applied sciences

MDPI

Review

Plant-Derived Bioactives and Oxidative Stress-Related Disorders: A Key Trend towards Healthy Aging and Longevity Promotion

Bahare Salehi [1], Elena Azzini [2], Paolo Zucca [3], Elena Maria Varoni [4], Nanjangud V. Anil Kumar [5], Luciana Dini [6], Elisa Panzarini [6], Jovana Rajkovic [7], Patrick Valere Tsouh Fokou [8], Ilaria Peluso [2], Abhay Prakash Mishra [9], Manisha Nigam [10], Youssef El Rayess [11], Marc El Beyrouthy [11], William N. Setzer [12], Letizia Polito [13,*], Marcello Iriti [14], Antoni Sureda [15,16], Maria Magdalena Quetglas-Llabrés [15], Miquel Martorell [17,18,*], Natália Martins [19,20,*], Mehdi Sharifi-Rad [21], Leticia M. Estevinho [22,23,*] and Javad Sharifi-Rad [24,*]

1 Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam 44340847, Iran; bahar.salehi007@gmail.com
2 CREA—Research Centre for Food and Nutrition, Via Ardeatina, 546-00178 Roma, Italy; elena.azzini@crea.gov.it (E.A.); ilaria.peluso@crea.gov.it (I.P.)
3 Department of Biomedical Sciences, University of Cagliari, 09124 Cagliari, Italy; paolozuc@gmail.com
4 Department of Biomedical, Surgical and Dental Sciences, Milan State University, 20142 Milan, Italy; elena.varoni@unimi.it
5 Department of Chemistry, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal 576104, India; nv.anil@manipal.edu
6 Department of Biological and Environmental Sciences and Technologies (Di.S.Te.B.A.), University of Salento, 73100 Lecce, Italy; luciana.dini@unisalento.it (L.D.); elisa.panzarini@unisalento.it (E.P.)
7 Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Belgrade, 11129 Belgrade, Serbia; jolarajkovic@yahoo.com
8 Department of Biochemistry, Faculty of Science, University of Yaounde 1, Yaounde 812, Cameroon; ptsouh@gmail.com
9 Department of Pharmaceutical Chemistry, H.N.B. Garhwal (A Central) University, Srinagar Garhwal, Uttarakhand 246174, India; abhaypharmachemhnbgu@gmail.com
10 Department of Biochemistry, Hemvati Nandan Bahuguna Garhwal University (A Central University), Srinagar, Garhwal, Uttarakhand 246174, India; anandmanisha23@gmail.com
11 Department Agricultural and Food Engineering, School of Engineering, Holy Spirit University of Kaslik, Jounieh B.P. 446, Lebanon; youssefrayess@usek.edu.lb (Y.E.R.); marcelbeyrouthy@usek.edu.lb (M.E.B.)
12 Department of Chemistry, University of Alabama in Huntsville, Huntsville, AL 35899, USA; setzerw@uah.edu
13 Department of Experimental, Diagnostic and Specialty Medicine-DIMES General Pathology Section, Via San Giacomo, 14, Alma Mater Studiorum-University of Bologna, 40126 Bologna, Italy
14 Department of Agricultural and Environmental Sciences, Milan State University, via G. Celoria 2, 20133 Milan, Italy; marcello.iriti@unimi.it
15 Research Group in Community Nutrition and Oxidative Stress, University of Balearic Islands & Health Research Institute of the Balearic Islands (IdISBa), E-07122 Palma, Balearic Islands, Spain; tosugo@hotmail.com (A.S.); mariamagdalenaqll@gmail.com (M.M.Q.-L.)
16 CIBEROBN (Physiopathology of Obesity and Nutrition), University of Balearic Islands, E- 07122 Palma, Balearic Islands, Spain
17 Department of Nutrition and Dietetics, Faculty of Pharmacy, University of Concepcion, Concepcion 4070386, Chile
18 Unidad de Desarrollo Tecnológico, Universidad de Concepción UDT, Concepcion 4070386, Chile
19 Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
20 Institute for Research and Innovation in Health (i3S), University of Porto, 4200-135 Porto, Portugal
21 Department of Medical Parasitology, Kerman University of Medical Sciences, Kerman 7616913555, Iran; mehdi_sharifirad@yahoo.com

[22] Department of Biology and Biotechnology, School of Agriculture of the Polytechnic Institute of Bragança (ESA-IPB), Campus de Santa Apolónia, 5301-854 Bragança, Portugal
[23] CIMO, Mountain Research Center, Polytechnic Institute of Bragança, Campus Santa Apolónia, 5301-855 Bragança, Portugal
[24] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran 1991953381, Iran
* Correspondence: letizia.polito@unibo.it (L.P.); mmartorell@udec.cl (M.M.); ncmartins@med.up.pt (N.M.); leticia@ipb.pt (L.E.M.); javad.sharifirad@gmail.com (J.S.-R.)

Received: 18 December 2019; Accepted: 8 January 2020; Published: 1 February 2020

Abstract: Plants and their corresponding botanical preparations have been used for centuries due to their remarkable potential in both the treatment and prevention of oxidative stress-related disorders. Aging and aging-related diseases, like cardiovascular disease, cancer, diabetes, and neurodegenerative disorders, which have increased exponentially, are intrinsically related with redox imbalance and oxidative stress. Hundreds of biologically active constituents are present in each whole plant matrix, providing promissory bioactive effects for human beings. Indeed, the worldwide population has devoted increased attention and preference for the use of medicinal plants for healthy aging and longevity promotion. In fact, plant-derived bioactives present a broad spectrum of biological effects, and their antioxidant, anti-inflammatory, and, more recently, anti-aging effects, are considered to be a hot topic among the medical and scientific communities. Nonetheless, despite the numerous biological effects, it should not be forgotten that some bioactive molecules are prone to oxidation and can even exert pro-oxidant effects. In this sense, the objective of the present review is to provide a detailed overview of plant-derived bioactives in age-related disorders. Specifically, the role of phytochemicals as antioxidants and pro-oxidant agents is carefully addressed, as is their therapeutic relevance in longevity, aging-related disorders, and healthy-aging promotion. Finally, an eye-opening look into the overall evidence of plant compounds related to longevity is presented.

Keywords: medicinal plants; bioactive molecules; phenolic compounds; oxidative stress; antioxidants; chronic disorders; health maintenance; longevity

1. Introduction

Since the beginning of human civilization, plants have been used in virtually all cultures as a source of remedy for multiple health conditions, as documented from the centers of civilization. They comprise a brilliant source of exogenous antioxidants, whose activity ranges from extremely slight to very great [1,2]. Indisputably, these natural antioxidants may act as reducing agents, free radical scavengers, singlet oxygen forming and pro-oxidant metals quenchers, localized O_2 concentration reducers, endogenous antioxidant defenses boosters, and avoid damage in repair systems, or any combination of the above. Also, they protect against oxidative stress, which in turn helps in maintaining the balance between oxidants and antioxidants levels [3].

Interestingly, reactive oxygen species (ROS) have been considered to be the uninvited companions of aerobic life ever since molecular oxygen was introduced in our environment about 2.7 billion years ago [4]. Under steady-state conditions, ROS molecules are scavenged by various antioxidant defense mechanisms [5]. In this sense, the antioxidant potential of plants has attracted a great deal of attention, because increased oxidative stress has been reported as a major contributing factor to both the development and progression of aging and numerous life-threatening disorders, including neurodegenerative and cardiovascular diseases [6,7].

Plants possess miraculous antioxidant effects because of their high oxygen exposure physiology. In fact, plants may have more sites of ROS generation. Therefore, they could evolve more proficient non-enzymatic antioxidant systems than humans [1,8]. Plants synthesize several enzymatic and

non-enzymatic antioxidants to avoid free radicals' toxic effects, in addition to be able to synthesize and accumulate a wide variety of low and high molecular weight secondary metabolites, which play important roles in ROS metabolism and effectively avoid the uncontrolled oxidation of essential biomolecules, thus, acting as antioxidants [1,8,9].

There is a broad diversity of naturally-occurring antioxidants found in plants, differing in their composition, physicochemical properties, site, and mechanism of action. The major antioxidant plant secondary metabolites are phenolic compounds, and they can be divided into five general groups, namely, phenolic acids, flavonoids, lignans, stilbenes, and tannins [10–12]. Briefly, they provide protection through scavenging numerous ROS, including hydroxyl radicals, peroxyl radicals, hypochlorous acids, superoxide anions and peroxynitrite [13]. Particularly, the antioxidant activity of polyphenols in cardiovascular diseases, such as the activity of hepatoprotective, anti-carcinogenic, antimicrobial, antiviral, and anti-inflammatory agents, has been broadly described [14,15]. In fact, anthocyanins play a key antioxidant role in plants against ROS-generated abiotic stress, such as in the case of ultraviolet light and extreme temperatures [16,17]. They also inhibit chemically-induced cancer and turn off genes involved in proliferation, inflammation, and angiogenesis [18]. Also, these secondary metabolites are known to prevent a key step in atherogenesis and are more potent antioxidants than vitamin C [19].

Moreover, a meta-analysis of epidemiological studies has shown that carotenoids act protectively against head and neck cancer [20], while other studies have suggested that carotenoid-rich diets appear to have a protective effect against Parkinson's disease (PD) [21] and prostate [22] and breast [23] cancers. In this sense, the objective of the present review is to provide a detailed overview of plant-derived bioactives and their effect on age-related disorders. Specifically, the role of phytochemicals as antioxidants and pro-oxidant agents is carefully addressed, as is their therapeutic relevance in longevity, aging-related disorders, and healthy-aging promotion. Finally, an eye-opening look into the overall evidence of plant compounds related to longevity is presented.

2. The Role of Phytochemicals in Oxidative Stress

Nowadays, ROS-related research is increasing due to the involvement of ROS in aging and aging related-diseases such as cardiovascular and neurodegenerative diseases, atherosclerosis, and others [24–26]. Thus, the importance of removing excessive ROS is becoming increasingly recognized, which is often achieved using antioxidants.

In a broad sense, an antioxidant is defined as "any substance that delays, prevents, or removes oxidative damage to a target molecule" [27]. Thus, oxidative stress represents an imbalance between humans' protective molecules, the antioxidants, and molecules that can damage all sorts of cellular components, such as free radicals. Nonetheless, some antioxidant molecules may also present pro-oxidant effects. For instance, ascorbic acid plays an important role in ameliorating photosynthesis' oxidative stress, besides having several other roles in cell division and protein modification, but also acting as a pro-oxidant [28]. Similarly, vitamin E also possesses pro-oxidant effects when used at high concentrations. Indeed, it has been reported that vitamin E reacts with free radicals to become a reactive radical (pro-oxidant) in the absence of co-antioxidants [8]. On the other hand, it has also been reported that some antioxidant phytochemicals from foods, spices, herbs, and medicinal plants may also act as pro-oxidant agents when a transition metal is available [29].

2.1. Phytochemicals as Antioxidant Agents

Phytochemicals exhibiting antioxidant effects are broadly categorized into the alkaloid, carotenoid, coumarin, flavonoid, phenolic, and terpenoid groups, among other organic compounds. However, given the focus of the present review, and based on the number of structures, they are grouped as follows (Table S1).

An extensive search of the existing published literature was performed, where the inclusion criteria were that the literature was from a journal listed in either the Scopus or Web of Science database

and that the isolated compounds were purified and assayed for antioxidant activity. Regarding the exclusion criteria, compounds known to possess antioxidant effects that have been isolated from various plant materials were excluded. Thus, given the above-established aspects and considering both the taxonomical classification and the family name listed in the plant list website, the literature search was carried out. All the obtained data are carefully organized and presented in Tables S2–S10.

2.2. Case Study: Antioxidant Activity of Flavonoids

Flavonoids comprise a large group of phenolic compounds. Their basic chemical structure is the flavan nucleus, which consists of 15 carbon atoms arranged in three rings (C_6-C_3-C_6), as seen in Figure 1. The different classes of flavonoids differ in their oxidation level and substitution pattern of the C ring, while units within a class differ in their substitution pattern of the A and B rings [30].

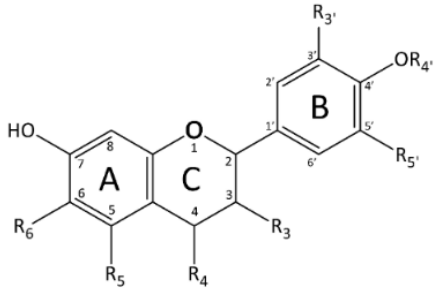

Figure 1. Basic structure of flavonoids.

Nowadays, flavonoids have gained huge interest due to their broad pharmacological activity. The interest in flavonoids' health benefits has been raised due to the prominent in vitro antioxidant effects that have been stated. Specifically, the antioxidant activity of flavonoids and their metabolites depends upon the arrangement of the functional groups around the basic structure. Several in vitro investigations have been carried to elucidate the relationship between flavonoid structure and the corresponding antioxidant effects [31–36]. Therefore, the chemical structures of flavonoids are predictive of their antioxidant potential in terms of their radical scavenging, hydrogen- or electron-donation, and metal-chelating capacities.

The following mechanisms have been cited in literature to explain the antioxidant activity of flavonoids: (1) The scavenging of free radicals or ROS, (2) metal chelation, (3) inhibition of enzymes associated with free-radicals generation (e.g., oxidases), and (4) the activation of antioxidant enzymes [30,37,38].

2.2.1. Free-Radical Scavenging

The antioxidant capacities of flavonoids can arise from free radical scavenging or direct ROS scavenging. Flavonoids are able to donate a hydrogen atom to neutralize free radicals. Also, flavonoids may act by single-electron transfer.

In the literature, it is well-known that some flavonoids present higher antioxidant activity than others, which is directly related to their chemical structure [37,39,40]. For efficient radical scavenging, the required structural features of flavonoids are summarized as follows: (i) An *o*-dihydroxy (catechol) structure in the B ring for electron delocalization (Figure 2, ring a); (ii) hydroxyl groups at position 3 on the C ring and 5 and 7 on the A ring provide an increase in antioxidant activity (Figure 2, ring b), and (iii) a C_2-C_3 double bond combined with the oxo-C_4 on the C ring (Figure 2, ring c).

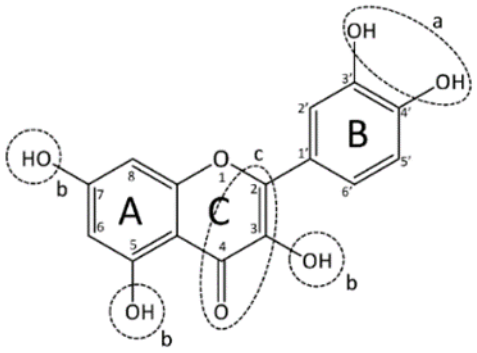

Figure 2. Antioxidant structure and activity relationships of flavonoids.

The most significant actor in scavenging free radicals is the B ring hydroxyl structure. The hydroxyl groups on this ring stabilize hydroxyl, peroxyl, and peroxynitrite radicals through the donation of hydrogen or electrons. Quercetin has shown to be a flavonoid expressing higher antioxidant activity due to the presence of hydroxyl groups and twisting angle of the B ring [41].

The total number of hydroxyl groups in the flavonoid structure influences the mechanism of antioxidant activity. To evaluate the antioxidant activity of flavonoids' hydroxyl groups, the bond dissociation energy (BDE) is used, where the lower the BDE value is, the easier the dissociation of the hydroxyl bond and the reaction with free radicals [30,42].

2.2.2. Metal-Ion Chelating

Metal ions, such as Fe^{2+} and Cu^{+}, are considered to be primary triggers of in vivo ROS generation. These redox-active metal ions can react with H_2O_2, and the result is OH^{-}, which damages DNA by strand breakage or base damage, leading to genetic mutations, cancer, or even cell death [43,44].

Some flavonoids can chelate these metal ions, decreasing one of the factors for the development of free radicals. The proposed binding sites for metal ions in flavonoid structure are the catechol moiety in the B ring, the 3-hydroxyl and 4-oxo groups in the C ring, and the 4-oxo and 5-hydroxyl groups between the C and A rings [45]. For the iron-chelating mechanism of flavonoids, the stability constants for flavonoid-iron interactions have been measured, providing insight into their antioxidant behavior [46].

2.2.3. Inhibition of Pro-Oxidant Enzymes

Enzymes such as nitric oxide synthase (NOS), xanthine oxidoreductase (XOR), lipoxygenase (LOX), and cyclooxygenase (COX) are responsible for ROS generation [24]. XOR is involved in the metabolism of xanthine to uric acid and is a source of oxygen free radicals [26]. XOR reacts with molecular oxygen and releases superoxide. Flavonoids have been shown to inhibit XOR, and, amongst them, quercetin and luteolin are the most widely cited for use [14,47]. Several reports have investigated the structure-activity relationships of flavonoids as XOR inhibitors [47–49]. All these studies have shown that the flavonoids' inhibitory activity is due to the planar flavone core (C_2-C_3 double bond), hydroxyl groups at C_5 and C_7, and the carbonyl group C_4 [47–49]. COX and LOX are responsible for the inflammatory process of mediator production. COX presents two isoforms, COX-1 and COX-2. During the inflammatory process, COX-1 mRNA and protein activity do not change, whereas a dramatic increase in COX-2 levels occurs, leading to increased proinflammatory prostanoid production [50].

Flavonoids have been investigated as selective COX-2 inhibitors, like quercetin and quercetin 3'-sulfate [51]. Those with an ortho-dihydroxy (catechol) moiety in rings A or B appear to be stronger inhibitors. In addition, the planar flavonoid structure (C_2-C_3 double bond) seems to be a prerequisite for inhibitory activity [52]. The same observation about structure-activity relationships was made for LOX inhibition [53,54]. It has been shown that quercetin and quercetin monoglucosides exert higher LOX inhibition potential [53]. Otherwise, it should be considered that the effect of plant antioxidants

on several enzymes, such as XOR, can have secondary effects on other drugs that are metabolized by XOR. In fact, as reported in a recent review [55], XOR activity is directly involved in the metabolism of antiblastic and antimetabolic drugs, which are used for treating neoplasia, autoimmune diseases, and viral infections. Sometimes, XOR activity has a degradative function toward a drug, while to other drugs it may present an activating role, and thus it is essential for pharmacological activity [55].

2.2.4. Activation of Antioxidant Enzymes

Another mechanism through which flavonoids can play an antioxidant role is the modulation of antioxidant enzyme expression. The enzymatic antioxidant system in humans is composed of glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase (SOD), NADPH-quinone oxidoreductase, glutathione *S*-transferase, and glutathione reductase.

Flavonoids have been shown to interact with cellular defense systems through the antioxidant-responsive element/electrophile-responsive element (ARE/EpRE) [56]. Quercetin has been shown to stimulate both antioxidant response genes and protein expression in various cell types, and these proteins may prevent damage from subsequent oxidative insults, such as heme oxygenase-1 (HO-1) in RAW264.7 macrophages [57], CAT in the trabecular meshwork cells of the eye [58], and the NAD(P)H dehydrogenase [quinone] 1 (NQO-1) enzyme in HepG2 cells [56]. Kaempferol has also been shown to be able to activate the ARE more potently than quercetin, and lower concentrations of the combination of both compounds have been shown to increase the mRNA expression of NADPH-quinone oxidoreductase and glutathione *S*-transferase to a higher extent than individual treatments at higher concentrations [59]. Lee-Hilz et al. [60] showed that flavonoids bearing a hydroxyl group at the 3-position of C ring, like quercetin and myricetin, were the most effective inducers of the firefly luciferase reporter gene in Hepa-1c1c7 mouse hepatoma cells.

2.3. Phytochemicals as Pro-Oxidant Agents: Friend or Foe?

Besides the already stated phytochemicals with antioxidant effects, it has also been shown that some of these molecules may possess pro-oxidant effects. In particular, flavonoids have been found to be mutagenic in vitro [61,62]. In fact, as described above, the chemical structure of flavonoids exerts a key role in determining their antioxidant activities, as well as their copper-initiated pro-oxidant activities. As long as the OH substitution is necessary for the antioxidant activity, the subclasses of flavone and flavanone, which have no OH substitutions and provide the basic chemical structures for flavonoids, do not show antioxidant or copper-initiated pro-oxidant activities [61]. Higher OH substitutions are associated with stronger redox activity. O-Methylation, probably as well as other O-modifications of the flavonoid OH substituents, inactivates both the antioxidant and pro-oxidant effects of flavonoids. In general, flavonoids occur in foods as O-glycosides with sugars bound at the C3 position. Methylation or glycosidic modification of the OH substitutions leads to inactivation of the transition metal-initiated pro-oxidant activity of a flavonoid [63].

On the other hand, flavonoids, such as quercetin and kaempferol, induce nuclear DNA damage and lipid peroxidation in the presence of transition metals. The in vivo copper-initiated pro-oxidant action of flavonoids is generally not considered significant, as copper ions are largely sequestered in tissues, except in the case of metal toxicity. In this context, flavonoids, such as catechins and quercetin, possess chelating properties, inhibiting their reactivity [64,65]. Besides, polyphenols are well-known as scavenger/chain breaking phytochemicals (Figure 3). Despite the well-known ability of flavonoids in preventing iron-induced lipid peroxidation in hepatocytes, including quercetin [66], it has been suggested that the pro-oxidant activity of some polyphenols is more prominent in vitro under particular conditions, such as high pH or the presence of high concentrations of transition metal ions and oxygen molecules [2]. Specifically, small phenolic molecules, which are easily oxidized, such as quercetin and gallic acid, have a known pro-oxidant activity, while, on the other hand, phenols with a high molecular weight (i.e., tannins), have little or no pro-oxidant activity [15]. The pro-oxidant properties of polyphenols may derive from different possible mechanisms, including metal reduction,

copper ion mobilization, chemical instability, cellular glutathione (GSH) depletion, and sulfhydryl (SH) interactions [67].

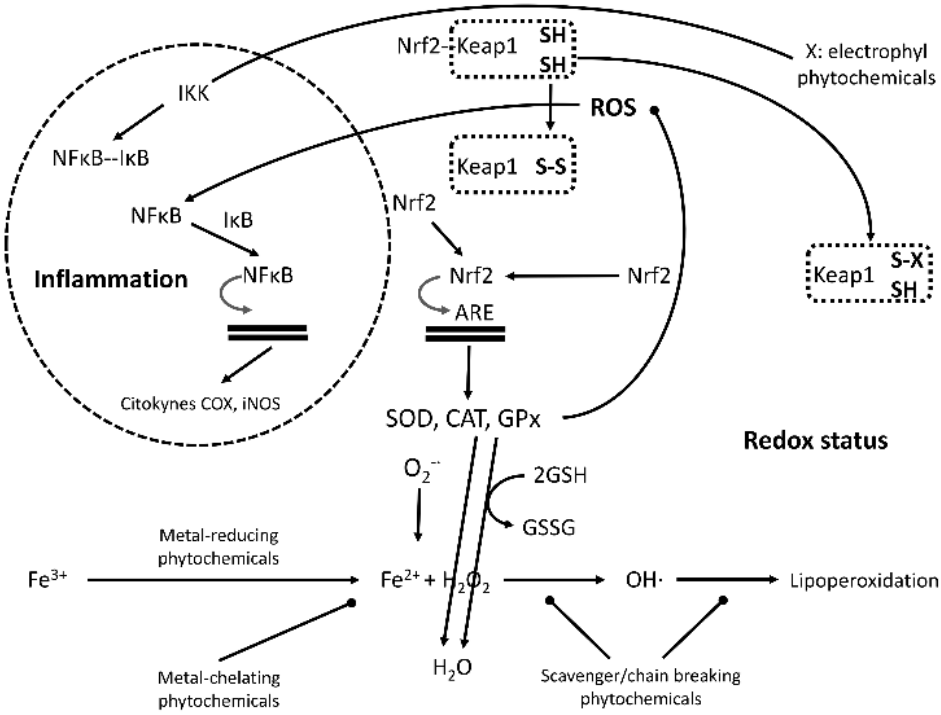

Figure 3. Glutathione (GSH); glutathione *S*-transferases (GSTs); glutathione peroxidase (GPX), superoxide dismutase (SOD); catalase (CAT); nuclear factor-erythroid 2-related factor 2 (Nfr2); antioxidant responsive elements (ARE); kelch-like ECH-associated protein-1 (Keap1); nuclear factor-kappa B (NF-κB); Iκ kinases (IKK); CREB-binding protein (CBP).

Although reduction and antioxidant capacity are related, it must be considered that the hydroxyl radical, the lipid peroxidation initiator, is produced from the reaction between reduced iron or copper and hydrogen peroxide (Figure 3). Moreover, some dietary polyphenols, such as resveratrol and caffeic acid, have been shown to trigger DNA damages through the mobilization of endogenous copper ions, suggestive of chromatin binding, leading to ROS production [68]. The preferential cytotoxicity towards tumor cells is probably due to the high levels of copper ions, and not of iron ions in cells and in tumor tissues. The mechanism through which copper concentration is increased in the tumor is not yet clear [68,69]. However, it has been shown that the copper transporter 1, with high affinity in humans, is over-expressed in malignant cells, resulting in the increased absorption and accumulation of the metal. Also, it has been hypothesized that copper may be necessary for ceruloplasmin expression, which is the main protein that binds it, which is over-expressed in cancer cells, and thus it has been proposed to be an endogenous stimulator of angiogenesis. Nonetheless, further in vivo studies are necessary to better understand these processes.

Regarding chemical instability, many polyphenols are structurally unstable and can undergo enzymatic or spontaneous oxidation in the presence of metal ions, particularly in cell cultures, to form ROS [29,70,71]. For instance, it has been shown that epigallocatechin gallate (EGCG) produces significant amounts of H_2O_2 in cell cultures [72].

Likewise, the cytotoxicity of green tea and red wine in PC12 rat phaeochromocytoma cells, when grown in Dulbecco's Modified Eagle's Medium (DMEM), can be attributed to H_2O_2 produced from these drinks, at least partially [73]. The same holds true for phytochemicals, including polyphenols that can become pro-oxidants, even if this has not yet been clearly elucidated. However, transition metal ions are known to be present in cell culture media. An example is DMEM, which contains

inorganic iron, usually $Fe(NO_3)_3$, which gives it greater pro-oxidant properties. Also, most of the cultured cells are kept in high O_2 conditions (95% air and 5% CO_2) and low ascorbate, vitamin E and selenium concentrations, which can lead to artefact results [29].

Through in vitro studies, several food polyphenols have been shown to determine cellular GSH depletion, which could contribute to apoptosis activation in tumor cells. For example, Kachadourian and Day [74] have shown that the flavones, cristine, and apigenin, deplete GSH in cell lines, while hydroxycarbonate and dihydroxycalcone perform this action more effectively in tumor prostate PC-3 cells. These authors found that the enhancement effects of these different flavones are related to mitochondrial dysfunction through the depletion of mitochondrial GSH levels, a decrease in mitochondrial membrane potential, and the increase of cytochrome C release [74]. In this context, isothiocyanates are conjugated with GSH by glutathione *S*-transferases (GSTs) [75,76]. GPX, which is involved in hydrogen peroxide removal, consumes GSH (Figure 3). On the other hand, it has been suggested that some polyphenols have a pro-oxidant activity, both in vitro and in vivo, which certainly contributes to their antioxidant and anti-cancer effects [29], through inducing antioxidant enzymes, such as SOD, which catalyzes the one-electron dismutation of superoxides into hydrogen peroxide and oxygen, and CAT, allowing two-electron dismutation into oxygen and water (Figure 3).

It is well-known that cysteine reduced form (SH) redox status has a primary role in the nuclear factor-erythroid 2-related factor 2 (Nfr2)/ARE pathway (Figure 3). Under physiological conditions, Nfr2 is bound to the kelch-like ECH-associated protein-1 (Keap1) and, thereby, sequestered in the cytoplasm, whereas, when under conditions of oxidative stress, Nfr2 dissociates from Keap1, translocating to the nucleus and inducing antioxidant enzyme transcription. The cysteine residues on Keap1, which are ultrasensitive to electrophiles, are critically important for Nrf2 binding. Antioxidants with catechol and electrophilic moieties induce Nrf2-mediated gene expression in antioxidant enzymes acting as pro-oxidants rather than antioxidants [77]. This effect is well-known for green tea catechins [78], but also other bioactive phytochemicals, like triterpenoids, caffeic acid, and isothiocyanates (the breakdown products of glucosinolates), which can induce the Nrf2 pathway, acting on cysteine residues of Keap1 [75,76,79–81].

As observed for Nrf2, ROS and some cysteine residues are involved in NF-κB translocation to the nucleus (Figure 3). In particular, cysteine 179 of Iκ kinases (IKK) is a target of the S-glutathionylation-induced inactivation [82]. Electrophilic modifications of cysteine 179 of IKK inhibit NF-κB activation and have been suggested to be one of the mechanisms involved in the anti-inflammatory and COX-inhibitory effects of phytochemicals [83,84]. On the other hand, it has been suggested that the crosstalk between Nrf2 and NF-κB can occur through other mechanisms, including common regulatory sequences in transactivation domains, the co-activator CREB-binding protein (CBP), and up-regulation exerted by the Nrf2 of antioxidant enzymes [75].

3. Therapeutic Relevance of Plant-Derived Antioxidants in Aging and Aging-Related Diseases

Redox homeostasis plays a crucial role in health maintenance and disease prevention. Oxidative stress, generated by the unbalance between ROS and antioxidants, leads to the degradation of lipids, proteins, and nucleic acids, resulting in oxidative damage to cells. Such damage may result or contribute significantly to oncogene over-expression, mutagen formation, atherogenic activity induction, or inflammation. In fact, oxidative stress has been reported to play a major role in aging and in aging-related diseases. As already stated, plants are rich sources of antioxidants which show health benefits through the direct reduction of oxidative stress. Here, we focus on some plants that involve an antioxidant-based mode of action in aging and disease management.

3.1. Anti-Aging

Aerobic life is possible thanks to oxygen, but this is what makes life not infinite at the same time. During aerobic respiration, cells are able to obtain energy through reduction-oxidation reactions [85]. The incomplete reduction of oxygen in aerobic respiration and other metabolic processes can produce

highly reactive molecules, known as ROS. These molecules play an important role in cells, since they can participate in the transmission of intracellular signals, regulating diverse redox-sensitive pathways but also oxidizing and altering biomolecules [85,86]. In 1956, Harman postulated the mitochondrial free radical theory of aging (MFRTA), suggesting that the aging process is related, in part, to the accumulation of oxidative damage to cellular components [87]. Aging is a multifactorial process, characterized by a gradual loss of homeostasis and, therefore, the loss of physiological functions in which numerous elements are involved, including ROS and a widespread decrease in antioxidant defense [88,89]. Accordingly, with aging, there is an accumulation of ROS, mainly in the mitochondria, which promotes a situation of chronic oxidative stress, favoring the appearance of oxidative damage to DNA, lipids, and proteins, inducing the degeneration of the tissues [90].

There are two main types of oxidant sources, namely, the mitochondrial source, which plays a major role in aging, and the non-mitochondrial source, which plays a role in the pathogenesis of age-related diseases [91]. The main place of intracellular oxygen consumption is in mitochondria derived from the electron transport chain. This is the reason why mitochondria seem to be the main source of endogenous oxidants involved in aging [91–93]. These reactive species include different free radicals, such as superoxides, singlet oxygen, and hydroxyl radicals, and non-free radicals, such as hydrogen peroxide [93]. All these reactive oxygen-formed species can be eliminated through the action of antioxidant defensive mechanisms. When a higher concentration of reactive species to antioxidants exists, a state of oxidative stress is established. This condition has been observed as a sign of many chronic age-related disorders, such as different metabolic disorders, Parkinson's disease (PD), kidney disease, and Alzheimer's disease (AD) [93].

An increase in ROS production has been related to an increase in cell senescence, characterized by a decrease in cell proliferation [89]. Oxidative stress also promotes mitochondrial DNA mutation, leading to the incorporation of defective subunits in the electron transport chain, and, consequently, a decrease in the synthesis of ATP. This situation contributes to the accumulation of dysfunctional mitochondria, which has been considered as one of the main causes of aging [90,91,94].

Antioxidants are endogenous and exogenous substances that prevent or eliminate ROS and protect against oxidative damage. Endogenous antioxidants include enzymatic and non-enzymatic molecules and are distributed within cytoplasm and cell organelles. Exogenous antioxidants are mainly found in vegetables and fruits as phytochemicals [93]. Many plants often contain a considerable amount of antioxidants (e.g., vitamins, carotenoids, terpenoids, polyphenols, alkaloids, tannins, and saponins) that can be consumed, participating in the elimination of ROS in the human body. It has been suggested that the amalgamation of antioxidant and anti-inflammatory phenolic compounds found in plants is important in aging, because the factors that increase the resistance to this oxidative stress could exert beneficial effects against aging [95,96]. Interestingly, polyphenols are also useful in ameliorating the adverse effects of the aging process on the nervous system or brain due to the ability of these compounds to cross the blood-brain barrier [97]. The most beneficial effects come from flavonoids, specifically from anthocyanins. Anthocyanins, which are highly abundant in brightly colored fruits, such as berries and grapes, have been shown to have strong antioxidant/anti-inflammatory activities, besides being able to inhibit lipid peroxidation and the inflammatory mediators COX-1 and COX-2 [98]. Shukitt-Hale et al. [97] showed that a diet supplementation with vitamin E (500 IU/Kg) for 8 months in Fischer 344 rats had protective effects on alterations in cell signaling associated with aging. The treatment improved growth neuronal communication, stress signaling pathways, calcium buffering capacity, neuroprotective stress shock proteins, and plasticity. In an in vitro study, it has been observed that the incubation of erythrocytes with catechins (10^{-5} mol/L) from tea protected cells from oxidative stress induced by tert-butyl hydroperoxide (t-BHP) [99]. Catechins decreased the levels of malonyldialdehyde (MDA) and reduced the oxidation of sulfhydryl groups (-SH) and reduced glutathione (GSH). Resveratrol has been found to act as an anti-aging agent, mimicking the effects observed after caloric restriction or partial food deprivation [100], leading to improved exercise performance, insulin sensitivity and increasing lipid mobilization in adipose tissue [101]. It has

been observed that resveratrol has protective effects against cerebral ischemic injury when injected in gerbils (30 mg/kg body weight), indicating that resveratrol can cross the blood-brain barrier [102]. Hydroxytyrosol is a phenylethanoid, a type of phenolic mainly found in the olive tree and its leaves, with reported effects as a cardioprotective agent. The Mediterranean diet, which includes olive oil as a primary source of fat, is associated with a lower incidence of chronic diseases and increased longevity [103]. A recent study with peripheral blood mononuclear cells (PBMCs) and HL60 cells showed that hydroxytyrosol extracted from virgin olive oil significantly reduced the DNA damage at concentrations as low as 1 mM when co-incubated in a medium containing H_2O_2 (40 mM) [104].

3.2. Aging-Related Diseases

3.2.1. Cardiovascular Diseases

Cardiovascular diseases are the leading cause of death globally. A plethora of herbal products are used to manage and/or treat chronic cardiovascular conditions and related problems. Evidence suggests that myocardial cell damage may be due to toxic ROS generation, such as the generation of superoxide radicals, hydrogen peroxide and hydroxyl radicals [105]. Several studies have demonstrated that polyphenol consumption limits the incidence of coronary heart diseases [106]. Quercetin, an ample polyphenol in onions, has been shown to decrease coronary heart disease-associated mortality through inhibiting metalloproteinase (MMP)-1 expression and disrupting atherosclerotic plaques [52]. *Centella asiatica*, from the Apiaceae family, has been shown to prevent blood coagulation, alleviate oxidative stress, and be usable as a hypotensive [107]. Tea catechins have been shown to inhibit smooth muscle cell invasion and proliferation in the arterial wall, thereby slowing down atheromatous lesion formation. Tea polyphenols lower blood pressure via antioxidant or estrogen-like activity [52]. *Convallaria majalis*, from the Smilacaceae family, has cardenolide glycosides. The other compounds in this plant are convallasaponin A, free flavonoids, heterosides, and mineral salts. Convallotoxin is used as cardiotonic [108]. The consumption of red wine or non-alcoholic wine reduces bleeding time and platelet aggregation. Resveratrol, the wine polyphenol, prevents platelet aggregation via the preferential inhibition of COX-1 activity, which synthesizes thromboxane A2, an inducer of the platelet aggregation and vasoconstrictor [109]. *Fraxinus excelsior*, a member of the Oleaceae family, has two phenolic classes of compounds, mainly iridoids and secoiridoid glucosides. It is vasoprotective and venotonic and has anti-hypertensive effects [110]. *Digitalis purpurea* and *Digitalis lanata*, from the Scrophulariaceae family, have cardiac glycosides. Being cardiotonic, these plants increase heterosides, increasing cardiac contractility, decreasing excitability, conductivity, and rhythm, and also decreasing the oxygen requirement for cardiac work [111].

3.2.2. Cancer

Cancer development in humans is a complex process that is mediated by various endogenous and exogenous stimuli. It has been reported that oxidative DNA damage is responsible for cancer development, involving free radical-induced promotion and oncogene activation [112].

Polyphenols have been reported to decrease tumor growth in human cancer cell lines [113]. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol, and curcumin, have been reported to show protective effects in some models, despite their different mechanisms of action [114]. Apigenin, a flavone present in vegetables and in the Egyptian plant *Moringa peregrine*, demonstrates cytotoxic activities against the breast cancer (MCF 7) and colon cell lines (HCT 116), comparable to that of doxorubicin [115]. Curcumin (diferuloylmethane) is the major component of the popular Indian spice turmeric (*Curcuma longa*), which is a member of the ginger family. Its anti-cancer effects have been studied for colon and breast cancers, lung metastases, and brain tumors [116,117]. Cyanidin is a pigment extracted from red berries, such as grapes, blackberries, cranberries, raspberries, or apples, plums, red cabbage, and red onion. It possesses antioxidant and radical-scavenging effects, which may reduce the risk of cancer. It has

been reported that cyanidin-3-glucoside (C3G) may prevent or reduce ethanol-induced breast cancer metastasis [118]. Indole-3-carbinol (I3C) is found in *Brassica* vegetables, such as broccoli, cauliflower, and collard greens. Diindolylmethane (DIM) is a digestion derivative of I3C. I3C and DIM have demonstrated exceptional anti-cancer effects against hormone responsive cancers, like breast, prostate, and ovarian cancers [119]. EGCG is the most abundant catechin compound in green tea. Increasing evidence has shown that EGCG can be beneficial in treating brain, prostate, cervical, and bladder cancers [120–122]. Theaflavins, thearubigins, and polyphenols, which are present mainly in black tea, have also been shown to possess inhibitory effects against HCT 116 colon cancer cells and HT 460 lung cancer cells [123]. Genistein, an isoflavone that originates from a number of plants, such as lupine, fava beans, soy beans, kudzu, and psoralea, *Flemingia vestita*, and coffee, acts as an antioxidant, and it is also useful in treating leukemia [124].

Beside this, gingerol (gingers), kaempferol (tea, broccoli, and grapefruit), lycopene (tomato), phenethyl isothiocyanate (PEITC), sulforaphane (cruciferous vegetable), resveratrol (grapes), rosmarinic acid (rosemary), vitamin D from mushrooms, vitamin E from plant oil, *Aegle marmelos* (bael), *Vernonia anthelmintica* (kalijiri), *Tinospora cordifolia*, and *Phyllanthus acidus* (amla), have also been reported to have potential anti-cancer properties due to the presence of antioxidants, similar to phenolic compounds [125]. The anti-cancer agents vinblastine and vincristine, from *Catharanthus roseus* (from the Apocynaceae family), have revolutionized the use of plant material as a medical treatment. These were the first agents put into clinical use for cancer treatment. The isolation of paclitaxel (Taxol®) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (*Taxaceae*), was another milestone in the search for novel natural anti-cancer drugs [126].

3.2.3. Diabetes

Diabetes is a metabolic disorder that mainly occurs due to defects in insulin secretion, insulin action, or both [127]. It has been postulated that the etiology of diabetes complications involves oxidative stress [127]. Medicinal plants have been revealed to be a rich source of molecules with excellent hypoglycemic properties, like flavonoids, tannins, phenolics, and alkaloids [128]. Tannins improve pancreatic beta cell function and increase insulin secretion, whereas quercetin is an antioxidant that acts by removing oxygen radicals, precluding lipid peroxidation [129]. The modes of action of hypoglycemic plants include (i) increasing insulin secretion, (ii) increasing glucose absorption by muscle and fat tissues, (iii) preventing glucose absorption from the intestine, and (iv) preventing glucose production from liver cells [130].

3.2.4. Neurodegenerative Disorders

Neurodegenerative disorders result from the progressive loss of neuron structure and/or function. Since oxidative stress has been reported to contribute to the etiology of neurological diseases, like Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis, among others [131], compounds with antioxidant and anti-inflammatory activities have the potential to treat neurodegenerative diseases. A novel C-glucosylated xanthone, mangiferin, acquired from mango extract, shows medicinal effects related to redox potential [132]. The velvet bean extract effectively manages memory impairment in PD through reducing GSH, DPPH radicals, and ROS content [133]. Quercetin, kaempferol, isorhamnetin, bilobalide, and ginkgolide from *Ginkgo biloba* each possess antioxidant effects and have been reported to improve the mini-mental state of AD [134]. Ginsenosides from *Panax ginseng* protect dopaminergic neurons from oxidative stress through the promotion of neurotrophic factors [135,136]. Furthermore, curcumin activates the Nrf2 antioxidant system in animals with AD [137]. Studies have reported that green tea consumption reduces the risk of developing PD. EGCG has been shown to protect neurons by activating several signaling pathways, involving MAP kinases. The therapeutic role of catechins in PD is also due to their ability to chelate iron, a property that contributes to their antioxidant activity. Moreover, antioxidant function is also related to the induction of the expression of antioxidants and detoxifying enzymes, particularly in the brain [1].

4. The Evidence in Humans

4.1. Cardiovascular Risk

Fruit juices have been investigated to control lipid profiles, antioxidants, and inflammatory status. In cigarette smokers, *Morinda citrifolia* (noni) fruit juice has a significant antioxidant activity, improving serum lipid profiles, like cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), and homocysteine [138]. F105, a phytochemical formulation resulting from the combination of bergamot fruit extract (*Citrus bergamia*) with nine phytoextracts, acting synergistically as antioxidant and anti-inflammatory agents, has been revealed in vitro to have a marked antioxidant activity, and, in a clinical case report, a great ability to decrease lipid profiles [139]. In normal-weight and overweight volunteers, the intake of red-fleshed orange juice (red orange juice) [140] and polyphenol-rich chokeberry juice had similar effects, thanks to the antioxidant and reducing properties of citrus flavonoids, carotenoids, and lycopene, improving the risk factors for metabolic syndrome, including improvements in insulin resistance and blood pressure [141]. Also, the combined supplementation of grape pomace and omija fruit extracts [142], as well as *Sambucus ebulus* fruit infusion [143], improved obesity-related dyslipidemia, inflammation, and serum oxidative stress, however, without evident effects on patient body weight. Both body weight and lipid profile were, instead, improved by green tea (*Camelia sinensis*) intake [144], which also had a positive effect on DNA repair via HO-1 expression, which is a cytoprotective enzyme against pro-oxidant changes [145].

Red grape seed extract, which contains antioxidant oligomeric proanthocyanidins, has been revealed to increase serum paraoxonase (PON) activity. Paraoxonase is an enzyme that protects against lipid oxidation in patients with mild to moderate hyperlipidemia [146] and in hemodialysis patients [147]. The red wine extract of onion, in particular, suppressed both the total cholesterol and LDL cholesterol levels, and also modulated inflammatory markers, such as factor VII [148]. A quercetin-rich onion skin extract was able to reduce day-time and night-time systolic blood pressure in overweight-to-obese patients with either pre-hypertension or stage I hypertension [149]. Red wine extract and red wine extract of onion did not produce significant changes in body weight or body mass index in hypercholesterolemic patients, however, they displayed remarkable antioxidant effects, delaying LDL oxidation [148].

Dietary wolfberry extract has reduced oxidative stress in overweight and hypercholesterolemic patients through decreasing erythrocyte SOD activity, increasing CAT activity, and controlling inflammatory mRNAs expression. Likewise, the percentage of DNA damage in lymphocytes was significantly lower after 8-week wolfberry extract intake [150]. The beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation were demonstrated in healthy individuals, following a regulatory mechanism of plasma SOD, GSH, and CAT [151].

Indian kudzu (*Pueraria tuberosa*) has been shown to have a pronounced ability to decrease blood pressure, enhancing plasma fibrinolytic activity and serum total antioxidant status in patients with stage 1 hypertension [151]. Dietary supplementation with *Heracleum persicum* fruit, which is a well-known spice with beneficial effect against oxidative stress, was associated with reduced MDA production, and increased GSH and total antioxidant capacity (TAC) in subjects undergoing coronary angiography [152]. Also, MDA levels, resulting from postprandial oxidative stress, decreased after the intake of an antioxidant-rich concentrate of berries, called BPC-350, as tested in healthy volunteers who ate a turkey burger [153].

On the other hand, some studies reported controversial results regarding the beneficial effect of certain plant products on cardiovascular risk factors. Indeed, the intake for 6 weeks of whole blueberry powder increased natural killer cell counts and reduced arterial stiffness in sedentary individuals, without any effect on mass body composition, overall blood pressure, or plasma redox potential [154]. Oral supplementation with pomegranate extract had beneficial effects in reducing

systolic and diastolic blood pressure without an impact on cardiovascular risk, physical function, oxidative stress, or inflammation in hemodialysis patients [155]. Moreover, a *Palmaria palmata*-enriched bread has been shown to have negative effects in terms of preventing cardiovascular disorders. In a randomized placebo-controlled trial conducted in healthy adults, the bread stimulated inflammation, increasing serum triglycerides and altering thyroid function, although these changes appeared to have negligible influence, since they remained within the normal clinical range [156].

4.2. Diabetes Mellitus

Oxidative stress plays an important role in diabetes mellitus (DM) pathogenesis and its complications. A plethora of medicinal plants have increasingly been tested to achieve glycemic control, specifically via antioxidant mechanisms of action [128].

Green tea has been extensively investigated at a pre-clinical level, but just one clinical trial has focused on its anti-diabetic potential via a redox effect. Indeed, in type-2 DM patients, green tea reduced DNA damage and enhanced DNA repair through increasing plasma 8-oxoguanine glycosylase (hOGG1) activity and HO-1 protein levels, which are recognized protective factors against pro-oxidant changes [157].

Ginger (*Zingiber officinale*) is one functional food which contains biological compounds, including gingerol, shogaol, paradol, and zingerone, and its effect, as a 3-month supplementation, has been shown to improve glycemic indices, TAC, and paraoxonase-1 (PON-1) activity in type-2 DM patients [158]. A similar finding was reported for *Nigella sativa* [159], and, in healthy volunteers, *Grewia asiatica* fruit [160].

Conversely, the antioxidant effect of Korean red ginseng in postmenopausal women was not associated with improved fasting glucose and insulin levels and insulin resistance in a double-blind randomized controlled trial [161].

5. Plant Compounds and Longevity

Human longevity has dramatically increased during the last century thanks to the great health advances that have significantly reduced premature deaths. However, although the rate of aging of the population is high, life expectancy has not followed the same degree of improvement [162]. Aging is a multifactorial process that includes numerous mechanisms, such as the shortening of telomeres, systemic inflammation, oxidative stress, and a deficiency of cellular energy, mainly due to autophagy and mitochondrial dysfunction, causing cells to enter a state of senescence and cellular cycle arrest [163]. In fact, many of the molecular mechanisms underlying aging coincide with the same altered pathways responsible for diseases such as cancer, neurodegeneration, or cardiovascular disease [164].

Assessing the potential effects of plant compounds on longevity is complex, since the process requires the entire life cycle of the studied subjects to be followed, something which is difficult in the case of organisms with a high life expectancy, such as mammals. In the case of humans, various epidemiological studies have shown a direct relationship between the high consumption of plant products with a higher life expectancy and a lower prevalence of non-communicable diseases. In this sense, the Mediterranean diet has long been linked to healthy aging and greater longevity [165–168]. A study conducted in an area of Sardinia, Italy, where there is one of the highest concentrations of centenarians in the world, related this fact to an improvement in the quality of the diet associated with the nutrition transition, maintaining, however, a high consumption of fruits and vegetables and a moderate meat intake [169]. In addition, a recent meta-analysis of prospective cohort studies has revealed significant inverse associations between the low consumption of fruits and/or vegetables with all-cause mortality [170]. Another interesting study analyzed the relation between food habits and all-cause mortality in the old Chinese population (≥80 years) [171]. Similarly to the Mediterranean diet, the consumption of fruits and vegetables was inversely associated with higher mortality risk. Another fascinating case of study is the long life of the Hunza people, who live in a remote and pristine area of the Himalayas, north of Pakistan [172,173]. This population lives in peace, happy and without stresses,

and consumes a moderate quantity of fruits and vegetables. They do not consume any processed foods, which could be related to low levels of oxidative stress and oxidative-related disorders. Altogether, this could contribute to the good health and high life expectancy of this group of people.

Most studies on the ability of different plant compounds to extend lifespan have been developed in a nematodal model organism for aging processes, specifically, using the roundworm *Caenorhabditis elegans*. In an interesting approach, the effects of the quassinoid (degraded triterpene lactone) glaucarubinone, which is present in several species of the plant family *Simaroubaceae*, were investigated [174]. Treatment with glaucarubinone significantly extended *C. elegans* lifespan in a process mediated by induction of the mitochondrial metabolism and the reduction of fat accumulation. Concretely, glaucarubinone has been shown to increase oxygen consumption, as measured with a Clark-type electrode. The authors suggest that the increased oxygen consumption also increases the production of mitochondrial ROS, which can act as cellular messengers, inducing endogenous antioxidant defense and longevity. The effects of 4-hydroxy-E-globularinin (4-HEG), an iridoid present in *Premna integrifolia*, usually used in the Indian medicine, were assayed in *C. elegans* [175]. 4-HEG treatment increased longevity in the worm and improved the resistance to paraquat-induced oxidative stress. The mechanism of action implies a reduction in the total production of ROS, quantified with dichlorodihydrofluorescin diacetate (H2DCF-DA), showing a lower accumulation of lipids and an activation of stress-inducible genes derived from an upregulation of the transcription factor DAF-16 and the downstream genes *hsp-16.2* and *sod-3*. Mutants for DAF-16 and for the cytochrome b subunit of mitochondrial complex II (*mev-1* strain), which lead to an overproduction of superoxide anions, did not respond to 4-HEG supplementation, suggesting that 4-HEG reduces oxidative stress but also needs an endogenous detoxification pathway in order to reduce it. The longevity-promoting activity of another plant used in Indian medicine, namely, *Withania somnifera* root extract, was also investigated in *C. elegans* [176]. The extract, which is considered as a traditional healthy long-life supplement did not exert significant effects on wild-type worms. Another interesting investigation analyzed the effects of *Viscum album coloratum* (Korean mistletoe) extract on *C. elegans* and *Drosophila melanogaster* lifespan [177]. The treatment with the extract significantly extended longevity in both species, without altering feeding or reproduction. Korean mistletoe extract, when administered together with full diet, increased the expression of sirtuin 2 (SIRT2), a target gene of dietary restriction, suggesting an effect as a dietary restriction mimetic. *Rosmarinus officinalis* ethanolic extract was also investigated as longevity agent in on *C. elegans* [178]. The treatment with *R. officinalis* extended *C. elegans* longevity in an insulin/insulin growth factor (IGF) signaling pathway-dependent manner, leading to the activation of a conserved phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) cascade, which, in turn, caused the phosphorylation of the DAF-16/FOXO, heat shock factor (HSF)-1, and skinhead 1 (SKN-1/Nrf2) transcription factors. The extract also increased the resistance against oxidative and thermal stress by reducing the production of ROS and protecting against oxidative damage, suggesting that *R. officinalis* modulates signaling pathways essential for defensive processes. Blueberry extract (*Vaccinium* spp.) increased the lifespan of *C. elegans* in a dose-dependent manner, reduced lipofuscin accumulation and ROS production, increased the activity of SOD, and diminished the levels of malondialdehyde (MDA). In addition, the extract increased stress tolerance by inducing the expression of genes related to antioxidant defense, including *cat-1*, *sod-3*, *daf-16*, *mev-1*, *skn-1*, *mek-1*, and *nhr-8* [179]. The use of RNAi to inhibit the transcription factor DAF-16 reduced lifespan and reduced the expression of the *sod-3*. In another study, the isoprenylated aurone damaurone D was tested for its longevity-promoting effect in *C. elegans* [180]. Similar to other studies, the compound increased the lifespan of wild-type nematodes, reduced ROS production, increased CAT and SOD activity, increased *sod-3* gene expression, and also improved stress tolerance under oxidative, thermal, and osmotic stress via the upregulation of *hsp-16.2* and *sod-3*. The mechanism of action seems to involve genes related to the insulin/IGF signaling pathway, *daf-2*, *age-1*, and *daf-16*, evidenced by gene-specific mutant studies. In addition, damaurone D supplementation augmented the translocation of *daf-16* to the nucleus, inducing the expression of genes involved in extending lifespan and protecting from oxidative damage. *Betula utilis* ethanolic extract, a medicinal plant from the Himalayan area,

increased the lifespan of the worms under normal conditions, but also under oxidative and thermal stress, reducing ROS production and lipofuscin accumulation in a process mediated by the insulin/IGF signaling pathway and also by *sir-2.1* gene expression [181]. *B. utilis* extract also induced the nuclear translocation of daf-16 and the subsequent gene expression of *sod-3* and *gst-4*. In addition, the extract exerted neuroprotective effects, reducing amyloid-β-induced paralysis and reducing α-synuclien aggregation in a CL4176 transgenic strain.

Other studies have analyzed the longevity-promoting effects of some plants using *Drosophila melanogaster* (common fruit fly) in an animal model. Piegholdt et al. [182] investigated the effects of the isoflavone prunetin on lifespan in *D. melanogaster*. A diet supplemented with prunetin was shown to extend life expectancy by three days in males and induce the expression of the longevity gene sirtuin 1, which is associated with AMP-activated protein kinase (AMPK) activation. The authors suggest that prunetin, as an isoflavone, may feminize male flies, thus affecting their health and lifespan. Moreover, *Rel* gene expression (*Rel* is a member of the NF-κB family), was significantly upregulated in male fly midguts after prunetin treatment with respect to the controls. The authors suggested that prunetine may improve resistance against microbiological stressors derived from food, promoting health and longevity. In another study, the administration of a methanol extract from the fruits of *Platanus orientalis*, which are rich in polyphenols, reduced ROS production, recovered proteasome activity associated to aging, and increased median and maximum longevity in *D. melanogaster* [183]. The administration of purified tiliroside, a major glycosidic flavonoid from *Platanus orientalis*, also exerted similar results to those observed with the methanolic extract, also enhancing lysosomal-cathepsin activity. Tiliroside treatment reduced the production of ROS and increased the expression of protective genes such as *hsp70* and *trxr1*, which are derived from the activation of antioxidant response elements. The authors indicate that the activation of the AMPK pathway could explain the upregulation of autophagy and lysosomal-cathepsins. Finally, tiliroside was also capable to delay the progression of cellular senescence in human fibroblasts (specifically, the IMR90 cell line). *Ilex paraguariensis*, known as yerba mate, significantly extended the lifespan of flies, modulating the expression of antioxidant enzymes and increasing tolerance to stressful situations [184]. Two interesting investigations analyzed the anti-aging effects of plant extracts on neurodegenerative disease models. In the first study, grape skin extract improved flight muscle function, extending lifespan in a *D. melanogaster* model of PD [185]. Among the mechanisms of action were the activation of autophagy, the preservation of mitochondrial function, and the reduction of aberrant mitochondrial aggregates. Autophagy activation was evidenced by a reduction in the autophagy receptor p62 and the conversion of LC3-I to LC3-II. In the second study, an extract of *Rhodiola rosea* was tested in a Huntington's disease model of *D. melanogaster* [186]. The extract improved locomotion and lifespan. The mechanism of action here is associated with the activation of autophagy, in part by the inhibition of the mTOR pathway, which would counteract the negative effects of Huntington mutant proteins. The flavonoid 4,4′-dimethoxychalcone, found in the plant *Angelica keiskei koidzumi*, with longevity- and health-promoting effects, which is traditionally used in Asian folk medicine, was also reported to prolong the median lifespan of *C. elegans* and *D. melanogaster* [187]. Moreover, the flavonoid prevented senescence in highly confluent human cells (HeLa cervical carcinoma, U2OS osteosarcoma, and H4 neuroblastoma cells) through the induction of a pro-autophagic response, increasing the formation of autophagosomes and autophagic flux. The mechanism of action of 4,4′-dimethoxychalcone involves specific GATA transcription factors, specifically, the GATA transcription factor Gln3. The flavonoid can interfere with the autophagy-repressive activity of Gln3, resulting in increased autophagic flux and cytoprotection in a process independent of TORC1 activity. On the contrary, another study reported no beneficial effects of garlic and onion or their main bioactive compounds diallyl disulphide and dipropyl disulphide on *D. melanogaster* lifespan, although, they exerted a protective role against H_2O_2-induced damage [188].

Some studies have analyzed the effects of some plants in mammalian models of accelerated senescence. In one approach, the longevity-promoting effects of the polyphenol oligonol were investigated in a mouse model of senescence acceleration (SAMP8). The effects were characterized

by increased oxidative stress and a neuronal deficit [189]. Oligonol treatment increased the mean life span, improved locomotive activity, and ameliorated the extent of inflammation around the eyes. However, in this study, the possible pathways involved in the extension of life expectancy were not investigated. Another study using the same SAMP8 mice model showed that resveratrol extends mean life expectancy and maximal life span, also reducing cognitive impairment [190]. The mechanism here was associated with an activation of the AMPK pathway and its downstream target, SIRT1, which protects against neurodegeneration. In addition, a reduction in the acetylated forms of p53, which are the main substrates of deacetylases (such as SIRT1), implicated in replicative senescence, was also observed.

In another work, the beneficial effects of a phenolic extract from *Portulaca oleracea* were investigated in a senescent mice model, induced by means of D-galactose/$NaNO_2$ treatment [191]. The phenolic extract reversed the reduced lifespan induced by D-galactose/$NaNO_2$ and improved spatial memory and learning ability. The underlying mechanism of survival and cognitive function seems have no relationship with acetylcholinesterase (AChE), since the extract did not affect brain AChE activity. In addition, *P. oleracea* ameliorated oxidative stress by increasing catalase activity and reducing MDA levels, reducing hippocampal morphological damage. Dutta et al. [192] studied the longevity-promoting effects of *Withania somnifera* extract in a $SOD1^{G93A}$ mouse model of amyotrophic lateral sclerosis. *W. somnifera* treatment expanded mice longevity, enhanced motor performance, and augmented the quantity of motor neurons in the lumbar spinal cord. The extract exerted neuroprotective effects, delaying disease onset in part by promoting autophagy, as evidenced by increased p62 positive autophagic granules and LC3-II. Also, the protective effects of the extract could be related to an increase in the levels of Hsp-70, Hsp-60, and Hsp-27, derived from the activation of heat shock factor 1 (HSF-1). In obese mice, which are characterized by a reduced median lifespan, the longevity-promoting effects of a commercial polyphenol-rich extract were analyzed [193]. Although the treatment did not reverse obesity, it increased the life expectancy of the mice, improved endotoxemia and reduced the degree of inflammation and accumulation in the adipose tissue of cholesterol and cholesterol oxides.

Finally, the regulation of the length and function of telomeres is an important factor in maintaining health and longevity, and, thus, the epigenetic effects of some bioactive compounds can be an interesting approach to maintain their activity. In this sense, the water extract of turmeric (*Curcuma longa*) was reported to increase the expression of telomerase reverse transcriptase, which participates in the reduction of replicative senescence and extends the lifespan of many cell types, including RAW264.7 macrophages [194]. In another study, the effects of *Euterpe oleracea* juice were studied. The juice was administered over four days to mice treated with lipopolysaccharide to induce a depressive-like behavior [195]. The treatment was capable of reducing despair-like and anhedonic behaviors and showed alterations in electromyographic analysis. In addition, *E. oleracea* prevented lipid peroxidation and increased the expression of telomerase reverse transcriptase in the hippocampus, striatum, and prefrontal cortex, suggesting a longevity-promoting action.

6. Concluding Remarks and Upcoming Perspectives

Overall, although antioxidants are not pharmaceuticals, they may markedly contribute to ameliorating aging-related diseases and even promote healthy longevity. Antioxidants, when consumed as a part of the daily diet and in balanced amounts, may supply a wide range of phytochemicals, which may constitute a promising strategy in longevity promotion and the treatment of aging-related diseases such as cardiovascular and neurodegenerative disorders and diabetes.

Nevertheless, and although much has been discovered, some pathological mechanisms remain unclear, and even several detrimental effects of medicinal plants must be studied further. For example, it should be considered that the effect of plant antioxidants on several enzymes, such as XOR, can have secondary effects on other drugs that are metabolized by the same enzyme. Anyway, it is broadly recognized that plant-derived bioactive molecules possess an extraordinary therapeutic relevance, both in disease prevention and treatment. So, further investigations are needed to deepen knowledge

on many other macro- and/or micro-molecular aspects, which are still poorly explored. Moreover, other pharmacokinetic and pharmacodynamic aspects need to be studied in order to provide an increased variety of functional foods, nutraceuticals, and even new bioactive molecules for new drug formulation in the future.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3417/10/3/947/s1.

Author Contributions: All authors contributed equally to this work. L.P., M.I., M.M., N.M., L.M.E., B.S., and J.S.-R. critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: N. Martins thank to the Portuguese Foundation for Science and Technology (FCT—Portugal) for Strategic project ref. UID/BIM/04293/2013 and "NORTE2020—Programa Operacional Regional do Norte" (NORTE-01-0145-FEDER-000012). A. Sureda was supported by Instituto de Salud Carlos III, Grant Number: CIBEROBN CB12/03/30038. Also, this work was supported by CONICYT PIA/APOYO CCTE AFB170007.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev.* **2009**, *2*, 270–278. [CrossRef]
2. Dai, J.; Mumper, R.J. Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. *Molecules* **2010**, *15*, 7313–7352. [CrossRef]
3. Sharifi-Rad, J.; Sharifi-Rad, M.; Salehi, B.; Iriti, M.; Roointan, A.; Mnayer, D.; Soltani-Nejad, A.; Afshari, A. In vitro and in vivo assessment of free radical scavenging and antioxidant activities of *Veronica persica* Poir. *Cell. Mol. Biol.* **2018**, *64*, 57–64. [CrossRef]
4. Halliwell, B. Reactive Species and Antioxidants. Redox Biology Is a Fundamental Theme of Aerobic Life. *Plant Physiol.* **2006**, *141*, 312–322. [CrossRef] [PubMed]
5. Foyer, C.H.; Noctor, G. Redox Homeostasis and Antioxidant Signaling: A Metabolic Interface between Stress Perception and Physiological Responses. *Plant Cell* **2005**, *17*, 1866–1875. [CrossRef] [PubMed]
6. Salehi, B.; Martorell, M.; Arbiser, J.L.; Sureda, A.; Martins, N.; Maurya, P.K.; Sharifi-Rad, M.; Kumar, P.; Sharifi-Rad, J. Antioxidants: Positive or Negative Actors? *Biomolecules* **2018**, *8*, 124. [CrossRef] [PubMed]
7. Haghi Aminjan, H.; Abtahi, S.R.; Hazrati, E.; Chamanara, M.; Jalili, M.; Paknejad, B. Targeting of oxidative stress and inflammation through ROS/NF-kappaB pathway in phosphine-induced hepatotoxicity mitigation. *Life Sci.* **2019**, *232*, 116607. [CrossRef] [PubMed]
8. Kasote, D.M.; Katyare, S.S.; Hegde, M.V.; Bae, H. Significance of antioxidant potential of plants and its relevance to therapeutic applications. *Int. J. Biol. Sci.* **2015**, *11*, 982–991. [CrossRef] [PubMed]
9. Williams, R.J.; Spencer, J.P.E.; Rice-Evans, C. Flavonoids: Antioxidants or signalling molecules? *Free Radic. Biol. Med.* **2004**, *36*, 838–849. [CrossRef] [PubMed]
10. Duthie, G.G.; Duthie, S.J.; Kyle, J.A.M. Plant polyphenols in cancer and heart disease: Implications as nutritional antioxidants. *Nutr. Res. Rev.* **2000**, *13*, 79. [CrossRef]
11. Myburgh, K.H. Polyphenol supplementation: Benefits for exercise performance or oxidative stress? *Sport Med.* **2014**, *44*, 57–70. [CrossRef] [PubMed]
12. Blokhina, O.; Virolainen, E.; Fagerstedt, K.V.; Dumas, F.; Alscher, R.G.; Erturk, N.; Heath, L.S.; Couée, I.; Sulmon, C.; Gouesbet, G.; et al. Antioxidants, oxidative damage and oxygen deprivation stress: A review. *Ann. Bot.* **2002**, *91*, 174–194. [CrossRef] [PubMed]
13. Halliwell, B. Flavonoids: A Re-Run of the carotenoids story? *Novartis Found Symp.* **2007**, *282*, 93–104. [PubMed]
14. Nijveldt, R.J.; Van Nood, E.; Van Hoorn, D.E.C.; Boelens, P.G.; Van Norren, K.; Van Leeuwen, P.A.M. Flavonoids: A review of probable mechanisms of action and potential applications. *Am. J. Clin. Nutr.* **2001**, *74*, 418–425. [CrossRef]
15. Serrano, J.; Puupponen-Pimiä, R.; Dauer, A.; Aura, A.M.; Saura-Calixto, F. Tannins: Current knowledge of food sources, intake, bioavailability and biological effects. *Mol. Nutr. Food Res.* **2009**, *53*, 310–329. [CrossRef]
16. Gill, S.S.; Tuteja, N. Reactive oxygen species and antioxidant machinery in abiotic stress tolerance in crop plants. *Plant Physiol. Biochem.* **2010**, *48*, 909–930. [CrossRef]

17. Jajic, I.; Sarna, T.; Strzalka, K. Senescence, Stress, and Reactive Oxygen Species. *Plants* **2015**, *4*, 393–411. [CrossRef]
18. Karlsen, A.; Retterstøl, L.; Laake, P.; Paur, I.; Kjølsrud-Bøhn, S.; Sandvik, L.; Blomhoff, R. Anthocyanins Inhibit Nuclear Factor-κB Activation in Monocytes and Reduce Plasma Concentrations of Pro-Inflammatory Mediators in Healthy Adults. *J. Nutr.* **2007**, *137*, 1951–1954. [CrossRef]
19. Wang, S.Y.; Jiao, H. Scavenging capacity of berry crops on superoxide radicals, hydrogen peroxide, hydroxyl radical's, and singlet oxygen. *J. Agric. Food Chem.* **2000**, *48*, 5677–5684. [CrossRef]
20. Leoncini, E.; Nedovic, D.; Panic, N.; Pastorino, R.; Edefonti, V.; Boccia, S. Carotenoid intake from natural sources and head and neck cancer: A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol. Biomarkers Prev.* **2015**, *24*, 1003–1011. [CrossRef]
21. Takeda, A.; Nyssen, O.P.; Syed, A.; Jansen, E.; Bueno-De-Mesquita, B.; Gallo, V. Vitamin A and carotenoids and the risk of parkinson's disease: A systematic review and meta-analysis. *Neuroepidemiology* **2014**, *42*, 25–38. [CrossRef]
22. Soares, N. da C.P.; Teodoro, A.J.; Lotsch, P.F.; Granjeiro, J.M.; Borojevic, R. Anticancer properties of carotenoids in prostate cancer. A review. *Histol. Histopathol.* **2015**, *30*, 1143–1154.
23. Chajès, V.; Romieu, I. Nutrition and breast cancer. *Maturitas* **2014**, *77*, 7–11. [CrossRef] [PubMed]
24. Battelli, M.G.; Polito, L.; Bortolotti, M.; Bolognesi, A. Xanthine oxidoreductase-derived reactive species: Physiological and pathological effects. *Oxid. Med. Cell. Longev.* **2016**, 3527579. [CrossRef]
25. Battelli, M.G.; Polito, L.; Bortolotti, M.; Bolognesi, A. Xanthine oxidoreductase in cancer: More than a differentiation marker. *Cancer Med.* **2016**, *5*, 546–557. [CrossRef]
26. Battelli, M.G.; Bolognesi, A.; Polito, L. Pathophysiology of circulating xanthine oxidoreductase: New emerging roles for a multi-tasking enzyme. *Biochim. Biophys. Acta Mol. Basis Dis.* **2014**, *1842*, 1502–1517. [CrossRef]
27. Gutteridge, J.C.; Halliwell, B. Free Radicals and Antioxidants in the Year 2000: A Historical Look to the Future. *Ann. N. Y. Acad. Sci.* **2006**, *899*, 136–147. [CrossRef]
28. McGregor, G.P.; Biesalski, H.K. Rationale and impact of vitamin C in clinical nutrition. *Curr. Opin. Clin. Nutr. Metab. Care* **2006**, *9*, 697–703. [CrossRef]
29. Halliwell, B. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? *Arch. Biochem. Biophys.* **2008**, *476*, 107–112. [CrossRef]
30. Heim, K.E.; Tagliaferro, A.R.; Bobilya, D.J. Flavonoid antioxidants: Chemistry, metabolism and structure-activity relationships. *J. Nutr. Biochem.* **2002**, *13*, 572–584. [CrossRef]
31. Bors, W.; Heller, W.; Michel, C.; Saran, M. Radical chemistry of flavonoid antioxidants. In *Antioxidants in Therapy and Preventative Medicine*; Springer: Berlin/Heidelberg, Germany, 1990; pp. 165–170, ISBN 978-1-4684-5732-2.
32. Bors, W.; Michel, C. Antioxidant capacity of flavanols and gallate esters: Pulse radiolysis studies. *Free Radic. Biol. Med.* **1999**, *27*, 1413–1426. [CrossRef]
33. Fu, L.; Xu, B.T.; Xu, X.R.; Gan, R.Y.; Zhang, Y.; Xia, E.Q.; Li, H. Bin Antioxidant capacities and total phenolic contents of 62 fruits. *Food Chem.* **2011**, *129*, 345–350. [CrossRef] [PubMed]
34. Gao, X.; Ohlander, M.; Jeppsson, N.; Björk, L.; Trajkovski, V. Changes in antioxidant effects and their relationship to phytonutrients in fruits of sea buckthorn (Hippophae rhamnoides L.) during maturation. *J. Agric. Food Chem.* **2000**, *48*, 1485–1490. [CrossRef] [PubMed]
35. Londhe, J.S.; Devasagayam, T.P.A.; Foo, L.Y.; Ghaskadbi, S.S. Radioprotective Properties of Polyphenols from Phyllanthus amarus Linn. *J. Radiat. Res.* **2009**, *50*, 303–309. [CrossRef] [PubMed]
36. Moharram, F.A.; Marzouk, M.S.A.; Ibrahim, M.T.; Mabry, T.J. Antioxidant galloylated flavonol glycosides from Calliandra haematocephala. *Nat. Prod. Res.* **2006**, *20*, 927–934. [CrossRef] [PubMed]
37. Procházková, D.; Boušová, I.; Wilhelmová, N. Antioxidant and prooxidant properties of flavonoids. *Fitoterapia* **2011**, *82*, 513–523. [CrossRef]
38. Trouillas, P.; Marsal, P.; Siri, D.; Lazzaroni, R.; Duroux, J.L. A DFT study of the reactivity of OH groups in quercetin and taxifolin antioxidants: The specificity of the 3-OH site. *Food Chem.* **2006**, *97*, 679–688. [CrossRef]
39. Bubols, G.B.; Vianna, D. da R.; Medina-Remon, A.; von Poser, G.; Lamuela-Raventos, R.M.; Eifler-Lima, V.L.; Garcia, S.C. The Antioxidant Activity of Coumarins and Flavonoids. *Mini-Rev. Med. Chem.* **2013**, *13*, 318–334.

40. Amic, D.; Davidovic-Amic, D.; Beslo, D.; Rastija, V.; Lucic, B.; Trinajstic, N. SAR and QSAR of the Antioxidant Activity of Flavonoids. *Curr. Med. Chem.* **2007**, *14*, 827–845. [CrossRef]
41. Moalin, M.; Van Strijdonck, G.P.F.; Beckers, M.; Hagemen, G.J.; Borm, P.J.; Bast, A.; Haenen, G.R.M.M. A planar conformation and the hydroxyl groups in the B and C rings play a pivotal role in the antioxidant capacity of quercetin and quercetin derivatives. *Molecules* **2011**, *16*, 9636–9650. [CrossRef]
42. Stepanić, V.; Trošelj, K.G.; Lučić, B.; Marković, Z.; Amić, D. Bond dissociation free energy as a general parameter for flavonoid radical scavenging activity. *Food Chem.* **2013**, *141*, 1562–1570. [CrossRef] [PubMed]
43. Lu, A.L.; Li, X.; Gu, Y.; Wright, P.M.; Chang, D.Y. Repair of oxidative DNA damage: Mechanisms and functions. *Cell Biochem. Biophys.* **2001**, *35*, 141–170. [CrossRef]
44. Rai, P.; Wemmer, D.E.; Linn, S. Preferential binding and structural distortion by Fe2+at RGGG-containing DNA sequences correlates with enhanced oxidative cleavage at such sequences. *Nucleic Acids Res.* **2005**, *33*, 497–510. [CrossRef] [PubMed]
45. Pietta, P.G. Flavonoids as antioxidants. *J. Nat. Prod.* **2000**, *63*, 1035–1042. [CrossRef]
46. Perron, N.R.; Brumaghim, J.L. A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. *Cell Biochem. Biophys.* **2009**, *53*, 75–100. [CrossRef]
47. Cos, P.; Ying, L.; Calomme, M.; Hu, J.P.; Cimanga, K.; Van Poel, B.; Pieters, L.; Vlietinck, A.J.; Vanden Berghe, D. Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. *J. Nat. Prod.* **1998**, *61*, 71–76. [CrossRef]
48. Lin, C.M.; Chen, C.S.; Chen, C.T.; Liang, Y.C.; Lin, J.K. Molecular modeling of flavonoids that inhibits xanthine oxidase. *Biochem. Biophys. Res. Commun.* **2002**, *294*, 167–172. [CrossRef]
49. Van Hoorn, D.E.C.; Nijveldt, R.J.; Van Leeuwen, P.A.M.; Hofman, Z.; M'Rabet, L.; De Bont, D.B.A.; Van Norren, K. Accurate prediction of xanthine oxidase inhibition based on the structure of flavonoids. *Eur. J. Pharmacol.* **2002**, *451*, 111–118. [CrossRef]
50. Ricciotti, E.; Fitzgerald, G.A. Prostaglandins and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 986–1000. [CrossRef]
51. O'Leary, K.A.; De Pascual-Tereasa, S.; Needs, P.W.; Bao, Y.P.; O'Brien, N.M.; Williamson, G. Effect of flavonoids and Vitamin E on cyclooxygenase-2 (COX-2) transcription. *Mutat. Res. Fundam. Mol. Mech. Mutagen.* **2004**, *551*, 245–254. [CrossRef]
52. García-Lafuente, A.; Guillamón, E.; Villares, A.; Rostagno, M.A.; Martínez, J.A. Flavonoids as anti-inflammatory agents: Implications in cancer and cardiovascular disease. *Inflamm. Res.* **2009**, *58*, 537–552. [CrossRef] [PubMed]
53. da Silva, E.L.; Tsushida, T.; Terao, J. Inhibition of mammalian 15-lipoxygenase-dependent lipid peroxidation in low-density lipoprotein by quercetin and quercetin monoglucosides. *Arch. Biochem. Biophys.* **1998**, *349*, 313–320. [CrossRef] [PubMed]
54. Sadik, C.D.; Sies, H.; Schewe, T. Inhibition of 15-lipoxygenases by flavonoids: Structure-activity relations and mode of action. *Biochem. Pharmacol.* **2003**, *65*, 773–781. [CrossRef]
55. Batteli, M.G. Xanthine Oxidoreductase in Drug Metabolism: Beyond a Role as a Detoxifying Enzyme. *Curr. Med. Chem.* **2016**, *23*, 4027–4036. [CrossRef]
56. Tanigawa, S.; Fujii, M.; Hou, D.X. Action of Nrf2 and Keap1 in ARE-mediated NQO1 expression by quercetin. *Free Radic. Biol. Med.* **2007**, *42*, 1690–1703. [CrossRef]
57. Boesch-Saadatmandi, C.; Loboda, A.; Wagner, A.E.; Stachurska, A.; Jozkowicz, A.; Dulak, J.; Döring, F.; Wolffram, S.; Rimbach, G. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: Role of miR-155. *J. Nutr. Biochem.* **2011**, *22*, 293–299. [CrossRef]
58. Miyamoto, N.; Izumi, H.; Miyamoto, R.; Bin, H.; Kondo, H.; Tawara, A.; Sasaguri, Y.; Kohno, K. Transcriptional regulation of activating transcription factor 4 under oxidative stress in retinal pigment epithelial ARPE-19/HPV-16 cells. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 1226–1234. [CrossRef]
59. Saw, C.L.L.; Guo, Y.; Yang, A.Y.; Paredes-Gonzalez, X.; Ramirez, C.; Pung, D.; Kong, A.N.T. The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: Involvement of the Nrf2-ARE signaling pathway. *Food Chem. Toxicol.* **2014**, *72*, 303–311. [CrossRef]
60. Lee-Hilz, Y.Y.; Boerboom, A.M.J.F.; Westphal, A.H.; Van Berkel, W.J.H.; Aarts, J.M.M.J.G.; Rietjens, I.M.C.M. Pro-oxidant activity of flavonoids induces EpRE-mediated gene expression. *Chem. Res. Toxicol.* **2006**, *19*, 1499–1505. [CrossRef]

61. Ahmad, M.S.; Fazal, F.; Rahman, A.; Hadi, S.M.; Parish, J.H. Activities of flavonoids for the cleavage of DNA in the presence of cu(II): Correlation with generation of active oxygen species. *Carcinogenesis* **1992**, *13*, 605–608. [CrossRef]
62. Cherubini, A.; Ruggiero, C.; Polidori, M.C.; Mecocci, P. Potential markers of oxidative stress in stroke. *Free Radic. Biol. Med.* **2005**, *39*, 841–852. [CrossRef] [PubMed]
63. Cao, G.; Sofic, E.; Prior, R.L. Antioxidant and prooxidant behavior of flavonoids: Structure-activity relationships. *Free Radic. Biol. Med.* **1997**, *22*, 749–760. [CrossRef]
64. Flora, S.J.S. Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. *Oxid. Med. Cell. Longev.* **2009**, *2*, 191–206. [CrossRef] [PubMed]
65. Lambert, J.D.; Elias, R.J. The antioxidant and pro-oxidant activities of green tea polyphenols: A role in cancer prevention. *Arch. Biochem. Biophys.* **2010**, *501*, 65–72. [CrossRef]
66. Sugihara, N.; Arakawa, T.; Ohnishi, M.; Furuno, K. Anti- and pro-oxidative effects of flavonoids on metal-induced lipid hydroperoxide-dependent lipid peroxidation in cultured hepatocytes loaded with α-linolenic acid. *Free Radic. Biol. Med.* **1999**, *27*, 1313–1323. [CrossRef]
67. Yordi, E.G.; Pérez, E.M.; Matos, M.J.; Villares, E.U. Antioxidant and Pro-Oxidant Effects of Polyphenolic Compounds and Structure-Activity Relationship Evidence. In *Nutrition, Well-Being and Health*; IntechOpen Limited: London, UK, 2012; ISBN 978-953-51-0125-3.
68. Azmi, A.S.; Sarkar, F.H.; Hadi, S. Pro-oxidant activity of dietary chemopreventive agents: An under-appreciated anti-cancer property. *F1000Research* **2013**, *2*, 135. [CrossRef]
69. Arif, H.; Sohail, A.; Farhan, M.; Rehman, A.A.; Ahmad, A.; Hadi, S.M. Flavonoids-induced redox cycling of copper ions leads to generation of reactive oxygen species: A potential role in cancer chemoprevention. *Int. J. Biol. Macromol.* **2018**, *106*, 569–578. [CrossRef]
70. Surh, Y.J. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer* **2003**, *3*, 768–780. [CrossRef]
71. Surh, Y.J.; Kundu, J.K.; Na, H.K. Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. *Planta Med.* **2008**, *74*, 1526–1539. [CrossRef]
72. Akagawa, M.; Shigemitsu, T.; Suyama, K. Production of Hydrogen Peroxide by Polyphenols and Polyphenol-rich Beverages under Quasi -physiological Conditions. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 2632–2640. [CrossRef]
73. Chai, P.C.; Long, L.H.; Halliwell, B. Contribution of hydrogen peroxide to the cytotoxicity of green tea and red wines. *Biochem. Biophys. Res. Commun.* **2003**, *304*, 650–654. [CrossRef]
74. Kachadourian, R.; Day, B.J. Flavonoid-induced glutathione depletion: Potential implications for cancer treatment. *Free Radic. Biol. Med.* **2006**, *41*, 65–76. [CrossRef] [PubMed]
75. Fuentes, F.; Paredes-Gonzalez, X.; Kong, A.N.T. Dietary Glucosinolates Sulforaphane, Phenethyl Isothiocyanate, Indole-3-Carbinol/3,3′-Diindolylmethane: Antioxidative Stress/Inflammation, Nrf2, Epigenetics/ Epigenomics and In Vivo Cancer Chemopreventive Efficacy. *Curr. Pharmacol. Rep.* **2015**, *1*, 179–196. [CrossRef]
76. Yang, L.; Palliyaguru, D.L.; Kensler, T.W. Frugal chemoprevention: Targeting Nrf2 with foods rich in sulforaphane. *Semin. Oncol.* **2016**, *43*, 146–153. [CrossRef] [PubMed]
77. Ishii, T.; Ishikawa, M.; Miyoshi, N.; Yasunaga, M.; Akagawa, M.; Uchida, K.; Nakamura, Y. Catechol type polyphenol is a potential modifier of protein sulfhydryls: Development and application of a new probe for understanding the dietary polyphenol actions. *Chem. Res. Toxicol.* **2009**, *22*, 1689–1698. [CrossRef] [PubMed]
78. Na, H.K.; Surh, Y.J. Modulation of Nrf2-mediated antioxidant and detoxifying enzyme induction by the green tea polyphenol EGCG. *Food Chem. Toxicol.* **2008**, *46*, 1271–1278. [CrossRef]
79. Copple, I.M.; Shelton, L.M.; Walsh, J.; Kratschmar, D.V.; Lister, A.; Odermatt, A.; Goldring, C.E.; Dinkova-Kostova, A.T.; Honda, T.; Park, B.K. Chemical tuning enhances both potency toward Nrf2 and in vitro therapeutic index of triterpenoids. *Toxicol. Sci.* **2014**, *140*, 462–469. [CrossRef]
80. Sirota, R.; Gibson, D.; Kohen, R. The role of the catecholic and the electrophilic moieties of caffeic acid in Nrf2/Keap1 pathway activation in ovarian carcinoma cell lines. *Redox Biol.* **2015**, *4*, 48–59. [CrossRef]
81. Wu, R.P.; Hayashi, T.; Cottam, H.B.; Jin, G.; Yao, S.; Wu, C.C.N.; Rosenbach, M.D.; Corr, M.; Schwab, R.B.; Carson, D.A. Nrf2 responses and the therapeutic selectivity of electrophilic compounds in chronic lymphocytic leukemia. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 7479–7484. [CrossRef]

82. Reynaert, N.L.; van der Vliet, A.; Guala, A.S.; McGovern, T.; Hristova, M.; Pantano, C.; Heintz, N.H.; Heim, J.; Ho, Y.-S.; Matthews, D.E.; et al. Dynamic redox control of NF- B through glutaredoxin-regulated S-glutathionylation of inhibitory B kinase beta. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 13086–13091. [CrossRef]
83. Heyninck, K.; Lahtela-Kakkonen, M.; Van Der Veken, P.; Haegeman, G.; Berghe, W. Vanden Withaferin A inhibits NF-kappaB activation by targeting cysteine 179 in IKKβ. *Biochem. Pharmacol.* **2014**, *91*, 501–509. [CrossRef]
84. Son, P.S.; Park, S.A.; Na, H.K.; Jue, D.M.; Kim, S.; Surh, Y.J. Piceatannol, a catechol-type polyphenol, inhibits phorbol ester-induced NF-κB activation and cyclooxygenase-2 expression in human breast epithelial cells: Cysteine 179 of IKKβ as a potential target. *Carcinogenesis* **2010**, *31*, 1442–1449. [CrossRef]
85. Weseler, A.R.; Bast, A. Oxidative stress and vascular function: Implications for pharmacologic treatments. *Curr. Hypertens. Rep.* **2010**, *12*, 154–161. [CrossRef]
86. Gastell, P.L.P.; De Alejo, J.L.P. Métodos para medir el daño oxidativo. *Rev. Cuba. Med. Mil.* **2000**, *29*, 192–198.
87. Harman, D. Aging: A Theory based on Free Radical and Radiation Chemestry. *J Gerontol.* **1956**, *11*, 298–300. [CrossRef]
88. Aitbaev, K.; Murkamilov, I.; Fomin, V. Molecular mechanisms of aging: The role of oxidative stress and epigenetic modifications. *Adv. Gerontol.* **2019**, *32*, 20–28.
89. Liguori, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; Della-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D.; et al. Oxidative stress, aging, and diseases. *Clin. Interv. Aging* **2018**, *13*, 757–772. [CrossRef]
90. Yoo, S.-Z.; No, M.-H.; Heo, J.-W.; Park, D.-H.; Kang, J.-H.; Kim, S.H.; Kwak, H.-B. Role of exercise in age-related sarcopenia. *J Exerc. Rehabil.* **2018**, *14*, 551–558. [CrossRef]
91. Gilca, M.; Stoian, I.; Atanasiu, V.; Virgolici, B. The oxidative hypothesis of senescence. *J. Postgrad. Med.* **2007**, *53*, 207–213. [CrossRef]
92. Hutcheson, R.; Rocic, P. The metabolic syndrome, oxidative stress, environment, and cardiovascular disease: The great exploration. *Exp. Diabetes Res.* **2012**, *2012*, 1–13. [CrossRef]
93. Milisav, I.; Ribari, S.; Poljsak, B. *Antioxidant Vitamins and Ageing*; Springer: Berlin/Heidelberg, Germany, 2018; ISBN 9789811328350.
94. Cooke, M.S.; Evans, M.D.; Dizdaroglu, M.; Lunec, J. Oxidative DNA damage: Mechanisms, mutation, and disease. *FASEB J.* **2003**, *17*, 1195–1214. [CrossRef]
95. Cao, G.; Booth, S.L.; Sadowski, J.A.; Prior, R.L. Increases in human plasma antioxidant capacity after consumption of controlled diets high in fruit and vegetables. *Am. J. Clin. Nutr.* **1998**, *68*, 1081–1087. [CrossRef]
96. Finkel, T.; Holbrook, N.J. Oxidants, oxidative stress and the biology of ageing. *Nature* **2000**, *408*, 239–247. [CrossRef]
97. Shukitt-Hale, B.; Lau, F.C.; Josep, J.A. Berry fruit supplementation and the aging brain. *J. Agric. Food Chem.* **2008**, *56*, 636–641. [CrossRef]
98. Seeram, N.P.; Cichewicz, R.H.; Chandra, A.; Nair, M.G. Cyclooxygenase inhibitory and antioxidant compounds from crabapple fruits. *J. Agric. Food Chem.* **2003**, *51*, 1948–1951. [CrossRef]
99. Maurya, P.K.; Rizvi, S.I. Protective role of tea catechins on erythrocytes subjected to oxidative stress during human aging. *Nat. Prod. Res.* **2009**, *23*, 1072–1079. [CrossRef]
100. Harikumar, K.B.; Aggarwal, B.B. Resveratrol: A multitargeted agent for age-associated chronic diseases. *Cell Cycle* **2008**, *7*, 1020–1037. [CrossRef]
101. Springer, M.; Moco, S. Resveratrol and Its Human Metabolites—Effects on Metabolic Health and Obesity. *Nutrients* **2019**, *11*, 143. [CrossRef]
102. Wang, Q.; Xu, J.; Rottinghaus, G.E.; Simonyi, A.; Lubahn, D.; Sun, G.Y.; Sun, A.Y. Resveratrol protects against global cerebral ischemic injury in gerbils. *Brain Res.* **2002**, *958*, 439–447. [CrossRef]
103. Tejada, S.; Pinya, S.; Del Mar Bibiloni, M.; Tur, J.; Pons, A.; Sureda, A. Cardioprotective Effects of the Polyphenol Hydroxytyrosol from Olive Oil. *Curr Drug Targets* **2017**, *18*, 1477–1486. [CrossRef]
104. Fabiani, R.; Rosignoli, P.; De Bartolomeo, A.; Fuccelli, R.; Servili, M.; Montedoro, G.F.; Morozzi, G. Oxidative DNA Damage Is Prevented by Extracts of Olive Oil, Hydroxytyrosol, and Other Olive Phenolic Compounds in Human Blood Mononuclear Cells and HL60 Cells. *J. Nutr.* **2008**, *138*, 1411–1416. [CrossRef]
105. Bolli, R. Oxygen-derived free radicals and myocardial reperfusion injury: An overview. *Cardiovasc. Drugs Ther.* **1991**, *5*, 249–268. [CrossRef]

106. Dubick, M.A.; Omaye, S.T. Evidence for grape, wine and tea polyphenols as modulators of atherosclerosis and ischemic heart disease in humans. *J. Nutraceuticals Funct. Med. Foods* **2001**, *3*, 67–93. [CrossRef]
107. Zhao, Y.; Shu, P.; Zhang, Y.; Lin, L.; Zhou, H.; Xu, Z.; Suo, D.; Xie, A.; Jin, X. Effect of centella asiatica on oxidative stress and lipid metabolism in hyperlipidemic animal models. *Oxid. Med. Cell. Longev.* **2014**, *2014*, 154295. [CrossRef]
108. Higano, T.; Kuroda, M.; Sakagami, H.; Mimaki, Y. Convallasaponin A, a New 5β-Spirostanol Triglycoside from the Rhizomes of Convallaria majalis. *Chem. Pharm. Bull. (Tokyo)* **2007**, *55*, 337–339. [CrossRef]
109. Pirola, L.; Fröjdö, S. Resveratrol: One molecule, many targets. *IUBMB Life* **2008**, *60*, 323–332. [CrossRef]
110. Montó, F.; Arce, C.; Noguera, M.A.; Ivorra, M.D.; Flanagan, J.; Roller, M.; Issaly, N.; D'Ocon, P. Action of an extract from the seeds of Fraxinus excelsior L. on metabolic disorders in hypertensive and obese animal models. *Food Funct.* **2014**, *5*, 786–796. [CrossRef]
111. da Chunga, A.P. Digitalis purpurea, Digitalis lanata. In *Plantas e Produtos Vegetais em Fitoterapia*; Fundação Calouste Gulbenkian: Lisboa, Portugal, 2006; pp. 274–275.
112. Valko, M.; Rhodes, C.J.; Moncol, J.; Izakovic, M.; Mazur, M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.* **2006**, *160*, 1–40. [CrossRef]
113. Yang, C.S.; Landau, J.M.; Huang, M.T.; Newmark, H.L. Inhibition of Carcinogenesis by Dietary Polyphenolic Compounds. *Ann. Rev. Nutr.* **2001**, *21*, 381–406. [CrossRef]
114. Johnson, I.T.; Williamson, G.; Musk, S.R.R. Anticarcinogenic Factors in Plant Foods: A New Class of Nutrients? *Nutr. Res. Rev.* **1994**, *7*, 175. [CrossRef]
115. Ezzat, S.; Hegazy, A.; Amer, A.M.; Kamel, G.; El-Alfy, T. Isolation of biologically active constituents from Moringa peregrina (Forssk.) Fiori. (family: Moringaceae) growing in Egypt. *Pharmacogn. Mag.* **2011**, *7*, 109. [CrossRef]
116. Bachmeier, B.E.; Mirisola, V.; Romeo, F.; Generoso, L.; Esposito, A.; Dell'Eva, R.; Blengio, F.; Killian, P.H.; Albini, A.; Pfeffer, U. Reference profile correlation reveals estrogen-like trancriptional activity of curcumin. *Cell. Physiol. Biochem.* **2010**, *26*, 471–482. [CrossRef]
117. Senft, C.; Polacin, M.; Priester, M.; Seifert, V.; Kögel, D.; Weissenberger, J. The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas. *BMC Cancer* **2010**, *10*, 491. [CrossRef]
118. Xu, M.; Bower, K.A.; Wang, S.; Frank, J.A.; Chen, G.; Ding, M.; Wang, S.; Shi, X.; Ke, Z.; Luo, J. Cyanidin-3-Glucoside inhibits ethanol-induced invasion of breast cancer cells overexpressing ErbB2. *Mol. Cancer* **2010**, *9*, 285. [CrossRef]
119. Acharya, A.; Das, I.; Singh, S.; Saha, T. Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogenesis. *Recent Patents Food Nutr. Agric.* **2010**, *2*, 166–177.
120. Das, A.; Banik, N.L.; Ray, S.K. Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes. *Cancer* **2010**, *116*, 164–176. [CrossRef]
121. Hsieh, T.C.; Wu, J.M. Targeting CWR22Rv1 prostate cancer cell proliferation and gene expression by combinations of the phytochemicals EGCG, genistein and quercetin. *Anticancer Res.* **2009**, *29*, 4025–4032.
122. Qiao, Y.; Cao, J.; Xie, L.; Shi, X. Cell growth inhibition and gene expression regulation by (-)-epigallocatechin-3-gallate in human cervical cancer cells. *Arch. Pharm. Res.* **2009**, *32*, 1309–1315. [CrossRef]
123. Imran, A.; Butt, M.S.; Xiao, H.; Imran, M.; Rauf, A.; Mubarak, M.S.; Ramadan, M.F. Inhibitory effect of black tea (Camellia sinensis) theaflavins and thearubigins against HCT 116 colon cancer cells and HT 460 lung cancer cells. *J. Food Biochem.* **2019**, *43*, e12822. [CrossRef]
124. Sánchez, Y.; Amrán, D.; de Blas, E.; Aller, P. Regulation of genistein-induced differentiation in human acute myeloid leukaemia cells (HL60, NB4). Protein kinase modulation and reactive oxygen species generation. *Biochem. Pharmacol.* **2009**, *77*, 384–396. [CrossRef]
125. Wang, H.; Oo Khor, T.; Shu, L.; Su, Z.-Y.; Fuentes, F.; Lee, J.-H.; Tony Kong, A.-N. Plants vs. Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability. *Anticancer Agents Med. Chem.* **2012**, *12*, 1281–1305. [CrossRef]
126. Ahmed, M.; Khan, M.I.; Muhammad, M.R.; Khan, A.U.; Khan, R.A. Role of medicinal plants in oxidative stress and cancer. *Sci. Rep.* **2013**, *2*, 641.
127. Rochette, L.; Zeller, M.; Cottin, Y.; Vergely, C. Diabetes, oxidative stress and therapeutic strategies. *Biochim. Biophys. Acta* **2014**, *1840*, 2709–2729. [CrossRef]

128. Salehi, B.; Ata, A.; Kumar, N.V.A.; Sharopov, F.; Ramírez-Alarcón, K.; Ruiz-Ortega, A.; Ayatollahi, S.A.; Fokou, P.V.T.; Kobarfard, F.; Zakaria, Z.A.; et al. Antidiabetic potential of medicinal plants and their active components. *Biomolecules* **2019**, *9*, 551. [CrossRef]
129. Das Gupta, P.; Amartya, D. Diabetes Mellitus and its herbal treatment. *Int. J. Res. Pharm. Biomed. Sci.* **2012**, *3*, 706–721.
130. Hegazy, G.A.; Alnoury, A.M.; Gad, H.G. The role of Acacia Arabica extract as an antidiabetic, antihyperlipidemic, and antioxidant in streptozotocin-induced diabetic rats. *Saudi Med. J.* **2013**, *34*, 727–733.
131. Halliwell, B. Role of free radicals in the neurodegenerative diseases: Therapeutic implications for antioxidant treatment. *Drugs Aging* **2001**, *18*, 685–716. [CrossRef]
132. Benard, O.; Chi, Y. Medicinal Properties of Mangiferin, Structural Features, Derivative Synthesis, Pharmacokinetics and Biological Activities. *Mini-Rev. Med. Chem.* **2015**, *15*, 582–594. [CrossRef]
133. Lampariello, L.; Cortelazzo, A.; Guerranti, R.; Sticozzi, C.; Valacchi, G. The magic velvet bean of mucuna pruriens. *J. Tradit. Complement. Med.* **2012**, *2*, 331–339. [CrossRef]
134. Iriti, M.; Vitalini, S.; Fico, G.; Faoro, F. Neuroprotective herbs and foods from different traditional medicines and diets. *Molecules* **2010**, *15*, 3517–3555. [CrossRef]
135. Chen, X.C.; Zhou, Y.C.; Chen, Y.; Zhu, Y.G.; Fang, F.; Chen, L.M. Ginsenoside Rg1 reduces MPTP-induced substantia nigra neuron loss by suppressing oxidative stress. *Acta Pharmacol. Sin.* **2005**, *26*, 56–62. [CrossRef] [PubMed]
136. Rudakewich, M.; Ba, F.; Benishin, C.G. Neurotrophic and neuroprotective actions of ginsenosides Rb1and Rg1. *Planta Med.* **2001**, *67*, 533–537. [CrossRef] [PubMed]
137. Cole, G.M.; Teter, B.; Frautschy, S.A. Neuroprotective effects of curcumin. *Adv. Exp. Med. Biol.* **2007**, *595*, 197–212. [PubMed]
138. Wang, M.Y.; Peng, L.; Weidenbacher-Hoper, V.; Deng, S.; Anderson, G.; West, B.J. Noni juice improves serum lipid profiles and other risk markers in cigarette smokers. *Sci. World J.* **2012**, *2012*, 594657. [CrossRef]
139. Babish, J.G.; Dahlberg, C.J.; Ou, J.J.; Keller, W.J.; Gao, W.; Kaadige, M.R.; Brabazon, H.; Lamb, J.; Soudah, H.C.; Kou, X.; et al. Synergistic in vitro antioxidant activity and observational clinical trial of F105, a phytochemical formulation including *Citrus bergamia*, in subjects with moderate cardiometabolic risk factors. *Can. J. Physiol. Pharmacol.* **2016**, *94*, 1257–1266. [CrossRef]
140. Silveira, J.Q.; Dourado, G.K.Z.S.; Cesar, T.B. Red-fleshed sweet orange juice improves the risk factors for metabolic syndrome. *Int. J. Food Sci. Nutr.* **2015**, *66*, 830–836. [CrossRef]
141. Kardum, N.; Milovanović, B.; Šavikin, K.; Zdunić, G.; Mutavdžin, S.; Gligorijević, T.; Spasić, S. Beneficial Effects of Polyphenol-Rich Chokeberry Juice Consumption on Blood Pressure Level and Lipid Status in Hypertensive Subjects. *J. Med. Food* **2015**, *18*, 1231–1238. [CrossRef]
142. Han, H.J.; Jung, U.J.; Kim, H.-J.; Cho, S.-J.; Kim, A.H.; Han, Y.; Choi, M.-S. Combined Supplementation with Grape Pomace and Omija Fruit Ethanol Extracts Dose-Dependently Improves Body Composition, Plasma Lipid Profiles, Inflammatory Status, and Antioxidant Capacity in Overweight and Obese Subjects. *J. Med. Food* **2016**, *19*, 170–180. [CrossRef]
143. Ivanova, D.; Tasinov, O.; Kiselova-Kaneva, Y. Improved lipid profile and increased serum antioxidant capacity in healthy volunteers after Sambucus ebulus L. fruit infusion consumption. *Int. J. Food Sci. Nutr.* **2014**, *65*, 740–744. [CrossRef]
144. Dostal, A.M.; Samavat, H.; Espejo, L.; Arikawa, A.Y.; Stendell-Hollis, N.R.; Kurzer, M.S. Green Tea Extract and Catechol-O-Methyltransferase Genotype Modify Fasting Serum Insulin and Plasma Adiponectin Concentrations in a Randomized Controlled Trial of Overweight and Obese Postmenopausal Women. *J. Nutr.* **2016**, *146*, 38–45. [CrossRef]
145. Ho, C.K.; Choi, S.W.; Siu, P.M.; Benzie, I.F.F. Effects of single dose and regular intake of green tea (Camellia sinensis) on DNA damage, DNA repair, and heme oxygenase-1 expression in a randomized controlled human supplementation study. *Mol. Nutr. Food Res.* **2014**, *58*, 1379–1383. [CrossRef] [PubMed]
146. Argani, H.; Ghorbanihaghjo, A.; Vatankhahan, H.; Rashtchizadeh, N.; Raeisi, S.; Ilghami, H. The effect of red grape seed extract on serum paraoxonase activity in patients with mild to moderate hyperlipidemia. *Sao Paulo Med. J.* **2016**, *134*, 234–239. [CrossRef] [PubMed]

147. Janiques, A.G.; Leal Vde, O.; Stockler-Pinto, M.B.; Moreira, N.X.; Mafra, D. Effects of grape powder supplementation on inflammatory and antioxidant markers in hemodialysis patients: A randomized double-blind study. *J. Bras. Nefrol.* **2014**, *36*, 461–501. [CrossRef] [PubMed]
148. Chiu, H.F.; Shen, Y.C.; Huang, T.Y.; Venkatakrishnan, K.; Wang, C.K. Cardioprotective Efficacy of Red Wine Extract of Onion in Healthy Hypercholesterolemic Subjects. *Phyther. Res.* **2016**, *30*, 380–385. [CrossRef] [PubMed]
149. Brüll, V.; Burak, C.; Stoffel-Wagner, B.; Wolffram, S.; Nickenig, G.; Müller, C.; Langguth, P.; Alteheld, B.; Fimmers, R.; Naaf, S.; et al. Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: A randomised double-blinded placebo-controlled cross-over trial. *Br. J. Nutr.* **2015**, *114*, 1263–1277. [CrossRef]
150. Lee, Y.J.; Ahn, Y.; Kwon, O.; Lee, M.Y.; Lee, C.H.; Lee, S.; Park, T.; Kwon, S.W.; Kim, J.Y. Dietary wolfberry extract modifies oxidative stress by controlling the expression of inflammatory mrnas in overweight and hypercholesterolemic subjects: A randomized, double-blind, placebo-controlled trial. *J. Agric. Food Chem.* **2017**, *65*, 309–316. [CrossRef]
151. Verma, S.K.; Jain, V.; Singh, D.P. Effect of Pueraria tuberosa DC. (Indian Kudzu) on blood pressure, fibrinolysis and oxidative stress in patients with stage 1 hypertension. *Pakistan J. Biol. Sci.* **2012**, *15*, 742–747. [CrossRef]
152. Panahi, Y.; Dadjou, Y.; Pishgoo, B.; Akbari, A.; Sahebkar, A. Antioxidant Activity of *Heracleum persicum* Fruit Extract: Evidence from a Randomized Controlled Trial. *J. Diet. Suppl.* **2016**, *13*, 530–537. [CrossRef]
153. Urquiaga, I.; Ávila, F.; Echeverria, G.; Perez, D.; Trejo, S.; Leighton, F. A Chilean Berry Concentrate Protects against Postprandial Oxidative Stress and Increases Plasma Antioxidant Activity in Healthy Humans. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 8361493. [CrossRef]
154. McAnulty, L.S.; Collier, S.R.; Landram, M.J.; Whittaker, D.S.; Isaacs, S.E.; Klemka, J.M.; Cheek, S.L.; Arms, J.C.; McAnulty, S.R. Six weeks daily ingestion of whole blueberry powder increases natural killer cell counts and reduces arterial stiffness in sedentary males and females. *Nutr. Res.* **2014**, *34*, 577–584. [CrossRef]
155. Wu, P.-T.; Fitschen, P.J.; Kistler, B.M.; Jeong, J.H.; Chung, H.R.; Aviram, M.; Phillips, S.A.; Fernhall, B.; Wilund, K.R. Effects of Pomegranate Extract Supplementation on Cardiovascular Risk Factors and Physical Function in Hemodialysis Patients. *J. Med. Food* **2015**, *18*, 941–949. [CrossRef] [PubMed]
156. Allsopp, P.; Crowe, W.; Bahar, B.; Harnedy, P.A.; Brown, E.S.; Taylor, S.S.; Smyth, T.J.; Soler-Vila, A.; Magee, P.J.; Gill, C.I.R.; et al. The effect of consuming Palmaria palmata-enriched bread on inflammatory markers, antioxidant status, lipid profile and thyroid function in a randomised placebo-controlled intervention trial in healthy adults. *Eur. J. Nutr.* **2016**, *55*, 1951–1962. [CrossRef] [PubMed]
157. Choi, S.W.; Yeung, V.T.F.; Collins, A.R.; Benzie, I.F.F. Redox-linked effects of green tea on DNA damage and repair, and influence of microsatellite polymorphism in HMOX-1: Results of a human intervention trial. *Mutagenesis* **2015**, *30*, 129–137. [CrossRef] [PubMed]
158. Shidfar, F.; Rajab, A.; Rahideh, T.; Khandouzi, N.; Hosseini, S.; Shidfar, S. The effect of ginger (Zingiber officinale) on glycemic markers in patients with type 2 diabetes. *J. Complement. Integr. Med.* **2015**, *12*, 165–170. [CrossRef]
159. Kaatabi, H.; Bamosa, A.O.; Badar, A.; Al-Elq, A.; Abou-Hozaifa, B.; Lebda, F.; Al-Khadra, A.; Al-Almaie, S. Nigella sativa improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: Placebo controlled participant blinded clinical trial. *PLoS ONE* **2015**, *10*, e0113486. [CrossRef]
160. Mesaik, M.A.; Ahmed, A.; Khalid, A.S.; Jan, S.; Siddiqui, A.A.; Perveen, S.; Azim, M.K. Effect of Grewia asiatica fruit on glycemic index and phagocytosis tested in healthy human subjects. *Pak. J. Pharm. Sci.* **2013**, *26*, 85–89.
161. Seo, S.K.; Hong, Y.; Yun, B.H.; Chon, S.J.; Jung, Y.S.; Park, J.H.; Cho, S.; Choi, Y.S.; Lee, B.S. Antioxidative effects of Korean red ginseng in postmenopausal women: A double-blind randomized controlled trial. *J. Ethnopharmacol.* **2014**, *154*, 753–757. [CrossRef]
162. Mercken, E.M.; Carboneau, B.A.; Krzysik-Walker, S.M.; De Cabo, R. Of mice and men: The benefits of caloric restriction, exercise, and mimetics. *Ageing Res. Rev.* **2012**, *11*, 390–398. [CrossRef]
163. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The hallmarks of aging. *Cell* **2013**, *153*, 1194. [CrossRef]
164. Niso-Santano, M.; González-Polo, R.A.; Paredes-Barquero, M.; Fuentes, J.M.; Aschner, M. Natural Products in the Promotion of Healthspan and Longevity. *Clin. Pharmacol. Transl. Med.* **2019**, *3*, 149–151.

165. Esposito, K.; Di Palo, C.; Maiorino, M.I.; Petrizzo, M.; Bellastella, G.; Siniscalchi, I.; Giugliano, D. Long-term effect of mediterranean-style diet and calorie restriction on biomarkers of longevity and oxidative stress in overweight men. *Cardiol. Res. Pract.* **2011**, *1*, 293916. [CrossRef] [PubMed]
166. Buckland, G.; Agudo, A.; Travier, N.; María Huerta, J.; Cirera, L.; Tormo, M.J.; Navarro, C.; Dolores Chirlaque, M.; Moreno-Iribas, C.; Ardanaz, E.; et al. Adherence to the Mediterranean diet reduces mortality in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). *Br. J. Nutr.* **2011**, *106*, 1581–1591. [CrossRef] [PubMed]
167. Martinez-Gonzalez, M.A.; Bes-Rastrollo, M. Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr. Opin. Lipidol.* **2014**, *25*, 20–26. [CrossRef] [PubMed]
168. Di Daniele, N.D.; Noce, A.; Vidiri, M.F.; Moriconi, E.; Marrone, G.; Annicchiarico-Petruzzelli, M.; D'Urso, G.; Tesauro, M.; Rovella, V.; De Lorenzo, A.D. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget* **2017**, *8*, 8947–8979. [CrossRef]
169. Pes, G.M.; Tolu, F.; Dore, M.P.; Sechi, G.P.; Errigo, A.; Canelada, A.; Poulain, M. Male longevity in Sardinia, a review of historical sources supporting a causal link with dietary factors. *Eur. J. Clin. Nutr.* **2015**, *69*, 411–418. [CrossRef]
170. Eleftheriou, D.; Benetou, V.; Trichopoulou, A.; La Vecchia, C.; Bamia, C. Mediterranean diet and its components in relation to all-cause mortality: Meta-analysis. *Br. J. Nutr.* **2018**, *120*, 1081–1097. [CrossRef]
171. Shi, Z.; Zhang, T.; Byles, J.; Martin, S.; Avery, J.C.; Taylor, A.W. Food habits, lifestyle factors and mortality among oldest old Chinese: The Chinese longitudinal healthy longevity survey (CLHLS). *Nutrients* **2015**, *7*, 7562–7579. [CrossRef]
172. Vlahchev, T.; Zhivkov, Z.T. Hunza—A Healthy and a Long Living People. *Asklepii* **2002**, *15*, 96–97.
173. Schmid, A. The Dom of Hunza (Northern Areas of Pakistan). In *Disappearing Peoples?* Routledge: London, UK, 2016; pp. 107–128, ISBN 9781315430416.
174. Zarse, K.; Bossecker, A.; Müller-Kuhrt, L.; Siems, K.; Hernandez, M.A.; Berendsohn, W.G.; Birringer, M.; Ristow, M. The phytochemical glaucarubinone promotes mitochondrial metabolism, reduces body fat, and extends lifespan of Caenorhabditis elegans. *Horm. Metab. Res.* **2011**, *43*, 241–243. [CrossRef]
175. Shukla, V.; Yadav, D.; Phulara, S.C.; Gupta, M.M.; Saikia, S.K.; Pandey, R. Longevity-promoting effects of 4-hydroxy-E-globularinin in Caenorhabditis elegans. *Free Radic. Biol. Med.* **2012**, *53*, 1848–1856. [CrossRef]
176. Kumar, R.; Gupta, K.; Saharia, K.; Pradhan, D.; Subramaniam, J.R. Withania somnifera root extract extends lifespan of Caenorhabditis elegans. *Ann. Neurosci.* **2013**, *20*, 13–16. [CrossRef]
177. Lee, S.H.; An, H.S.; Jung, Y.W.; Lee, E.J.; Lee, H.Y.; Choi, E.S.; An, S.W.; Son, H.; Lee, S.J.; Kim, J.B.; et al. Korean mistletoe (Viscum album coloratum) extract extends the lifespan of nematodes and fruit flies. *Biogerontology* **2014**, *15*, 153–164. [CrossRef] [PubMed]
178. Zamberlan, D.C.; Amaral, G.P.; Arantes, L.P.; Machado, M.L.; Mizdal, C.R.; Campos, M.M.A.; Soares, F.A.A. Rosmarinus officinalis L. increases caenorhabditis elegans stress resistance and longevity in a DAF-16, HSF-1 and SKN-1-dependent manner. *Braz. J. Med. Biol. Res.* **2016**, *49*. [CrossRef] [PubMed]
179. Wang, H.; Liu, J.; Li, T.; Liu, R.H. Blueberry extract promotes longevity and stress tolerance via DAF-16 in Caenorhabditis elegans. *Food Funct.* **2018**, *9*, 5273–5282. [CrossRef] [PubMed]
180. Kim, Y.S.; Han, Y.T.; Jeon, H.; Cha, D.S. Antiageing properties of Damaurone D in Caenorhabditis elegans. *J. Pharm. Pharmacol.* **2018**, *70*, 1423–1429. [CrossRef] [PubMed]
181. Pandey, S.; Phulara, S.C.; Mishra, S.K.; Bajpai, R.; Kumar, A.; Niranjan, A.; Lehri, A.; Upreti, D.K.; Chauhan, P.S. Betula utilis extract prolongs life expectancy, protects against amyloid-β toxicity and reduces Alpha Synuclien in Caenorhabditis elegans via DAF-16 and SKN-1. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* **2020**, *228*, 108647. [CrossRef]
182. Piegholdt, S.; Rimbach, G.; Wagner, A.E. The phytoestrogen prunetin affects body composition and improves fitness and lifespan in male Drosophila melanogaster. *FASEB J.* **2016**, *30*, 948–958. [CrossRef]
183. Chatzigeorgiou, S.; Thai, Q.D.; Tchoumtchoua, J.; Tallas, K.; Tsakiri, E.N.; Papassideri, I.; Halabalaki, M.; Skaltsounis, A.L.; Trougakos, I.P. Isolation of natural products with anti-ageing activity from the fruits of Platanus orientalis. *Phytomedicine* **2017**, *33*, 53–61. [CrossRef]
184. Niraula, P.; Ghimire, S.; Lee, H.; Kim, M.S. Ilex paraguariensis extends lifespan and increases an ability to resist environmental stresses in drosophila. *Rejuvenation Res.* **2018**, *21*, 497–505. [CrossRef]

185. Wu, Z.; Wu, A.; Dong, J.; Sigears, A.; Lu, B. Skin extract improves muscle function and extends lifespan of a Drosophila model of Parkinson's disease through activation of mitophagy. *Exp. Gerontol.* **2018**, *113*, 10–17. [CrossRef]
186. Arabit, J.G.J.; Elhaj, R.; Schriner, S.E.; Sevrioukov, E.A.; Jafari, M. Rhodiola rosea Improves Lifespan, Locomotion, and Neurodegeneration in a Drosophila melanogaster Model of Huntington's Disease. *Biomed Res. Int.* **2018**, *2018*, 6726874. [CrossRef] [PubMed]
187. Carmona-Gutierrez, D.; Zimmermann, A.; Kainz, K.; Pietrocola, F.; Chen, G.; Maglioni, S.; Schiavi, A.; Nah, J.; Mertel, S.; Beuschel, C.B.; et al. The flavonoid 4,4′-dimethoxychalcone promotes autophagy-dependent longevity across species. *Nat. Commun.* **2019**, *10*, 651. [CrossRef] [PubMed]
188. Fernández-Bedmar, Z.; Demyda-Peyrás, S.; Merinas-Amo, T.; Del Río-Celestino, M. Nutraceutic potential of two allium species and their distinctive organosulfur compounds: A multi-assay evaluation. *Foods* **2019**, *8*, 222. [CrossRef]
189. Tomobe, K.; Fujii, H.; Sun, B.; Nishioka, H.; Aruoma, O.I. Modulation of infection-induced inflammation and locomotive deficit and longevity in senescence-accelerated mice-prone (SAMP8) model by the oligomerized polyphenol Oligonol. *Biomed. Pharmacother.* **2007**, *61*, 427–434. [CrossRef]
190. Porquet, D.; Casadesús, G.; Bayod, S.; Vicente, A.; Canudas, A.M.; Vilaplana, J.; Pelegrí, C.; Sanfeliu, C.; Camins, A.; Pallàs, M.; et al. Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8. *Age (Omaha)* **2013**, *35*, 1851–1865. [CrossRef]
191. Wang, P.; Sun, H.; Liu, D.; Jiao, Z.; Yue, S.; He, X.; Xia, W.; Ji, J.; Xiang, L. Protective effect of a phenolic extract containing indoline amides from Portulaca oleracea against cognitive impairment in senescent mice induced by large dose of D-galactose /NaNO2. *J. Ethnopharmacol.* **2017**, *203*, 252–259. [CrossRef]
192. Dutta, K.; Patel, P.; Julien, J.P. Protective effects of Withania somnifera extract in SOD1 G93A mouse model of amyotrophic lateral sclerosis. *Exp. Neurol.* **2018**, *309*, 193–204. [CrossRef]
193. Aires, V.; Labbé, J.; Deckert, V.; Pais de Barros, J.P.; Boidot, R.; Haumont, M.; Maquart, G.; Le Guern, N.; Masson, D.; Prost-Camus, E.; et al. Healthy adiposity and extended lifespan in obese mice fed a diet supplemented with a polyphenol-rich plant extract. *Sci. Rep.* **2019**, *9*, 9134. [CrossRef]
194. Pan, M.H.; Wu, J.C.; Ho, C.T.; Badmaev, V. Effects of water extract of Curcuma longa (L.) roots on immunity and telomerase function. *J. Complement. Integr. Med.* **2017**, *14*. [CrossRef]
195. Souza-Monteiro, J.R.; Arrifano, G.P.F.; Queiroz, A.I.D.G.; Mello, B.S.F.; Custódio, C.S.; Macêdo, D.S.; Hamoy, M.; Paraense, R.S.O.; Bittencourt, L.O.; Lima, R.R.; et al. Antidepressant and Antiaging Effects of Açaí (Euterpe oleracea Mart.) in Mice. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 3614960. [CrossRef]