseases like Parkinson's and Alzheimer's.

The most of the research on aging focus on structural and functional alterations of the brain during aging, age-associated imbalances of defenses against oxidative stress and age-related alterations of the metabolism of extracellular amyloid beta plaques, because today, around 24 million people suffer from dementia and with aging of industrial populations this number will significantly increase throughout the next decades [22]. AGEs/ALEs modifications may explain many of the neuropathological and biochemical features of Alzheimer's diseases such as extensive protein cross-linking, inflammation, oxidative stress and neuronal cell death [23]. In Parkinson's disease, telomere is shorter in the presence of high oxidative stress as measured by carbonyl protein levels [24]. With age, senescent cells accumulate and express a senescence-

associated secretory phenotype that is the robust secretion of many inflammatory cytokines, growth factors and proteases. On the basis of recently reported findings, authors propose that environmental stressors associated with Parkinson's disease may act in part by eliciting senescence and the senescence-associated secretory phenotype within non neuronal glial cells in the aging brain, thus contributing to the characteristic decline in neuronal integrity that occurs in this disorder [25]. In prostate cancer, oxidative damage, an innate key event characterized by supraphysiological ROS concentrations, has been identified as one of the hallmarks of the aggressive disease phenotype [26]. Age-specific mortality rates from cardiovascular diseases and strokes increase with age throughout the later years of life [27, 28]. It was found that the content of lipofuscin (advanced cross-linked carbonyl protein adduct) is positively correlated with mitochondrial damage as well as with the production of ROS and associated with cardiovascular decline [29, 30]. Structural remodeling of dilated atria manifested as intracellular accumulation of fibrillar aggregates, lipofuscin, signs of myolysis and autophagy [31]. Large studies demonstrated that in the absence of other risk factors, aging per se causes the development of atherosclerosis [32]. Aging is also an independent factor associated with endothelial dysfunction even in the absence of other cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking or a sedentary lifestyle, as well as genetic factors [33, 34]. In addition, age-associated ocular morbidity, including macular degeneration, diabetic retinopathy and cataract has been linked with increased carbonyl stress [35, 36]. Skin aging is another complex biological process influenced by a combination of endogenous or intrinsic and exogenous or extrinsic factors, which trigger oxidative degeneration in dermal cell [37,38]. Many hormone levels such as dehydroepiandrosterone, insulin-like growth factor 1 fall with age in men and women, (reaching sometimes values as low as 10-20% of those encountered in young individuals), that is accompany to general failure [39, 40]. Carbonyl stress due to unmitigated hyperglycemia is important factor in complications development like cardiomyopathy, vasculopathy, neuropathy, nephropaty in diabetics captive with accelerated aging [41, 42, 43, 44]. Older adults with diabetes and altered glucose status likely represent a subset of the population at high risk for complications and adverse geriatric syndromes [45].

Cellular response to carbonyl stress in aging and age-related pathologies

Aging is a complex process which cannot be explained by a single pathway or even a set of closely related pathways. Redox biochemistry influences on most of cellular processes and has been shown to underpin aging and many human diseases. Integrating the complexity of redox signaling and regulation is perhaps one of the most challenging areas of biology [46]. Protein oxidative modifications, also known as protein oxidation, are a major class of protein posttranslational modifications. They are caused by reactions between protein amino acid residues and reactive oxygen species (ROS) or reactive nitrogen species (RNS) and can be classified into two categories: irreversible modifications and reversible modifications. Protein oxidation has been often associated with functional decline of the target proteins, which are thought to contribute to normal aging and age-related pathogenesis [9, 47]. It has now been recognized, however, that protein oxidation can also play a positive role in many cellular functions. This gradual realization of the beneficial roles of protein oxidation may be attributed to accumulating evidence that ROS and RNS are indispensible for cell survival and regeneration, and in many cases, they are required for recovery of cellular functions by creating positive stress conditions whereby cell survival mechanisms are reprogrammed to extend life span or to counteract severe, or lethal challenges [47, 48, 49]. Apparently, the adaptation to the increased oxidant or reductant status is important to cell survival and the cellular redox homeostasis is essential to maintain a normal long life.

Proteins can be modified by lipids as well as carbohydrates. Advanced glycation end products (AGE) formation has initially been described as a non-enzymatic reaction between proteins and glucose in the so-called Maillard reaction, but they are also more rapidly formed during oxidative stress and subsequent formation of reactive carbonyl compounds such as formaldehyde, acetaldehyde, acrolein, crotonaldehyde, glyoxal, methylglyoxal, glycolaldehyde, glycidaldehyde [50, 51]. Glyco-oxidation is a term used for glycation processes involving oxidation, and AGEs like pentosidine accumulate in tissue where they cross-link with proteins, e.g., collagen, inducing stiffness in arterioles and skin. They may also interact with receptor of AGE (RAGE) and other receptors, which lead to activation of intracellular transduction mechanisms resulting in cytokine release and further tissue damage in many diseases [11, 52-55]. During oxidative stress, reactive oxygen species also attack to polyunsaturated fatty acids (PUFAs) either in the cell membrane or circulating lipoprotein molecules. This oxidative decomposition of PUFAs initiates chain reactions that lead to the formation of a variety of reactive carbonyl species. Among them is 4-hydroxy-trans-2-nonenal (4-HNE), which is subsequently react by the so-called Michael addition mechanism with cysteine, histidine and lysine residues in proteins, generating

relatively stable adducts known as advanced lipid peroxidation end products (advanced lipo-oxidation end products ALEs) [52, 53, 56]. Reactive carbonyl compounds (RCCs) may induce "carbonyl stress" characterized by the increased formation of adducts and cross-links on proteins. The growing number of evidence have demonstrated that carbonyl stress associates the promotion of cytotoxic events such as cell growth arrest, mitochondrial dysfunction, apoptosis, and necrosis by modifying cellular proteins and nucleic acids, contributing to the dysfunction and damages in tissues and to the progression of diseases [52, 53, 57, 58, 59, 60].

Serum AGEs (N(epsilon)-carboxymethyl-lysine [CML] or methylglyoxal [MG] derivatives) have been found higher in older compared to younger persons [61]. It has been reported that a certain subtype of schizophrenic patients exhibit idiopathic carbonyl stress with high plasma pentosidine levels and the depletion of vitamin B6, without underlying diabetes or chronic kidney disease, the two major causes of elevated AGEs [62]. In addition to brain [34, 63], there are many reports indicating increased advanced oxidative and glyco-oxidative protein damage markers in kidney [64, 65], heart [57, 34, 66], pancreas [67], aorta [68, 69], liver [70] and serum [71] by aging or accelerated aging models such as diabetes. Advanced oxidation protein products (AOPPs) represent dityrosine-containing cross-linked protein modifications formed mainly via myeloperoxidase reaction, has been demonstrate to accelerate the uremia-associated atherogenesis and renal fibrosis in children and adolescents [72]. Increased nitroxidative stress causes mitochondrial dysfunctions through oxidative modifications of mitochondrial DNA, lipids, and proteins, and the persistent mitochondrial dysfunction has been suggested to contribute to the development of alcoholic and nonalcoholic fatty liver disease [73]. It has been reported that the increased level of serum or tissue advanced glycation or glyco-oxidation end products (AGEs) is a risk factor for the production of colorectal cancer [74] and impairment of cognitive and memory functions [75, 76], associate with insulin resistance [77] and promote diabetic complications [78] such as diabetic peripheral sensory neuropathy [79].They also atherosclerotic risk markers in prediabetic and diabetic elderly subjects [71], markers for ocular complications in in vitro and in vivo models of human age-related eye diseases, such as cataracts [80]. Inhibition of ROS signaling pathways or blockade of sources of ROS in the pulmonary vasculature, targeting in particular Nox enzymes represent promising new therapeutic strategies in pulmonary hypertension [81]. AGEs and RAGE-mediated ROS production are involved in vascular aging. Proteins of the extracellular matrix and vascular basement membrane have longer half-lives and they thus accumulate AGEs to a greater extent [82]. Cross-linking of collagen and other proteins by AGEs/ALEs in the arteries increased the stiffness of the vasculature leading to changes in contractile mechanics of the vasculature [83].

In fact, the physiological levels of ROS are viewed as signaling molecules acting as redox signals, and their harmful effects are seen mostly as a result of shaded signaling, rather than due to direct damage to sensitive targets. According to this view, ROS such as hydrogen peroxide and superoxide are not just causative agents of aging but may also be agents that increase the life span by acting, for example, as prosurvival signals [2, 47, 84]. ROS have crucial roles in redox regulation of protein phosphorylation, ion channels, and transcription factors. ROS are also required for biosynthetic processes, including thyroid hormone production, cross-linking of extracellular matrix [85] and insulin release from pancreatic beta-cells [86, 87]. In pancreatic β-cells evidence is emerging that acute and transient glucose-dependent H_2O_2 contributes to normal glucose-stimulated insulin secretion. However, chronic and persistent elevation of H_2O_2, resulting from inflammation or excessive metabolic fuels such as glucose and fatty acids, may elevate antioxidant enzymes such that they blunt H_2O_2-induced physiologically redox signaling, thus impairing β-cell function [86, 87, 88, 89]. In association with this, the balance between the oxidized (NAD^+) and the reduced (NADH) forms of nicotinamide adenine dinucleotides is critical for the cell's proper function and ultimately, for its survival. A decrease in the NAD^+/NADH ratio causes these enzymes to decrease in activity (reductive stress), resulting in an altered metabolic situation that has been suggested recently be the first insult toward several pathologies, such as diabetes [90].

Vitamins as cellular redox regulators

Mammalian cells may induce several mechanisms to protect themselves against the detrimental effects of carbonyl stress. The effects of ROS are diminished by enzymatic antioxidants and by non-enzymatic dietary antioxidants (water- and lipid-soluble) that accumulate within the cells [91, 92, 93]. Enzymatic antioxidant defense systems include enzymes such as superoxide dismutase (SOD), catalase, glutathione dependent enzymatic system, existing within the cell to neutralize free radicals [94, 95]. It is believed that these enzymes are induced to protect cellular functions which continue in vivo homeostasis [96, 97]. On the other hand, nonenzymatic defenses contains water-soluble agents like glutathione, ascorbic acid, uric acid, plasma proteins and lipid-soluble agents like α-tocopherol, β-carotene,

bilirubin, ubiquinone, isoflavones [92, 94, 98, 99]. Some of the dietary antioxidants like α-tocopherol, ascorbic acid and β-carotene neutralize radicals outside the cell [94]. Most carotenoids can be metabolized to vitamin A and have antioxidant activity especially against singlet oxygen. β-carotene is the most prominent member of the group of carotenoids, natural colorants that can be found in the human diet [100]. β-carotene supplementation can significantly reduce the rate of mitochondrial mutation in human dermal fibroblasts after UV irradiation [101]. A recent meta-analysis suggested that higher intake of carotenoids (beta-carotene, alpha- carotene, lycopene, beta-cryptoxanthin, lutein, and zeaxanthin) is associated with lower risk of esophageal cancer [102]. The results of another recent study showed that there is a significant inverse association between pancreatic cancer and nutrient/supplement groupings in a dose-dependent manner including magnesium, potassium, selenium, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin, niacin, total alpha-tocopherol, total vitamin A activity, vitamin B6, and vitamin C [103].

Ubiquinone which is a small molecule (CoQ10) helps to generate energy for mitochondria by transporting electrons [104]. Coenzyme Q10 (CoQ10) is a fat-soluble, endogenous (synthesized by the body), vitamin-like substance that is mainly stored in the fat tissues of our body. Primary dietary sources of CoQ10 include oily fish (such as salmon and tuna), organ meats (such as liver), and whole grains. The amount of CoQ10 needed in human organism can be gained through a balanced diet; however in the market CoQ10 is available in several forms as a supplement, including soft gel capsules and tablets. As a fat-soluble substance it is better absorbed when taken with fat rich meals. The combined treatment of insulin with coenzyme Q10 has been shown to reduce lipid peroxidation, increase activity of antioxidant enzymes, total NO metabolites and bioavailability, decrease the level of atherogenic LDLP, normalize the elasticity of microvessels and modulate the elasticity of arterioles and capillaries in type 1 diabetic patients [105]. Q10 suppresses age-related inflammatory reactions and osteoclast differentiation by inhibiting oxidative stress in rats [106]. In another recent study indicates the protection of rat skeletal muscle fibers by either L-carnitine or coenzyme Q10 against statins toxicity mediated by mitochondrial reactive oxygen generation [107]. CoQ may improve spatial learning and attenuates oxidative damage when administered in relatively high doses and delayed until early senescence, after age-related declines have occurred. Thus, in individuals with age-associated symptoms of cognitive decline, high-CoQ intake has been suggested to be beneficial [108].

In this respect, Cod Liver Oil, is another studied antioxidant in our laboratory and mainly comprised of; omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid as well as vitamin A, has been shown to improve redox homeostasis, endogenous antioxidant enzyme activities in the heart and blood vessels of diabetic models [109, 110]. Vitamin C, also named L-ascorbic acid, is water soluble, photosensitive and is the most important antioxidant in the hydrophilic phase. Vitamin C is not naturally synthesized by the human body and therefore adequate dietary intake of vitamin C is required and essential for a healthy human diet. Recent results indicate that ascorbic acid plays an important role in regulating the intracellular ROS levels in senescent cells and that the need for ascorbic acid is enhanced by cellular senescence [111]. The ascorbic acid synthesizing capacity declines over time to become a major factor in senescence-related diseases [112]. Alpha lipoic acid and vitamin E are other antioxidants in the focus of our laboratory. Alpha lipoic acid treatment of diabetic animals exerted low levels of superoxide and hydrogen peroxide, was able to reverse vessel antioxidative defense and improve hypertension [113, 114]. Alpha lipoic acid acts as a protective role on apoptotic cell death and suppress hyperglycaemia-induced apoptosis in rat cardiac tissue and down-regulates caspase-6, -8 and -9 activity, as well as expression levels of proapoptotic Bcl-2 proteins [115]. Dietary supplementation with N-acetyl cysteine, α-tocopherol and α-lipoic acid reduces the extent of oxidative stress and pro-inflammatory state in aged rat brain [116].The vitamin E complex is a group of 8 compounds called tocopherols. Tocopherol is a fat-soluble membrane bound and non-enzymatic antioxidant and consequently a free-radical scavenger especially of highly reactive singlet oxygen. Vitamin C and vitamin E act synergistically against UV-activated molecular oxidation. Protective role of vitamins E and C against oxidative stress caused by intermittent cold exposure has been reported in aging rat's frontoparietal cortex [117]. Vitamin E administration produced significant improvement in red blood cell deformability and decrement in total oxidant status and oxidative stress index in aged rats with respect to young and aged control groups [118]. The average daily dietary and supplement intake of micronutrients (vitamin C, vitamin E, b-carotene, zinc, and folate) is associated with improved sperm DNA quality in older men [119]. In addition, there are a lot of data exist showing anti-cataract [120], anticancer [121] and anti-Alzheimer [122] effect of vitamin C or vitamin E which have proved that they are capable of preventing lipid peroxidation, thereby preventing the generation of free radicals. We showed that in diabetic animals, vitamin E prevents nerve conduction velocity impairment and increase the resistance to ischaemic conduction failure [123, 124], and also protect

against retinal capillary basement membrane thickness and increment in vascular endothelial growth factor expression [125]. This vitamin was also able to reverse impaired sympathetic neurotransmission and abnormal vas deferens function [126], kidney dysfunction and abnormal microsomal Ca^{2+}-ATPase activity [127] and leukocyte free radical generation in streptozotocin-diabetic rats [128]. The functions of brain and aorta [129] as well as heart and liver [66, 130, 131] also protected by vitamin E through the inhibition of carbonyl stress-induced cellular destructions in diabetic rats.

Studies suggest that effects of UVA radiation, such as skin sagging or wrinkling can be prevented or at least minimized by topical or oral administration of astaxanthin, which is found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish and crustacean [132]. Many other studies that tested oral vitamin D treatment showed the skin cancer prevention, which is linked to anti-aging effects [133]. In fact, laboratory investigations have now convincingly shown that vitamin D compounds protect the skin against the hazardous effects of various skin aging-inducing agents, including ultraviolet (UV) radiation [134]. Newly, the role of vitamin D has been revived regarding its potential advantage on delaying the aging process [135].

Phytochemicals in redox homeostasis and cell function

Undoubtedly, phytochemicals exhibit a wide array of physiological activities in humans. Ancient people had empirical knowledge that some plants and/or their extracts have great impact on health and disease regulation. For example, "Ayurveda" [136] and "Jamu" [137] recognized as a part of holistic, traditional medicine. In addition, the traditional uses many medicinal herbs including saffron and its pharmacological activities has been described Avicenna in Book II, Canon of Medicine (al-Qanun fi al-tib) and modern pharmacological findings on these compounds are compared with those mentioned in Avicenna's monograph [138]. The evidence coming from the last 20 years research, showing that many dietary phytochemicals have exhibited pronounced bioactivities in a number of experimental models, increased attention to medicinal herbs again as phytotherapeutics [137]. In addition, a variety of epidemiological analysis have demonstrated that frequent ingestion of vegetables and fruits, which contain numerous phytochemicals, lowers the risk of onset of some diseases such as diabetes [89] and cardiovascular compliance [57, 109, 110]. However, the action mechanisms by which dietary phytochemicals show bioactivity still needs to be investigation and a fundamental question is why this class of chemicals has great potential for regulating health. As is well known that, the maintenance of redox signaling at physiological levels [88], protect and repair of biological proteins by molecular chaperones, such as heat shock proteins [57], and clearance of abnormal proteins by the ubiquitin-proteasome system [139] and autophagy [140] play central roles in health, some disease prevention, and longevity. Several recent studies have revealed that polyphenols, including curcumin (yellow pigment in turmeric), resveratrol (phytoalexin in grapes), oleuropein (olive leaf compound), quercetin (general flavonol in onions), isothiocyanates (present in cruciferous vegetables, such as broccoli and cabbage) and punicic acid (omega-5 fatty acids in pomegranate seed) are remarkable regulators of redox-dependent protein quality control systems, suggesting that their physiological and biological functions are exerted, at least in part, through activation of such unique mechanisms [88, 89, 140, 141].

Humans consume a wide range of foods, drugs, and nutraceuticals that are derived from plants and which modify the functioning of the nervous system, cardiovascular system and other organ functions and cellular signaling. Polyphenols are mostly found in fruits and plant-derived beverages such as fruit juices, tea, coffee, and red wine. Vegetables, cereals, chocolate and dry legumes are also sources for the total polyphenol intake [142]. Depending on the number of phenol rings and the way that these rings bind to one another, polyphenols can be classified into many different functional groups such as the phenolic acids, flavonoids, stilbenes, and lignans [143]. As cellular redox regulator, some phenolic compounds or polyphenolic-rich herbals have been shown to prevent formation or accumulation of AGEs in vivo [37, 144, 145, 146, 147]. Many studies showed that different polyphenols such as green and black tea polyphenols, grape seed proanthocyanidins, resveratrol, silymarin and genistein ameliorate adverse skin reactions following UV exposure [148, 149]. Polyphenols display a number of pharmacological properties in the gastrointestinal tract area, acting as antisecretory, cytoprotective, and antioxidant agents. Various polyphenolic compounds have been reported for their anti-ulcerogenic activity with a good level of gastric protection. Besides their action as gastroprotective, phenolic compounds namely, baicalein, cinnamic acid, oleuropein, rutin, quercetin, and tephrosin can be an alternative for the treatment of gastric ulcers [150]. Groving evidence demonstrating that prevention of formation or accumulation of AGEs by phenolic compounds or polyphenolic-rich herbals as cellular redox regulators is mediating their protective effect of tissues against oxidative damage in vivo [37, 144, 145, 146, 147].

There are variety of phenolics from simple low-molecular weight compounds, such as the simple phenylpropanoids, coumarins, and benzoic acid derivatives, to more complex structures such as

flavanoids, stilbenes, and tannins. Flavanoids can be subdivided according to modifications of basic skeleton into chalcones, flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanins [151]. Resveratrol is an antioxidant, natural polyphenol, abundant in the skin of grapes (but not in the flesh) works both as a chelating agent and as a radical scavenger and in addition it takes part in inflammation by inhibiting the production of IL-8 by LPS-induced MAPK phosphorylation and a block of NFκB activation and IL-1β [152]. Resveratrol inhibits lipid peroxidase and protein carbonyl, protects spinal cord dorsal column from hypoxic injury by activating Nrf-2 [153]. Resveratrol possesses cancer chemopreventive activities [154], and has cardiovascular benefits via increased nitric oxide production and lowered levels of oxidized low-density lipoprotein [155]. Nuclear SIRT-1 enhanced by resveratrol was found to induce superoxide dismutase, an antioxidant enzyme which suppressed cell death in cardiomyocytes [156]. Resveratrol increases longevity through SirT1, which is activated with NAD+ supplied by an anti-aging enzyme PBEF. SirT1 interacts with an anti-aging transcription factor, FoxO1, which is negatively regulated by Akt [157]. There is a large body of evidence showing that curcumin has versatile biological and physiological activities, such as anti-inflammatory, anti-neurodegenerative, anti-Alzheimer's disease, anti-obesity, anti-oxidative, anti-cancer, and anti-HIV activities [158]. At present, the binding proteins of curcumin are known to include cell survival proteins, protein kinases, protein reductases, histone acetyltransferase, histone deacetylase, glyoxalase I, xanthine oxidase, proteasome, HIV1 integrase, HIV1 protease, sarco (endo) plasmic reticulum Ca^{2+}-ATPase, DNA methyltransferases 1, FtsZ protofilaments, carrier proteins, and others [159]. Furthermore, curcumin was found to protect from oxidative stress-induced damage in human endothelial cells via autophagy, which was executed by cytoplasmic localization and acetylation of FOXO1 for Atg7 activation [140, 160].

In fact the low levels of stress from physical, chemical and biological stressors often result in the functional improvement of cells, tissues, organs and organisms, a phenomenon termed physiological hormesis [161, 162].The seven major pathways of stress response like heat shock response, unfolded protein response, autophagy, antioxidant response, inflammatory response, DNA repair response and sirtuin response can be used as the screening platform for discovering, testing and monitoring the effects of novel hormetins [162]. As indicated largly by Rattan et al., such hormetins may be categorized as: (1) physical hormetins, such as exercise, hypergravity, heat and radiation; (2) biological and nutritional hormetins, such as infections, micronutrients, spices and other natural and synthetic compounds; and (3) psychological hormetins, such as mental challenge and focused attention or meditation [2, 161, 162]. According to this, several research articles have been published with respect to testing potential anti-aging herbalic hormetins, such curcumin, kinetin, rosmarinic acid, ferulic acid, hydroxytyrasol, slymarin and oleuropein [88, 89, 163].

A new approach that is feasible nowadays involves drug targeting for specific pathways that control oxidative, inflammatory and "proteotoxic stress". In this new continuity, the transcription factor NF-E2-related factor-2 (Nrf2), master regulator of redox homeostasis, takes central role. Aged garlic extract containing S-allylcysteine (SAC) has been highlighting the ability to activate Nrf2 factor in cerebral cortex [164]. An herbal chemopreventive agent, oridonin, represents a novel class of Nrf2 activator, has enhancing effect on cellular redox capacity, reduces ROS, and improves survival of cells after arsenic exposure [165]. In glyco-oxidative conditions, high sulforaphane content broccoli, sprouts have been reported to activate the Nrf2-dependent antioxidant response-signaling pathway, attenuates oxidative stress, and inactivates inflammatory NF-κB [166].

A Chinese plant having iridoids, total glycosides such as morroniside and loganin and also a few polyphenols such as cornusiin A, B, and C, monomeric and trimeric hydrolysable tannins, were shownt to ameliorate hyperglycemia, proteinuria, renal AGE formation, and related protein expressions, i.e., receptor for AGEs, nuclear factor-kappaB, transforming growth factor-beta1, and Nepsilon-(carboxymethyl)lysine, in the same way as with aminoguanidine [167, 168].The anthraquinones, aurantio-obtusin, chryso-obtusin, obtusin, chryso-obtusin-2-O-beta-D-glucoside, physcion, emodin, chrysophanol, obtusifolin, and obtusifolin-2-O-beta-D-glucoside, isolated from an ethanolic extract of the seeds of Cassia tora, has been characterized as inhibitory against AGEs formation and rat lens aldose reductase and ocular dysfunction [169]. The phenolic compounds of pomegranate, Punica granatum L., which is our current research showed similar effects on aldose reductase and AGEs with wide-ranging health benefits [170].

On the other hand, phytochemicals have important signaling properties in the management of diabetes induction or the development of complications, and functional foods and their nutraceutical components are now considered as supplementary agents in type II diabetes. In this respect, a recent study showed that different fractions of Catharanthus roseus L. (Apocynaceae), Ocimum sanctum L. (Labiatae), Tinospora cordifolia Willd. (Menispermaceae), Aegle marmelos L. (Rutaceae), Ficus golmerata L. (Moraceae), Psoralea corlifolia L. (Fabaceae), Tribulus terrestris L.

(Zygophyllaceae), and Morinda cetrifolia L. (Rubiaceae) have inhibitory activity on aldose reductase, a key enzyme implicated in cataractogenesis, and antioxidant agents [171,172]. The compounds with combined antioxidant and antiglycation properties seem to be more effective in treating diabetes mellitus or its complications [173]. Oral-treatment with anti-inflammatory and AGE-inhibitor, pyridoxamine inhibits AGE-induced ROS and inflammation and slow progression of degenerative spine changes in diabetes [174]. Almond skin is an abundant source of bioactive compounds and antioxidants, including polyphenolic flavonoids, catechin, epicatechin, contributing to rescued serum albumin from protein carbonylation induced by methylglyoxal, decreases gloxal induced hepatocyte cell death and ROS formation [175]. The effects of conventional reactive carbonyl species (RCS)-trapping agents including hydralazine, methoxylamine, aminoguanidine, pyridoxamine, carnosine, taurine and z-histidine hydrazide compared with herbal compounds in several experiments, and found that Cinnamon bark proanthocyanidins behave in a similar fashion as aminoguanidine, indicating great potential to be developed as agents to alleviate diabetic complications [176]. Natural Polyphenols including flavan-3-ols, thea flavins, cyanomaclurin, and dihydrochalcones or phenolic acids exert direct trapping agents of lipid peroxidation-derived adducts as acrolein and 4-hydroxy-trans-2-nonenal [177- 179].

In our laboratory, we have testing antioxidant, redox regulator and anti-cytotoxic capacity of herbal compounds and natural products by using different in vitro cellular-based and biochemical assays and in vivo animal models. For example, we examined ethanolic seed and hull extracts of pomegranate with potential therapeutic use in prevention of diabetic complications [170]. We also found that a flavonol quercetin [141] and oleuropein [88, 89 180, 181] are able to reduce the risk for diabetes production or diabetic complications, age-related protein dysfunctions or protein adduct formations via affecting different cellular cascades related with carbonyl stress. Olive leaf polyphenols are the special interest of our laboratory, under the OLEA project we found that olive leaf poyphenolic mixture has cytoprotective and anti-inflamatory signaling effects tested in cardiomyocytes, insulin releasing β-cell or skin cell cultures stimulated by H_2O_2, 4-HNE or cytokine cocktail [88, 89, 180, 181]. In comparison with each phenolic component as oleuropein and hydroxytyrosol, the ethanolic olive leaf extract even in low concentrations was demonstrated more protective effectiveness in β-cell toxicity. Our studies using diabetic models showed improved insulin sensitivity, ameliorated antioxidant enzyme activity [34, 57, 64, 68, 70, 171], dysregulated glycated protein levels and lipid peroxidation products [34, 66, 70] by different antioxidant compounds.

In pancreatic β-cells, a hallmark of glucotoxicity is a profound oxidative stress, and the persistent oxidative stress is deleterious due to accumulation of oxidized proteins, lipids, and DNA. In the classic pathway of glucotoxicity, the spontaneous reactions of glucose and other sugars with amine residues of proteins, lipids, and nucleic acids are present [88, 89, 182-184]. In pancreatic β-cells an antioxidant defense can be considered as low [89] and polyol pathway is activated when excess glucose is converted to sorbitol in the presence of aldose reductase, consuming NADPH and thus contributing to pro-oxidation state [185]. Moreover, new discoveries have identified NADPH oxidases in β-cells as contributors to elevated cellular ROS leading to β-cell dysfunction and failure [186, 187]. B-cell function may be easily impaired under yet mild oxidative stress. Such stress imposes also activation of ROS-sensitive second messengers, such as p38 mitogen-activated protein kinase, p38MAPK [188], or c-Jun N-terminal kinase, JNK/SAPK [189] and then β-cell goes to apoptosis via caspases-dependent mechanisms without a significant increase in cytochrome c release [88, 89]. Activation of JNK pathway during oxidative stress results in decreased insulin gene expression by affecting the DNA binding activity of the epigenetic regulation of transcriptional factor pancreatic duodenal homeobox (PDX1) [190]. Thus, in turn, the beneficial effect of herbal antioxidants on diabetic patient could be explained besides the protection of oxidative destructions of macromolecules also by maintenance of PDX1. PDX1 plays pivotal role in proliferation, survival, and function of β-cells and activation of insulin gene expression [191, 192]. The cytokine-induced β-cell dysfunction and apoptosis is also based on ROS-induced intracellular signaling pathways [88, 193]. Cytokine-generated ROS induce expression of inducible nitric oxide synthase (iNOS) which results in NO• release and translocation of NFκB. In turn, NFκB induces NADPH oxidase as a major cytosolic ROS source [194]. Recently it has been demonstrated that quercetin, quercitrin are potential candidates to prevent β-cell death via the mitochondrial pathway and NF-κB signaling, and quercetin may be more efficacious than quercitrin as an anti-diabetic agent [195]. Similarly, myricetin protects against cytokine-induced cell death in RIN-m5f β-cells [196], and naringenin inhibit cytokine-induced toxicity in β-cells by enhancing cell survival through PI3-kinase pathway, independent of p-p38 MAPK or iNOS [197]. According to these, under the OLEA projects we found that olive leaf polyphenolic mixture or some olive leaf phenolic compounds, which are the special interest of our laboratory, carried out cytoprotective and anti-

inflamatory effects tested insulin releasing β-cell by H_2O_2, 4-HNE or cytokine cocktail[88, 89, 180, 181] (Figure 1).

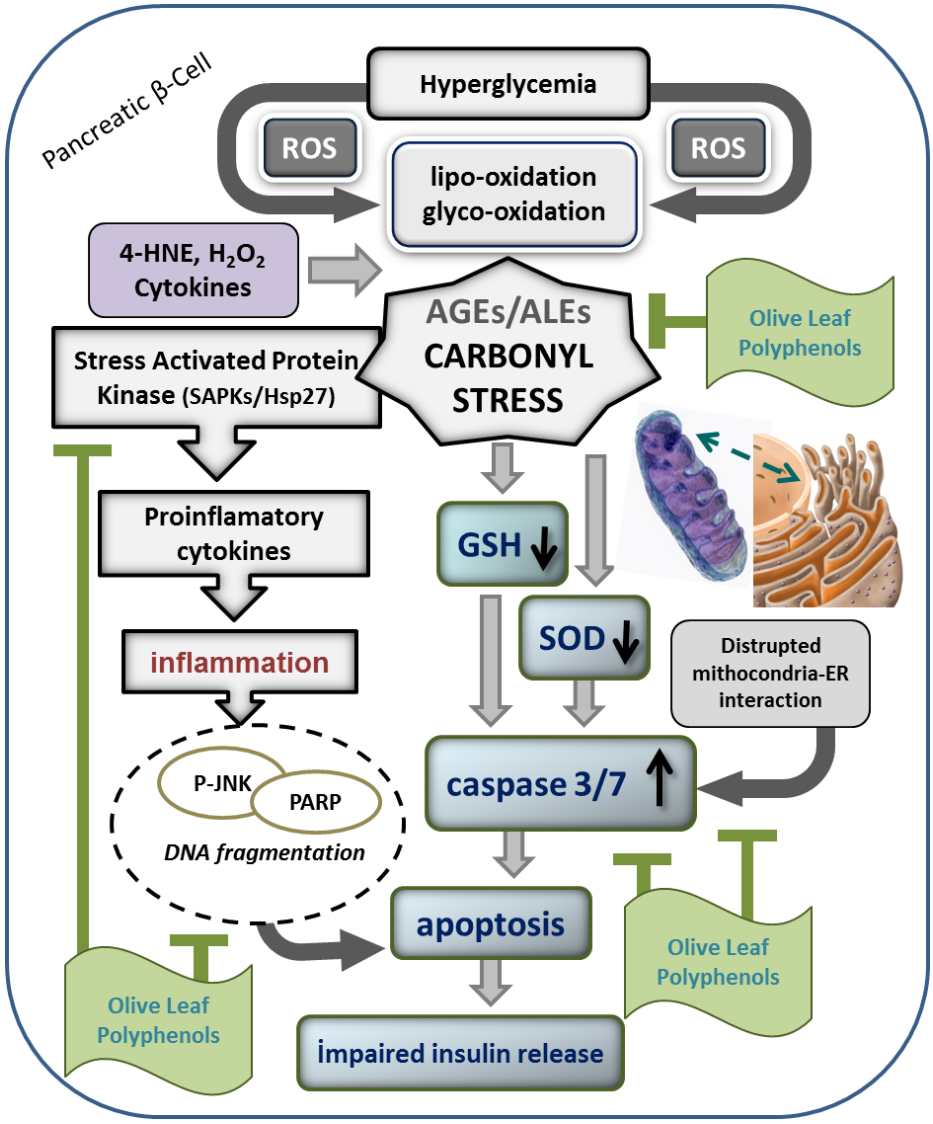

Figure 1. Inhibitory action mechanism of olive leaf polyphenolic mixture on down-stream apoptotic pathways triggering by carbonyl stress in pancreatic β-cells. ROS: Reactive oxygen species; SOD: Superoxide dismutase; GSH: Glutathione; AGEs: Advenced glyco-oxidation end products; ALEs: Advanced lipo-oxidation end products; PARP: Poly(ADP-ribose) polymerase; P-JNK: Phospho-c-Jun N-terminal kinase.

Cellular redox stress has been postulated as one major mechanism involved in the endothelial aging process and increased production of ROS leads to endothelial dysfunction in aging both in animals [57, 198] and in humans [32, 199]. There is a greater consensus over the reduced activity of the eNOS enzyme in aging [200]. Also, eNOS is regulated at post-transcriptional level involving PI3 kinase/Akt-dependent phosphorylation at Ser117, resulting in an increase in NO production from endothelial cells [32]. In aged animals, the PI3K/Akt pathway is diminished and eNOS gene expression and enzymatic activity levels decrease [201]. According to this, early experiments of our group showed that insulin-dependent and noninsulin-dependent diabetes lead to

specific alterations in endothelium-dependent relaxation of rat aorta in basal and stimulated conditions [202-204]. This impaired relaxant feature of endothelium was accompanied to increased vasoconstrictor properties of diabetic resulting in high arterial blood pressure [203,204]. Our experiments also revealed that NIDDM causes a deficit in the vasorelaxation by endothelium, leading to an increase in contractility of human internal mammary artery and saphenous vein observed in patients under coronary artery bypass surgery [205]. In chronic state of disease, arterioles and arteries showed more sensitivity than non-diabetics to exogenously added ROS such as H_2O_2 [206, 207] and peroxynitrite [208] and excess superoxide was major mediator responsible for the enhanced transient nature of endothelium-dependent relaxation in aorta due to impaired NO bioavailability [209]. Furthermore, to the maintenance of physiological endothelium-mediated relaxation in chronically diabetic vessels, the involvement of H_2O_2 to acetylcholine-stimulated vasorelaxation was increased [209].

Under the Antioxidants in Diabetes-Induced Complications (ADIC) Study Group, we reported that vitamin E or lipoic acid treatment of STZ-diabetic rats can prevent abnormal contractility, structure and endothelial dysfunction in aorta, and the triglyceride-, lipid peroxidation-lowering and the endogen antioxidant enzyme activity modulating properties associate with the protective effect of these vitamins on the vasculature [110, 114, 130, 131, 210]. The elimination of superoxide/hydrogen peroxide by lipoic acid mediated the recovery of basal NO availability and the reversal of superoxide dismutase-induced relaxation in diabetic rat aorta [113]. On the other hand, using of vitamin A together with insulin provided a better metabolic control against cellular redox abnormalities and development of vascular complications in diabetes than using of insulin alone [210]. Vitamin E also ameliorated aldose reductase enzyme activity, protein adduct formation, retinal capillary basement membrane thickness and vascular endothelial growth factor expression in aged diabetic animals [125].

Additionally, some herbal polyphenols have ability to activate SIRT1 directly or indirectly judged in various animal models. Therefore, activation of SIRT1 by polyphenols may be essential for regulation of endothelial dysfunction as well as inflammation, senescence, and apoptosis. Molecular basis of SIRT1 in these processes is due to its ability to deacetylate miscellaneous proteins, such as NF-κB, p53, FOXO3, PPAR-γ, and eNOS [211, 212]. Several intervention studies have suggested that the consumption of flavonoid-, flavanone- or polyphenolic rich foods such as tea, grape polyphenols, cocoa, pomegranate juice and soya can improve endothelial function in patients with manifest cardiovascular and cerebrovascular disease [213-215]. Consumption of polyphenolic rich diet emphasized to be effective at reducing cardiovascular disease risk factors, particularly with respect to anti-hypertensive effects, inhibition of platelet aggregation and increasing endothelial-dependent vasodilation [216-218]. The studies performed with elderly people demonstrated that the consumption of a Mediterranean diet leads to an increase in NO bioavailability and vascular regeneration capacity [219]. Perez-Martinez et al., showed that the consumption of a Mediterranean diet reduced postprandial levels of cellular stress biomarkers such as lipid peroxide, protein carbonyl, SOD activity and plasma H_2O_2 compared to a saturated fat-rich diet in metabolic syndrome subjects [220]. Peña-Orihuela reported that monounsaturated fat consumption reduces oxidative stress as compared to saturated fat by inducing higher postprandial antioxidant response in adipose tissue, and thus, replacing saturated fatty acid for monounsaturated fatty acid may be an effective dietary strategy to reduce the oxidative stress in metabolic syndrome patients and its pathophysiological consequences [221]. Similarly, this diet significantly attenuated the postprandial inflammatory state, including NF-κB, metalloproteinase-9 and tumor necrosis factor-α [222, 223]. The results of the Yubero-Serrano's study support the antioxidant effect of a Mediterenian diet and that exogenous CoQ supplementation has a protective effects against free radical over generation through the lowering of postprandial oxidative stress modifying the postprandial antioxidant protein levels and reducing the postprandial expression of antioxidant genes in peripheral blood mononuclear cells [224]. A recent study demonstrates for a first time that polyphenols, when used in conjunction with an intermittent feeding protocol, can enhance the longevity-promoting effects at least in mice [225].

Conclusion and Future Expectations

Aging is not controlled by a single mechanism and mainly depends on three major characteristics: stress response, the ability for damage prevention, repair and removal, and the ability for continuous remodeling and adaptation.

Accumulation of damaged macromolecules, including oxidatively damaged (carbonylated) proteins, is a hallmark of cellular and organismal aging. Thus understanding the molecular and cellular mechanisms that underlie the aging process would provide a good strategy to address the problems presented by the aging of the world's population. Considering that micronutrients, phyto-chemicals are a very important source of redox regulators, in this review we analyzed the relationship between cellular redox stress, aging, and the mechanisms which may be involved in a higher survival rate and a

lower incidence of the diseases associated with aging in populations which follow a healthy diet.

The large scale of findings show that cellular oxidative stress and also reductive stress (as indicated recently) are the major sources of damage in the dysregulation of biological systems and closely linked to the generation of impaired cellular stress response, physiological redox signaling and homeostasis, which contribute to the development of cellular senescence and accelerated aging of the organism. The contribution of carbonyl compounds and then protein adduct formations by advanced interaction of sugars/lipids with amino acids/peptides to the abnormal cellular redox metabolism is great interest of the recent research. The accumulation of adduct formation such as lipofuscin is implicated in normal aging and age-related diseases including Alzheimer's disease, Parkinson's disease, chronic obstructive pulmonary disease, myopathy, cardiovascular dysfunction and diabetes. Antioxidant plant extracts rich in polyphenols suggested to be increase lifespan. Polyphenols, natural cellular redox regulators or herbal compounds allowing physiological modulation of cells to redox stressors (when used in conjunction with an intermittent feeding) can enhance the longevity-promoting effects through reduction of cellular degenerative chaos and inflammation-related activity with a lower incidence of the diseases associated with aging. In the absence of large definitive clinical trials, present experimental findings at least in part have clear practical relevance for humans seeking to engage in health promoting behaviors.

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