Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can play, and in fact they do it, several physiological roles (i.e., cell signaling), and they are normally generated as by-products of oxygen metabolism; despite this, environmental stressors (i.e., UV, ionizing radiations, pollutants, and heavy metals) and xenobiotics (i.e., antiblastic drugs) contribute to greatly increase ROS production, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress). Several antioxidants have been exploited in recent years for their actual or supposed beneficial effect against oxidative stress, such as vitamin E, flavonoids, and polyphenols. While we tend to describe oxidative stress just as harmful for human body, it is true as well that it is exploited as a therapeutic approach to treat clinical conditions such as cancer, with a certain degree of clinical success. In this review, we will describe the most recent findings in the oxidative stress field, highlighting both its bad and good sides for human health.

1. Introduction

Superoxide radicals (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hydroxyl radicals (•OH), and singlet oxygen (¹²O$_2$) are commonly defined reactive oxygen species (ROS); they are generated as metabolic by-products by biological systems [1, 2]. Processes, like protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation, are all dependent on a proper ROS production and presence inside cells that need to be kept at a low level [3]. When ROS production increases, they start showing harmful effects on important cellular structures like proteins, lipids, and nucleic acids [4]. A large body of evidences shows that oxidative stress can be responsible, with different degrees of importance, in the onset and/or progression of several diseases (i.e., cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular diseases) [5].

ROS are mainly produced by mitochondria, during both physiological and pathological conditions, that is, Q$^-$ can be formed by cellular respiration, by lipoxgenases (LOX) and cyclooxygenases (COX) during the arachidonic acid metabolism, and by endothelial and inflammatory cells [6]. Despite the fact that these organelles have an intrinsic ROS scavenging capacity [7], it is worth to note that this is not enough to address the cellular need to clear the amount of ROS produced by mitochondria [8].

Cells deploy an antioxidant defensive system based mainly on enzymatic components, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), to protect themselves from ROS-induced cellular damage [9].

2. Oxidants and Free Radical Production

ROS production basically relies on enzymatic and nonenzymatic reactions. Enzymatic reactions able to generate ROS are those involved in respiratory chain, prostaglandin synthesis, phagocytosis, and cytochrome P450 system [10–20]. Superoxide radical (O$_2^-$) is generated by NADPH oxidase, xanthine oxidase, and peroxidases. Once formed, it is involved in several reactions that in turn generate hydrogen peroxide, hydroxyl radical (OH•), peroxynitrite (ONOO$^-$), hypochlorous acid (HOCl), and so on. H$_2$O$_2$ (a nonradical) is produced by multiple oxidase enzymes, that is, amino acid oxidase and xanthine oxidase. Hydroxyl radical (OH•), the most reactive among all the free radical species in vivo, is generated by reaction of O$_2^-$ with H$_2$O$_2$, with Fe$^{3+}$ or Cu$^+$ as a reaction catalyst (Fenton reaction) [12–19]. Nitric oxide radical (NO•), which plays some important physiological roles, is synthesized from arginine-to-citrulline oxidation by nitric oxidase.
oxide synthase (NOS) [12–19].

Even nonenzymatic reactions can be responsible for free radical production, that is, when oxygen reacts with organic compounds or when cells are exposed to ionizing radiations. Nonenzymatic free radical production can occur as well during mitochondrial respiration [15, 16, 19].

Free radicals are generated from both endogenous and exogenous sources. Immune cell activation, inflammation, ischemia, infection, cancer, excessive exercise, mental stress, and aging are all responsible for endogenous free radical production. Exogenous free radical production can occur as a result from exposure to environmental pollutants, heavy metals (Cd, Hg, Pb, Fe, and As), certain drugs (cyclosporine, tacrolimus, gentamycin, and bleomycin), chemical solvents, cooking (smoked meat, used oil, and fat), cigarette smoke, alcohol, and radiations [15–25]. When these exogenous compounds penetrate the body, they are degraded or metabolized, and free radicals are generated as by-products.

3. Physiological Activities of Free Radicals

When maintained at low or moderate concentrations, free radicals play several beneficial roles for the organism. For example, they are needed to synthesize some cellular structures and to be used by the host defense system to fight pathogens. In fact, phagocytes synthesize and store free radicals, in order to be able to release them when invading pathogenic microbes have to be destroyed [16, 21]. The pivotal role of ROS for the immune system is well exemplified by patients with granulomatous disease. These individuals are unable to produce $O_2^-$ because of a defective NADPH oxidase system, so they are prone to multiple and in most of the cases persistent infections [15, 16]. Free radicals are also involved in a number of cellular signaling pathways [18–20]. They can be produced by nonphagocytic NADPH oxidase isoforms; in this case, free radicals play a key regulatory role in intracellular signaling cascades, in several cell types such as fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. Probably, the most well-known free radical acting as a signaling molecule is nitric oxide (NO). It is an important cell-to-cell messenger required for a proper blood flow modulation, involved in thrombosis, and is crucial for the normal neural activity [18]. NO is also involved in nonspecific host defense, required to eliminate intracellular pathogens and tumor cells. Another physiological activity of free radicals is the induction of a mitogenic response [18, 19]. Summarizing, free radicals, when maintained at low or moderate levels, are of crucial importance to human health.

4. Detrimental Effects of Free Radicals on Human Health

As stated before, if in excess, free radicals and oxidants give rise to a phenomenon known as oxidative stress; this is a harmful process that can negatively affect several cellular structures, such as membranes, lipids, proteins, lipoproteins, and deoxyribonucleic acid (DNA) [16–21]. Oxidative stress emerges when an imbalance exists between free radical formation and the capability of cells to clear them. For instance, an excess of hydroxyl radical and peroxynitrite can cause lipid peroxidation, thus damaging cell membranes and lipoproteins. This in turn will lead to malondialdehyde (MDA) and conjugated diene compound formation, which are known to be cytotoxic as well as mutagenic. Being a radical chain reaction, lipid peroxidation spreads very quickly affecting a large amount of lipidic molecules [25]. Proteins may as well being damaged by oxidative stress, undergoing to conformational modifications that could determine a loss, or an impairment, of their enzymatic activity [20, 25].

Even DNA is prone to oxidative stress-related lesions, the most representative of which is the 8-oxo-2′-deoxyguanosine (8-OHdG) formation; this is a particularly pernicious DNA lesion, which can be responsible for both mutagenesis, as pointed out by Nishida et al. [26]. It can also cause a loss in the epigenetic information, probably due to an impairment in CpG island methylation asset in gene promoters [27]. It is worth to note that Valavanidis and colleagues [28] have already proposed 8-OHdG levels in a tissue as biomarker of oxidative stress. Of course cells can put in place several mechanisms, such as the base excision repair (BER) or antioxidants, as defense response against DNA lesions [17–20].

If not strictly controlled, oxidative stress can be responsible for the induction of several diseases, both chronic and degenerative, as well as speeding up body aging process and cause acute pathologies (i.e., trauma and stroke).
4.1. Cancer and Oxidative Stress

Cancer onset in humans is a complex process, which requires both cellular and molecular alterations mediated by endogenous and/or exogenous triggers. It is already well known that oxidative DNA damage is one of those stimuli responsible for cancer development \[14, 15, 22\]. Cancer can be driven and/or promoted by chromosomal abnormalities and oncogene activation determined by oxidative stress. Hydrolyzed DNA bases are common by-products of DNA oxidation and are considered one of the most relevant events in chemical carcinogenesis \[14, 22\]. The formation of such kind of adducts impairs normal cell growth by altering the physiological transcriptomic profile and causing gene mutations. Oxidative stress can also cause a variegated amount of modifications against DNA structure, for example, base and sugar lesions, DNA-protein cross-links, strand breaks, and base-free sites. For instance, tobacco smoking, environmental pollutants, and chronic inflammation are sources of oxidative DNA damage that could contribute to tumor onset \[14, 17, 29\]. Oxidative stress resulting from lifestyle reasons can also play an important role in cancer development, as suggested by the strong correlation between dietary fat consumption (a factor that exposes the organism at greater risk of lipid peroxidation) and death rates from different types of cancer \[16, 21\].

4.2. Cardiovascular Disease and Oxidative Stress

Cardiovascular diseases (CVDs) are clinical entities with a multifactorial etiology, generally associated with a very large amount of risk factors, the most broadly recognized of which are hypercholesterolaemia, hypertension, smoking habit, diabetes, unbalanced diet, stress, and sedentary life \[11, 30, 31\]. During the last years, research data pointed out that oxidative stress should be considered either a primary or a secondary cause for many CVDs \[18\]. Oxidative stress acts mainly as a trigger of atherosclerosis. It is well known that atheromatous plaque formation results from an early endothelial inflammation, which in turn leads to ROS generation by macrophages recruited in situ. Circulating LDL are then oxidized by reactive oxygen species, thus leading to foam cell formation and lipid accumulation. The result of these events is the formation of an atherosclerotic plaque. Both in vivo and ex vivo studies provided evidences supporting the role of oxidative stress in atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy, and congestive heart failure \[11, 16, 30, 31\].

4.3. Neurological Disease and Oxidative Stress

Oxidative stress has been linked to several neurological diseases (i.e., Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, depression, and memory loss) \[32–35\]. In AD, several experimental and clinical researches showed that oxidative damage plays a pivotal role in neuron loss and progression to dementia \[34\]. β-amyloid, a toxic peptide often found present in AD patients' brain, is produced by free radical action and it is known to be at least in part responsible for neurodegeneration observed during AD onset and progression \[35\].

4.4. Respiratory Disease and Oxidative Stress

Several researches pointed out that lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), determined by systemic and local chronic inflammation, are linked to oxidative stress \[36–39\]. Oxidants are known to enhance inflammation via the activation of different kinases involving pathways and transcription factors like NF-kappa B and AP-1 \[38, 39\].

4.5. Rheumatoid Arthritis and Oxidative Stress

Rheumatoid arthritis is a chronic inflammatory disorder affecting the joints and surrounding tissues, characterized by macrophages and activated T cell infiltration \[15, 40, 41\]. Free radicals at the site of inflammation play a relevant role in
both initiation and progression of this syndrome, as demonstrated by the increased isoprostane and prostaglandin levels in synovial fluid of affected patients [41].

### 4.6. Kidney Diseases and Oxidative Stress

Oxidative stress is involved in a plethora of diseases affecting renal apparatus such as glomerulo- and tubule-interstitial nephritis, renal failure, proteinuria, and uremia [16, 42]. The kidneys are negatively affected by oxidative stress mainly because of the fact that ROS production induces the recruitment of inflammatory cells and proinflammatory cytokine production, leading to an initial inflammatory stage. In this early phase, a predominant role is played by TNF-alpha and IL-1b, as proinflammatory mediators, as well as by NF-κB as transcriptional factor required to sustain the inflammatory process. The latter stage is characterized by an increase in TGF-beta production, which orchestrates the extracellular matrix synthesis. So, when the oxidative stress stimuli act chronically on kidney tissues, the results will be an initial stage of inflammation and later the formation of abundant fibrotic tissue that impairs organ function potentially leading to renal failure. Certain drugs, such as cyclosporine, tacrolimus, gentamycin, and bleomycin, are known to be nephrotoxics mainly because of the fact that they increase free radical levels and oxidative stress via lipid peroxidation [42–45]. Heavy (Cd, Hg, Pb, and As) and transition metals (Fe, Cu, Co, and Cr), acting as powerful oxidative stress inducers, are responsible for various forms of nephropathy, as well as for some types of cancers [22, 23].

### 4.7. Sexual Maturation and Oxidative Stress

Several authors pointed out that oxidative stress could be responsible for a delayed sexual maturation and puberty onset [46, 47]. This seems to be true when children in prepubertal age are exposed to Cd, a well known responsible for an increase in free radicals and oxidative stress, as well as when pregnant women are exposed to the same metallic element.

Summarizing, we can affirm that oxidative stress and free radicals are confirmed to be responsible for several pathological conditions affecting different tissues and systems, thus being one of the most important and pervasive harms to human health.

#### 5. Exogenous Antioxidants and Human Health

Human body put in place several strategies to counteract the effects of free radicals and oxidative stress, based on enzymatic (e.g., SOD, CAT, and GPx) and nonenzymatic (e.g., lipoic acid, glutathione, L-arginine, and coenzyme Q10) antioxidant molecules, all of them being endogenous antioxidants. Beside these, there are several exogenous antioxidant molecules of animal or vegetal origin, mainly introduced by diet or by nutritional supplementation.

Here, we will discuss the most relevant nutritional antioxidants and their protective effects for human health.

#### 5.1. Vitamin E

The term vitamin E encompasses a constellation of lipophilic molecules (α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol) synthesized by vegetal organisms [48] and contained in edible oils and seeds, as well as in food artificially enriched in α-tocopherol [49, 50].

The most active form of vitamin E, RRR-α-tocopherol, showed in vitro an antiproliferative activity against vascular smooth muscle cells via PKC modulation [51], even when under stimulation from low-density lipoproteins (LDL) [52]. These results were confirmed in vivo, both in mouse and rabbit models of atherosclerosis [53–55].

Macrophage transition to foam cells is one of the earlier and important steps in atherosclerotic lesion formation; CD36 receptor is one of the key players involved, being a scavenger receptor responsible for oxidized-LDL (oxLDL) uptake.
Several studies described that vitamin E is able to prevent CD36 mRNA expression induced by cholesterol, thus playing a beneficial role in preventing foam cell formation. This was true in vivo, as well as in vitro on human macrophages and vascular smooth muscle cells [58, 59]; vitamin E supplementation was also useful to upregulate PPARγ, LXRα, and ABCA1, in ApoE knockout mice, ameliorating early (but not advanced) atherosclerotic lesions [60].

Vitamin E modulates the oxidative stress-induced NF-κB pathway and oxLDL-induced foam cell formation, decreases c-Jun phosphorylation (thus inhibiting inflammation and monocyte invasion), and matrix metalloprotease (MMP) expression [61–65].

A degree of CD36 mRNA reduction was also observed in animals undergoing to vitamin E supplementation under a regimen of high-fat diet [66–68].

RRR-γ-tocopherol (the most abundant after RRR-α-tocopherol) showed a potent proinflammatory function during allergic inflammation [69–77].

Each form of vitamin E seems to have different regulatory effects when it comes to recruit leukocytes to allergic inflammation site, which is however strictly dependent on vascular cell adhesion molecule-1 (VCAM-1) [78]. VCAM-1 is responsible also for the activation of several signals in endothelial cells which are causative of ROS generation, such as NOX2 complex activation that generates ROS which lead to PKCα activation [79]. This rapid and transient PKCα activation is consistent with a leukocyte migration across endothelia required in a timeframe of minutes, consistent with the rapid migration of leukocytes across endothelial cells in minutes at sites of migration.

Endothelial cells pretreated with α-tocopherol are less prone to let the lymphocytes and eosinophils migrate, while the opposite is true when pretreated with γ-tocopherol, this is due to the fact that the first strategy decreases VCAM-1 expression, while the latter increases it [80]. This phenomenon was observed even in vivo, in a mouse model of allergic lung inflammation [80, 81].

Interestingly, a research found a correlation between the prevalence of asthma and the average plasma tocopherol in several countries, based on nutritional consumption of foods and oils rich in tocopherol. Briefly, countries with an average plasma γ-tocopherol concentration of 2–7 μmol/L had the highest asthma prevalence compared to those with a concentration of 1-2 μmol/L, independently from α-tocopherol plasma levels [74].

Olive and sunflower oils, which have little or not at all γ-tocopherol [74], seem to have to be preferred to soybean oil, because the latter one seems responsible for an increase in plasma γ-tocopherol [82].

A large prospective study, covering 4500 individuals and spanning 20 years, demonstrated an association between α- or γ-tocopherol serum concentrations and lung function [72]. The results highlighted as in those individuals with highery-tocopherol serum levels (>10 μmol/L) demonstrated significantly lower FEV1/FVC (10–17%); it is relevant to point out that similar degrees of lung function impairments were observed in individuals exposed to other respiratory stressors (e.g., particulate matter) [83–87]. These observations suggest that γ-tocopherol could negatively affect pulmonary function.

It has been also observed, from in vivo experiments, that α- and γ-tocopherol supplementation of allergic and nonallergic pregnant mice can alter the allergic responsiveness development in offspring of mice.

It is known that (i) proper dendritic cell development and responsiveness are crucial for an optimal allergen sensitization, (ii) it relies on PKC isoforms activity, and (iii) all of the PKCs include a C1A regulatory domain, which is targeted by both α- and γ-tocopherol [88–107].

In mice prone to allergic disease, supplementing allergic mothers (at the time of mating) with α-tocopherol was enough to inhibit the pup allergic responses [67], while γ-tocopherol supplementation amplified pup responses to allergens [70].

These differences in allergic response development exerted by α- or γ-tocopherol supplementation are dependent from their modulation of eosinophils and CD11c+ CD11b+ dendritic cell numbers in the lungs; α-tocopherol reduced both the
cellular species, without affecting the number of CD11c+ CD11b− regulatory dendritic cells, while γ-tocopherol increased both eosinophils and CD11c+ CD11b+ dendritic cells [69, 70].

Summarizing, α- and γ-tocopherol forms of vitamin E exert a differential set of biological effects, which cannot be always regarded as positive to human health; this is something that needs to be taken in account when considering to enrich the content of vitamin E into a diet with antioxidant purposes.

5.2. Flavonoids

Flavonoids are a class of polyphenolic compounds with a benzoγ-pyrone structure largely represented in plants, responsible for several pharmacological activities [108, 109]. These substances have been investigated because of their potential health benefits as antioxidants, action mediated by their functional hydroxyl groups, which are able to scavenge free radicals and/or chelate metal ions [109–116].

Their antioxidant activity relies on the conformational disposition of functional groups; configuration, substitution, and total number of hydroxyl groups are important factors in determining mechanisms of antioxidant activity like ROS/RNS scavenging and metal chelation [111, 117].

Flavonoid determines (i) ROS synthesis suppression, inhibition of enzymes, or chelation of trace elements responsible for free radical generation; (ii) scavenging ROS; and (iii) improvement of antioxidant defenses [118, 119].

Genistein is a soy isoflavone that is probably the most interesting and well-studied flavonoid compound, due to its broad pharmacological activities.

Genistein has been extensively employed as antioxidant in a plethora of studies, showing the potential to scavenge ROS and RNS with a high degree of efficacy. This flavonoid compound is able to improve the antioxidant defenses of a cell, thus prevents apoptotic process through the modulation of several genes and proteins [120]. In nonhuman primates and rabbits [121, 122], dietary-supplemented genistein delayed atherogenesis. An additional study observed an increase in antioxidant protection of LDL and an atheroprotective effect [123]. In general, soy isoflavones confer protection against lipoprotein oxidation [124–126], as well as against oxidative DNA damage in postmenopausal women [127], but the point is still debated [128–130]. There are other mechanism that genistein can be used to suppress oxidative stress and related inflammation in the vascular intima layer. Genistein inhibits NF-κB activation (inducible by oxidative stress) and regulates the expression of genes relevant to immune and inflammatory processes [131]. Genistein increases the expression of antioxidant enzymes in human prostate cancer cells conferring protection against oxidative DNA damage [132, 133].

Briefly, flavonoids are a class of natural compounds extensively present in foods of vegetal origin (fruits, oils, seeds, etc.) showing a good potential in terms of usefulness for human health, as antioxidant molecules but also because of some ancillary yet pharmacologically interesting properties. Nonetheless, they need to be managed carefully, and their supplementation into the diet (as diet enrichment or as nutraceuticals) have to take in account also some potential drawback concerning human health and wellness.

6. Prooxidant Agents in Therapy

Prooxidant agents, beside their well-known detrimental effects on human health, have been investigated and, in some cases, actually used, as therapeutic agents mainly against cancer diseases.

Here, we will briefly discuss two emerging prooxidant compounds showing interesting pharmacological activities, such as ascorbic acid (AA) and polyphenols, and the most well-known and employed prooxidant in therapy, ionizing radiation.

6.1. Ascorbic Acid
Ascorbic acid (vitamin C) is a water-soluble compound classified under the group of natural antioxidants. Ascorbate reacts with ROS, quenching them and promoting the conversion into semihydroascorbate radical, which is a poorly reactive chemical species, thus efficiently reducing the risk of cancer by suppressing free radicals and oxidative stress [134].

Apart from this, ascorbate also reduces metal ions like Fe^{2+} and Cu^{2+}, thus promoting a reaction that gives rise to highly reactive free radical (by the so-called Fenton reaction) [135, 136]; these radicals have been reported to be able to induce cytotoxicity by causing DNA backbone breaks and base modifications [134].

This effect seems to be more relevant on cancer cells, in fact while normal cells take advantage from redundant mechanisms for H2O2 clearing and/or repair of H2O2-induced damage, to counteract the effects of pro-oxidant concentrations of AA; cancer cells lacking of these compensatory mechanisms (e.g., catalase deficiency, mutated DNA repair, and tumor suppressor genes) are more susceptible to pharmacologic ascorbate concentrations [132]. The authors reported that 10 mM AA induces apoptosis in leukemia cell lines; the authors proposed that AA-induced O2^{-}/H2O2 production led to NF-kB-p53-caspase 3 signaling axis, by which this proapoptotic effect is exerted [137–139]. Another study pointed out that AA was able to inhibit Raji cell proliferation, apparently by downregulating the set of genes needed for S-phase progression in actively proliferating cells [140]. In an in vivo study, guinea pigs supplemented with AA at various doses showed a complete regression of fibrosarcoma and liposarcoma tumors [141]. In general, there have been several studies assessing the antiblastic activities of AA, mostly in vitro on different cell lines [142–156].

Despite these somehow surprising but still very interesting results, there is the urge of conducting more researches, both in vitro and in vivo, to definitely assess the mode of action and efficacy of AA as prooxidative anticancer agent.

### 6.2. Polyphenols

Under conditions like high concentrations, high pH, and the presence of redox-active metals, phenolic compounds can acquire a prooxidant behavior [157, 158], mainly based on the generation of an aroxyl radical or a labile complex with a metal cation exerting redox activity. Aroxyl radical can lead the formation of O2^- or of ternary compound between DNA, copper, and flavonoids [159]. Polyphenols, like caffeic acid, ferulic acid, and apigenin, can exert a prooxidant effect through the increased intracellular production of ROS by NOX [160, 161]. Polyphenols can as well induce oxidative stress via transition metals, promoting the generation of hydroxyl radicals through Fenton and Fenton-like reactions; it is important to note that transition metal ions are more represented into cancer than into normal cells [162].

Prooxidant polyphenols seem to exert their cytotoxic activity by inducing apoptosis and cell cycle arrest via several pathways. Anthocyanins, pigments present in red wine and berry (Aronia melanocarpa, Rosaceae, Vaccinium myrtillus, and Ericaceae) fruits, cause apoptosis in cancer cells by increasing intracellular ROS formation [162–164].

Esculetin, a coumarin derivative present in plants such as chicory (Cichorium intybus and Asteraceae), showed both in vivo and in vitro antiproliferative activity against hepatocellular carcinoma. Esculetin delay Hepa 1–6 cell growth inoculated subcutaneously in C57BL/6J mice in a time- and dose-dependent manner [165]. Human hepatocellular carcinoma SMMC-7721 cells incubated with esculetin undergo to mitochondrial membrane potential collapse, with Bcl-2, caspase-9-, and caspase-3-mediated apoptosis [165]. In addition, esculetin also exerted a cytotoxic effect on HeLa cells inducing redox-dependent apoptosis, even in this case by causing the disruption of mitochondrial membrane potential, cytochrome C release, and caspase activation [166].

Curcumin, a compound extracted from Curcuma longa, induced ROS-mediated apoptosis in human gastric BGC-823 cells by activating the apoptosis signal-regulating kinase 1 (ASK1) signaling cascade (ASK1/MKK4/JNK) [167].

During the last years, a very large amount of in vitro studies investigated the prooxidative effects of polyphenols against cancer cell proliferation and survival, all of them presenting interesting results that nonetheless need to be confirmed by more in-depth researches [168–190].
Although polyphenols showed the pharmacological potential to inhibit tumorigenesis and arrest cancer cell proliferation in animal models, the role of ROS generation is still poorly understood, mainly because a large majority of the in vivo studies are limited to cancer growth arrest and apoptosis evaluation, and rarely or not at all they go deeper in the mechanistic explanation of a potential prooxidant action in vivo [191, 192].

6.3. Radiation Therapy

The ability of ionizing radiation to counteract proliferation of cancer cells is well explained [193–195] and widely used in clinical practice. In the last decades, there has been an extensive effort to understand the physical and molecular cellular response that follow the exposure to ionizing radiation. It is well recognized that damage to DNA operated by generation of radicals that indirectly cause DNA double-strand breaks (DSBs) is the most severe kind of damage induced by this prooxidant physical agent [196, 197]. These lesions are promptly repaired, as the results of the rapid activation of DSB damage repair mechanism, most importantly nonhomologous end joining or homologous recombination and the execution of a complex and finely tuned sequelae of those cellular signaling pathways belonging to the DNA damage response (DDR) [194, 198]. These responses span from posttranslational modifications and/or differential gene expression of proteins to start cell cycle reprogramming (e.g., radiation-induced arrest) or to execute cell death by mitotic catastrophe, apoptosis, autophagy, or induction of senescence [194, 195, 198].

Radiotherapy plays a key role in cancer treatment, so that almost 40% of cancer patients have been treated with this approach at least once [199]. In the last 2 decades, several technological advancements, like intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic radiotherapy (SRT), were put in place to address the need to reach that level of precision required to take advantage from radiation prooxidant activity avoiding, as much as possible, the side effects in terms of oxidative stress-induced cellular damage on healthy cells and tissues.

7. Conclusions

Oxidative stress and free radicals are generally known to be detrimental to human health. A large amount of studies demonstrates that in fact free radicals contribute to initiation and progression of several pathologies, ranging from CVD to cancer.

Antioxidants, as class of compounds able to counteract oxidative stress and mitigate its effects on individuals' health, gained enormous attention from the biomedical research community, because these compounds not only showed a good degree of efficacy in terms of disease prevention and/or treatment but also because of the general perception that they are free from important side effects. If it is true that antioxidants can be very useful in preventing, managing, or treating human pathologies, it is true as well that they are not immune to generating adverse effects. On the other hand, some prooxidant compounds or agents can be as well useful to human health, particularly regarding cancer treatment.

We can reach to the conclusion that oxidative stress, as phenomenon, although being one of the major harms to individuals' wellness and health, it can also be exploited as a treatment tool when and if we will be able to operate a fine tuning of this process inside human organism.

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Conflicts of Interest
The authors state no conflict of interest.

Authors' Contributions
Gabriele Pizzino and Natasha Irrera equally contributed to this paper.

References
1. Sato H., Shibata H., Shimizu T., Shishita S., Toriumi H., Ebine T. Differential cellular localization of antioxidant enzymes in the trigeminal ganglion. *Neuroscience*. 2013;248:345–358. doi: 10.1016/j.neuroscience.2013.06.010. [PubMed] [CrossRef] [Google Scholar]

2. Navarro-Yepes J., Zavala-Flores L., Anandhan A., Wang F., Skotak M., Chandra N. Antioxidant gene therapy against neuronal cell death. *Pharmacology & Therapeutics*. 2014;142:206–230. doi: 10.1016/j.pharmthera.2013.12.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Rajendran P., Nandakumar N., Renganarajan T., Palaniswami R., Gnanadhars E. N., Lakshminarasaiah U. Antioxidants and human diseases. *Clinica Chimica Acta*. 2014;436:332–347. doi: 10.1016/j.cca.2014.06.004. [PubMed] [CrossRef] [Google Scholar]

4. Wu J. Q., Kosten T. R., Zhang X. Y. Free radicals, antioxidant defense system, and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2013;46:200–206. doi: 10.1016/j.pnpbp.2013.02.015. [PubMed] [CrossRef] [Google Scholar]

5. Taniyama Y., Gregidiing K. K. Reactive oxygen species in the vasculature. *Hypertension*. 2003;42:1075–1081. doi: 10.1161/01.HYP.000010443.09293.4F. [PubMed] [CrossRef] [Google Scholar]

6. Al-Gubory K. H., Garrel C., Faure P., Sugino N. Roles of antioxidant enzymes in corpus luteum rescue from reactive oxygen species-induced oxidative stress. *Reproductive Biomedicine Online*. 2012;25:551–560. doi: 10.1016/j.rbmo.2012.08.004. [PubMed] [CrossRef] [Google Scholar]

7. Hansen J. M., Go Y. M., Jones D. P. Nuclear and mitochondrial compartmentation of oxidative stress and redox signalling. *Annual Review of Pharmacology and Toxicology*. 2006;46:215–234. doi: 10.1146/annurev.pharmtox.46.120604.141122. [PubMed] [CrossRef] [Google Scholar]

8. Glasauer A., Chandel N. S. Targeting antioxidants for cancer therapy. *Biochemical Pharmacology*. 2014;92:90–101. doi: 10.1016/bcp.2014.07.017. [PubMed] [CrossRef] [Google Scholar]

9. Deponte M. Glutathione catalysis and the reaction mechanism of glutathione-dependent enzymes. *Biochimica et Biophysica Acta*. 1830;2013:3217–3266. doi: 10.1016/bbagen.2012.09.018. [PubMed] [CrossRef] [Google Scholar]

10. Halliwell B., Gutteridge J. M. C. *Free Radicals in Biology and Medicine*. 4th. Oxford, UK: Clarendon Press; 2007. [Google Scholar]

11. Bahrani T., Soobrattee M. A., Luximon-Ramma V., Aruoma O. I. Free radicals and antioxidants in cardiovascular health and disease. *Internet Journal of Medical Update*. 2006;1:1–17. [Google Scholar]

12. Kumar S., Pandey A. K. Free radicals: health implications and their mitigation by herbs. *British Journal of Medicine and Medical Research*. 2015;7:438–457. [Google Scholar]

13. Kumar S., Pandey A. K. Chemistry and biological activities of flavonoids: an overview. *The Scientific World Journal*. 2013;2013:16. doi: 10.1155/2013/162750. [PubMed] [CrossRef] [Google Scholar]

14. Valko M., Izakovic M., Mazur M., Rhodes C. J., Telser J. Role of oxygen radicals in DNA damage and cancer incidence. *Molecular and Cellular Biochemistry*. 2004;266:37–56. [PubMed] [CrossRef] [Google Scholar]

15. Valko M., Leibfritz D., Moncola J., Cronin M. D., Mazur M., Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*. 2007;39:44–84. doi: 10.1016/j.biocel.2006.07.001. [PubMed] [CrossRef] [Google Scholar]

16. Droge W. Free radicals in the physiological control of cell function. *Physiological Reviews*. 2002;82:47–95. doi: 10.1152/physrev.00188.2001. [PubMed] [CrossRef] [Google Scholar]

17. Willcox J. K., Ash S. L., Catignani G. L. Antioxidants and prevention of chronic disease. *Critical Reviews in Food Science and Nutrition*. 2004;44:275–295. doi: 10.1080/10408690490468489. [PubMed] [CrossRef] [Google Scholar]

18. Pacher P., Beckman J. S., Libertini L. Nitric oxide and peroxynitrite in health and disease. *Physiological Reviews*. 2007;87:315–424. doi: 10.1152/physrev.00029.2006. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

19. Genestra M. Oxyl radicals, redox-sensitive signalling cascades and antioxidants. *Cellular Signalling*. 2007;19:1807–1819. doi: 10.1016/j.cellsig.2007.04.009. [PubMed] [CrossRef] [Google Scholar]

20. Halliwell B. Biochemistry of oxidative stress. *Biochemical Society Transactions*. 2007;35:1147–1150. doi: 10.1042/BST0351147. [PubMed] [CrossRef] [Google Scholar]

21. Young I., Woodside J. Antioxidants in health and disease. *Journal of Clinical Pathology*. 2001;54:176–186. [PMC free article] [PubMed] [Google Scholar]

22. Valko M., Rhodes C. J., Moncol J., Izakovic M., Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-Biological Interactions*. 2006;160:1–40. doi: 10.1016/j.chembi.2005.12.009. [PubMed] [CrossRef] [Google Scholar]

23. Valko M., Morris H., Cronin M. T. D. Metals, toxicity and oxidative stress. *Current Medicinal Chemistry*. 2005;12:1161–1208. [PubMed] [CrossRef] [Google Scholar]

24. Parthasarathy S., Santanam N., Ramachandran S., Meilicke C. Oxidants and antioxidants in atherogenesis: an appraisal. *Journal of Lipid Research*. 1999;40:2143–2157. [PubMed] [CrossRef] [Google Scholar]

25. Frei B. Reactive Oxygen Species and Antioxidant Vitamins. *Oregon State University: Linus Pauling Institute; 1997. http://lpi.oregonstate.edu/f-w97/reactive.html*. [Google Scholar]

26. Nishida N., Arizumi T., Takita M., et al. Reactive oxygen species induce epigenetic instability through the formation of β-hydroxydeoxyguanosine in human hepatocarcinogenesis. *Digestive Diseases*. 2013;31(5-6):459–466. doi: 10.1159/000355245. [PubMed] [CrossRef] [Google Scholar]

27. Yasui M., Kanemaru Y., Kamoshita N., Suzuki T., Arakawa T., Honma M. Tracing the fates of site-specifically introduced DNA adducts in the human genome. *DNA Repair (Amst)*. 2014;15:11–20. doi: 10.1016/j.dnarep.2014.01.003. [PubMed] [CrossRef] [Google Scholar]

28. Valavanidis A., Vlachogianni T., Fiotakis K., Loridas S. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *International Journal of Environmental Research and Public Health*. 2013;10(9):3868–3907. doi: 10.3390/ijerph1009.3868. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

29. Pizzino G., Bitto A., Interdonato M., et al. Oxidative stress and DNA repair and detoxification gene expression in adolescents exposed to heavy metals living in the Milazzo-Valle del Mela area (Sicily, Italy) *Redox Biology*. 2014;2:686–693. doi: 10.1016/j.redox.2014.05.003. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

30. Chatterjee M., Saluja R., Kanneganti S., Chinta S., Dixit M. Biochemical and molecular evaluation of neutrophil NOS in spontaneously hypertensive rats. *Cellular and Molecular Biology*. 2007;53:84–93. [PubMed] [CrossRef] [Google Scholar]

31. Ceriello A. Possible role of oxidative stress in the pathogenesis of hypertension. *Diabetes Care*. 2008;31(Supplement 2):S181–S184. doi: 10.2337/dc08-s245. [PubMed] [CrossRef] [Google Scholar]
65. Huang Z. G., Liang C., Han S. F., Wu Z. G. Vitamin E ameliorates ox-LDL-induced foam cells formation through modulating the activities of oxidative stress-induced NF-kappaB pathway. *Molecular and Cellular Biochemistry.* 2012;363:11–19. doi: 10.1007/s11010-011-1153-2. [PubMed] [CrossRef] [Google Scholar]

66. Gaeckle S., Zhang X., Schmelzer C., et al. Vitamin E dependent microRNA regulation in rat liver. *FEBS Letters.* 2008;582:3542–3546. doi: 10.1016/j.febslet.2008.09.032. [PubMed] [CrossRef] [Google Scholar]

67. Barella L., Muller P. Y., Schlachter M., et al. Identification of hepatic molecular mechanisms of action of alpha-tocopherol using global gene expression profile analysis in rats. *Biochimica et Biophysica Acta.* 2004;1689:66–74. doi: 10.1016/j.bbadis.2004.02.002. [PubMed] [CrossRef] [Google Scholar]

68. Podsuzn M. C., Grebenstein N., Spruss A., et al. Dietary alpha-tocopherol and atorvastatin reduce high-fat-induced lipid accumulation and down-regulate CD36 protein in the liver of guinea pigs. *The Journal of Nutritional Biochemistry.* 2014;25:573–579. doi: 10.1016/j.jnutbio.2014.01.008. [PubMed] [CrossRef] [Google Scholar]

69. Abdala-Valencia H., Berdnikovs S., Soveg F., Cook-Mills J. M. Alpha-tocopherol supplementation of allergic female mice inhibits development of CD11c+CD11b+ dendritic cells in utero and allergic inflammation in neonates. *American Journal of Physiology - Lung Cellular and Molecular Physiology.* 2014;307:L482–L496. doi: 10.1152/ajplung.00312.2014. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

70. Abdala-Valencia H., Soveg F., Cook-Mills J. M. y-Tocopherol supplementation of allergic female mice augments development of CD11c+CD11b+ dendritic cells in utero and allergic inflammation in neonates. *American Journal of Physiology - Lung and Cellular Molecular Physiology.* 2016;310:L759–L771. doi: 10.1152/ajplung.00301.2015. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

71. Cook-Mills J. M., Avila P. C. Vitamin E and D regulation of allergic asthma immunopathogenesis. *International Immunopharmacology.* 2014;23:364–372. doi: 10.1016/j.intimp.2014.08.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

72. Marchese M. E., Kumar R., Colangelo L. A., et al. The vitamin E isoforms alpha-tocopherol and gamma-tocopherol have opposite associations with spirometric parameters: the CARDIA study. *Respiratory Research.* 2014;15.p. 31. doi: 10.1186/1465-9292-15-31. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

73. Cook-Mills J. M. Isoforms of vitamin E differentially regulate PKC alpha and inflammation: a review. *Journal of Clinical & Cellular Immunology.* 2013;4(137). doi: 10.4172/2155-9899.1000137. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

74. Cook-Mills J. M., Abdala-Valencia H., Hartert T. Two faces of vitamin e in the lung. *American Journal of Respiratory and Critical Care Medicine.* 2013;188:279–284. doi: 10.1164/rccm.201303-0303ED. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

75. Abdala-Valencia H., Berdnikovs S., Cook-Mills J. M. Vitamin E isoforms differentially regulate intercellular adhesion molecule-1 activation of PKCalpha in human microvascular endothelial cells. *PLoS One.* 2012;7, article e41054. doi: 10.1371/journal.pone.0041054. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

76. McCary C. A., Abdala-Valencia H., Berdnikovs S., Cook-Mills J. M. Supplemental and highly elevated tocopherol doses differentially regulate allergic inflammation: reversibility of alpha-tocopherol and gamma-tocopherol’s effects. *Journal of Immunology.* 2011;186:3674–3685. doi: 10.4049/jimmunol.1000307. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

77. Cook-Mills J. M., McCary C. A. Isoforms of vitamin E differentially regulate inflammation. *Endocrine, Metabolic & Immune Disorders Drug Targets.* 2010;10:348–366. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

78. Cook-Mills J. M., Marchese M. E., Abdala-Valencia H. Vascular cell adhesion molecule-1 expression and signaling during disease: regulation by reactive oxygen species and antioxidants. *Antioxidants & Redox Signaling.* 2011;15:1607–1638. doi: 10.1089/ars.2010.3522. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

79. Abdala-Valencia H., Cook-Mills J. M. VCAM-1 signals regulates endothelial cell protein kinase C α via oxidation. *Journal of Immunology.* 2006;177:6379–6387. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

80. Berdnikovs S., Abdala-Valencia H., McCary C., et al. Isoforms of vitamin E have opposing immunoregulatory functions during inflammation by regulating leukocyte recruitment. *Journal of Immunology.* 2009;182:4395–4405. doi: 10.4049/jimmunol.0803659. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

81. Cook-Mills J. M., Gebretsadik T., Abdala-Valencia H., et al. Brief research report: interaction of vitamin E isoforms on asthma and allergic airway disease. *Thorax.* 2016;71:954–956. doi: 10.1136/thoraxjnl-2016-208494. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

82. Wu D., Han S. N., Meydani M., Meydani S. N. Effect of concomitant consumption of fish oil and vitamin E on T cell mediated function in the elderly: a randomized double-blind trial. *The American Journal of Medicine of Nutrition.* 2006;25:300–306. [PubMed] [Google Scholar]

83. Christiansi D. C., Ye T. T., Wegman D. H., Eisen E. A., Dai H. L., Lu P. L. Pulmonary function among cotton textile workers. A study of variability in symptom reporting, across-shift drop in FEV1, and longitudinal change. *Chest.* 1994;105:1713–1721. [PubMed] [Google Scholar]

84. Jacobs R. R., Boehlecke B., van Hage-Hamsten M., Rylander R. Bronchial reactivity, atopy, and airway response to cotton dust. *The American Review of Respiratory Disease.* 1993;148:19–24. doi: 10.1164/ajrccm.148.1.19. [PubMed] [Google Scholar]

85. Delfino R. J., Quintana P. J., Flora J., et al. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environmental Health Perspectives.* 2004;112:932–941. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

86. Koskela H., Tukkainen H., Kononoff A., Pekkarinen H. Effect of whole-body exposure to cold and wind on lung function in asthmatic patients. *Chest.* 1994;105:1728–1731. [PubMed] [Google Scholar]

87. Blanc P. D., Eisner M. D., Katz P. P., et al. Impact of the home indoor environment on adult asthma and rhinitis. *Journal of Occupational and Environmental Medicine.* 2005;47:362–372. [PubMed] [Google Scholar]

88. Fedulov A. V., Kobzik L. Allergy risk is mediated by dendritic cells with congenital epigenetic changes. *American Journal of Respiratory Cell and Molecular Biology.* 2011;44:285–292. doi: 10.1165/rcmb.2009-0400OC. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

89. Lim H. R., Kobzik L. Maternal transmission of asthma risk. *American Journal of Reproductive Immunology.* 2009;61:1–10. doi: 10.1111/j.1600-0897.2008.00671.x. [PubMed] [CrossRef] [Google Scholar]

90. Langlet C., Springael C., Johnson J., et al. PKC-alpha controls MYD88-dependent TLR/IL-1R signaling and cytokine production in mouse and human dendritic cells. *European Journal of Immunology.* 2010;40:505–515. doi: 10.1002/eji.200939391. [PubMed] [CrossRef] [Google Scholar]

91. Cejas P. J., Carlson L. M., Zhang J., et al. Protein kinase C betaII plays an essential role in dendritic cell differentiation and autoregulates its own expression. *The Journal of Biological Chemistry.* 2005;280:28412–28423. doi: 10.1074/jbc.M50345200. [PubMed] [CrossRef] [Google Scholar]
macrophages and dendritic cells, respectively. Journal of Cellular Biochemistry. 2007;102:429–441. doi: 10.1002/jcb.21305. [PubMed]  
[CrossRef] [Google Scholar]

93. Lin Y. F., Lee S. J., Huang H. M., Tsai Y. H. Selective activation of specific PKC isoforms dictating the fate of CD14(+) monocytes towards differentiation or apoptosis. Journal of Cellular Physiology. 2011;226:122–131. doi: 10.1002/jcp.22312. [PubMed] [CrossRef] [Google Scholar]

94. Asehounke N., Strassheim D., Mitra S., Yeol Kim J., Abraham E. Involvement of PKCalpha/beta in TLR4 and TLR2 dependent activation of NF-kappaB. Cellular Signalling. 2005;17:385–394. doi: 10.1016/j.cellsig.2004.08.005. [PubMed] [CrossRef] [Google Scholar]

95. Ramadan G., Schmidt R. E., Schubert J. In vitro generation of human CD86+ dendritic cells from CD34+ haematopoietic progenitors by PMA and in serum-free medium. Clinical and Experimental Immunology. 2001;125:237–244. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

96. Davis T. A., Saini A. A., Blair P. J., et al. Phorbol esters induce differentiation of human CD34+ hematopoietic progenitors to dendritic cells: evidence for protein kinase C-mediated signaling. Journal of Immunology. 1998;160:3693–3697. [PubMed] [CrossRef] [Google Scholar]

97. Rajotte D., Haddad P., Haman A., Cragoe E. J., Jr., Hoang T. Role of protein kinase C and the Na+/H+ antipporter in suppression of apoptosis by granulocyte macrophage colony-stimulating factor and interleukin-3. The Journal of Biological Chemistry. 1992;267:9980–9987. [PubMed] [CrossRef] [Google Scholar]

98. Salih B., Hoelflick K., Kwan W., Pelech S. Granulocyte-macrophage colony-stimulating factor and interleukin-3 potentiate interferon-gamma-mediated endothelin production by human monocytes: role of protein kinase C. Immunology. 1998;95:473–479. [PMC free article] [PubMed] [Google Scholar]

99. St Louis D. C., Woodcock J. B., Franzoso G., et al. Evidence for distinct intracellular signaling pathways in CD34+ progenitor to dendritic cell differentiation from a human cell line model. Journal of Immunology. 1999;162:3237–3248. [PubMed] [CrossRef] [Google Scholar]

100. Cejas P. J., Carlson L. M., Kolonia D., et al. Regulation of ReB expression during the initiation of dendritic cell differentiation. Molecular and Cellular Biology. 2005;25:7900–7916. doi: 10.1128/MCB.25.17.7900-7916.2005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

101. Farren M. R., Carlson L. M., Lee K. I. T. Lymph-mediated inhibition of dendritic cell differentiation is mediated by down regulation of protein kinase C beta II expression. Immunologic Research. 2010;46:165–176. doi: 10.1007/s12026-009-8118-5. [PubMed] [CrossRef] [Google Scholar]

102. Geijsen J., Spaargaren M., Raaijmakers J. A., Lammers J. W., Koenderman L., Coffer P. J. Association of RACK1 and PKCbeta with the common beta-chain of the IL-5/IL-3/GM-CSF receptor. Oncogene. 1999;18:5126–5130. doi: 10.1038/occ.2012896. [PubMed] [CrossRef] [Google Scholar]

103. Verdelli D., Nobili L., Todoerti K., et al. Molecular targeting of the PKC-beta inhibitor enzastaurin (LY371765) in multiple myeloma involves a coordinated downregulation of MYC and IRF4 expression. Hematological Oncology. 2009;27:23–30. doi: 10.1002/hon.875. [PubMed] [CrossRef] [Google Scholar]

104. Hamdorff M., Berger A., Schule S., Reinhardt J., Flory E. PKCdelta-induced PU.1 phosphorylation promotes hematopoietic stem cell differentiation to dendritic cells. Stem Cells. 2011;29:297–306. doi: 10.1002/stem.564. [PubMed] [CrossRef] [Google Scholar]

105. Lee J. S., Kim I. S., Ryu J. S., Yun C. Y. House dust mite, Dermatophagoides pteronissinus increases expression of MCP-1, IL-6, and IL-8 in human monocyteic THP-1 cells. Cytokine. 2001;42:385–386. doi: 10.1006/cyto.2008.03.010. [PubMed] [CrossRef] [Google Scholar]

106. Guler R., Afshar M., Arendse B., et al. PKCdelta regulates IL-12p40/p70 production by macrophages and dendritic cells, driving a type 1 healer phenotype in cutaneous leishmaniasis. European Journal of Immunology. 2011;41:706–715. doi: 10.1002/eji.201040985. [PubMed] [CrossRef] [Google Scholar]

107. McCoy C. A., Yoon Y., Panagabko C., Cho W., Atkinson J., Cook-Mills J. M. Vitamin E isoforms directly bind PKCalpha and differentially regulate activation of PKCalpha. The Biochemical Journal. 2012;441:189–198. doi: 10.1042/BJ20111318. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

108. Mahomboodally M. F., Gurib-Fakim A., Subratty A. H. Antimicrobial activities and phytochemical profiles of endemic medicinal plants of Mauritius. Pharmaceutical Biology. 2005;43(3):237–242. [Google Scholar]

109. Pandey A. K. Anti-staphylococcal activity of a pan-tropical aggressive and obnoxious weed Parthenium hysterophorus: an in vitro study. National Academy Science Letters. 2007;30(11-12):383–386. [Google Scholar]

110. Heim K. E., Tagliaferro A. R., Bobilya D. J. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. Journal of Nutritional Biochemistry. 2002;13(10):572–584. [PubMed] [CrossRef] [Google Scholar]

111. Kumar S., Mishra A., Pandey A. K. Antioxidant mediated protective effect of Parthenium hysterophorus against oxidative damage using in vitro models. BMC Complementary and Alternative Medicine. 2013;13, article 120 doi: 10.1186/1472-6882-13-120. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

112. Kumar S., Pandey A. K. Phenolic content, reducing power and membrane protective activities of Solanum xanthocarpum root extracts. Vegetos-An International Journal of Plant Research. 2013;26:301–307. doi: 10.5958/2229-4473.26.1.043. [CrossRef] [PubMed]

113. Leopoldini M., Russo N., Chiodo S., Toscano M. Iron chelation by the powerful antioxidant flavonoid quercetin. Journal of Agricultural and Food Chemistry. 2006;54(17):6343–6351. doi: 10.1021/jf060986h. [PubMed] [CrossRef] [Google Scholar]

114. Kumar S., Gupta A., Pandey A. K. Cotropis procerus root extract has capability to combat free radical mediated damage. ISRN Pharmacology. 2013;2013:8. doi: 10.1155/2013/691372.6913722 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

115. Cook N. C., Samman S. Review: flavonoids-chemistry, metabolism, cardioprotective effects and dietary sources. Journal of Nutritional Biochemistry. 1996;7(2):66–76. [Google Scholar]

116. Rice-Evans C. A., Miller N. J., Bolwell P. G., Broamley P. M., Pridham J. B. The relative antioxidant activities of plant-derived polyphenolic flavonoids. Free Radical Research. 1995;25(4):375–383. [PubMed] [CrossRef]

117. Pandey A. K., Mishra A. K., Mishra A. Antifungal and antioxidative potential of oil and extracts derived from leaves of Indian spice plant Cinnamonum tamala. Cellular and Molecular Biology. 2012;58:142–147. [PubMed] [Google Scholar]

118. Hallibew B., Gutteridge J. M. C. Free Radicals in Biology and Medicine. Oxford, UK: Oxford University Press; 1998. [Google Scholar]

119. Mishra A., Kumar S., Pandey A. K. Scientific validation of the medicinal efficacy of Tinospora cordifolia. The Scientific World Journal. 2013;2013:8. doi: 10.1155/2013/292934.292934 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

120. Ganai A. A., Khan A. A., Malik Z. A., Farooqi H. Genistean modulates the expression of NF-κB and MAPK (p-38 and ERK1/2), thereby attenuating d-galactosamine induced fulminant hepatic failure in Wistar rats. Toxicology and Applied Pharmacology. 2015;283:139–146. doi: 10.1016/j.taap.2015.01.012. [PubMed] [CrossRef] [Google Scholar]
121. Clarkson T. B., Anthony M. S., Morgan T. M. Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens. The Journal of Clinical Endocrinology and Metabolism. 2001;86:41–47. doi: 10.1210/jc.6.8.1715. [PubMed] [CrossRef] [Google Scholar]

122. Adams M. R., Golden D. L., Williams J. K., Franke A. A., Register T. C., Kaplan J. R. Soy protein containing isoflavones reduces the size of atherosclerotic plaques without affecting coronary artery reactivity in adult male monkeys. The Journal of Nutrition. 2005;135:2852–2856. [PubMed] [Google Scholar]

123. Yamakoshi J., Piskula M. K., Izuimi T., et al. Isoflavone aglycone-rich extract without soy protein attenuates atherosclerosis development in cholesterol-fed rabbits. The Journal of Nutrition. 2000;130:1887–1893. [PubMed] [Google Scholar]

124. Kanazawa T., Osanai T., Zhang X. S., et al. Protective effects of soy protein on the peroxidizability of lipoproteins in cerebrovascular diseases. The Journal of Nutrition. 1995;125:695S–646S. [PubMed] [Google Scholar]

125. Tikkolen M., Wahala K., Ojala S., Vihrma V., Adlercreutz H. Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance. Proceedings of the National Academy of Sciences of the United States of America. 1998;95:3106–3110. [PMC free article] [PubMed] [Google Scholar]

126. Wiseman H., O'Reilly J. D., Adlercreutz H., et al. Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. The American Journal of Clinical Nutrition. 2000;72:395–400. [PubMed] [Google Scholar]

127. Ryan-Borchers T. A., Park J. S., Chew B. P., McGuire M. K., Fournier L. R., Beerman K. A. Soy isoflavones modulate immune function in healthy postmenopausal women. The American Journal of Clinical Nutrition. 2006;83:1118–1125. [PubMed] [Google Scholar]

128. Hodgson J. M., Muddey I. B., Crotte C. D., Mori T. A., Rivera J., Bellin L. J. Isoflavonoids do not inhibit in vivo lipid peroxidation in subjects with high-normal blood pressure. Atherosclerosis. 1999;145:167–172. [PubMed] [Google Scholar]

129. Samman S., Lyons Wall P. M., Chan G. S., Smith S. J., Petocz P. The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women. Atherosclerosis. 1999;147:277–283. [PubMed] [Google Scholar]

130. Vega-Lopez S., Yeum K. J., Lecker J. L., et al. Plasma antioxidant capacity in response to diets high in soy or animal protein with or without isoflavones. The American Journal of Clinical Nutrition. 2005;81:1–39. [PubMed] [Google Scholar]

131. Choi C., Cho J., Park J., Cho C., Song Y. Suppressive effects of genistein on oxidative stress and NFκB activation in RAW 264.7 macrophages. Bioscience, Biotechnology, and Biochemistry. 2003;67:1916–1922. doi: 10.1271/bbb.67.1916. [PubMed] [CrossRef] [Google Scholar]

132. Naidu K. A. Vitamin C in human health and disease is still a mystery? An overview. Nutrition Journal. 2003;2.p. 7. doi: 10.1186/1475-2891-2-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

133. Crott J. W., Fenech M. Effect of vitamin C supplementation on chromosome damage, apoptosis and necrosis ex vivo. Carcinogenesis. 1999;20(6):1035–1041. [PubMed] [Google Scholar]

134. Carr A. C., Frei B. Does vitamin C act as pro-oxidant under physiological conditions? FASEB Journal. 1999;13:1007–1024. [PubMed] [Google Scholar]

135. Suzuki K., Koike H., Matsui H., et al. Genistein, a soy isoflavone, induces glutathione peroxidase in the human prostate cancer cell line LNCaP and PC-3. International Journal of Cancer. 2000;92:846–852. doi: 10.1002/(SICI)1097-0215(20001110)92:5<846::AID-IJC5>3.0.CO;2-U. [PubMed] [CrossRef] [Google Scholar]

136. Raschke M., Rowland I. R., Magee P. J., Pool-Zobel B. L. Genistein protects prostate cells against hydrogen peroxide-induced DNA damage and induces expression of genes involved in the defence against oxidative stress. Carcinogenesis. 2006;27:2322–2330. doi: 10.1093/carcin/bgl082. [PubMed] [CrossRef] [Google Scholar]

137. Takada Y., Mukhopadhyay A., Kundu G. C., Mahabeleswar G. H., Singh S., Aggarwal B. B. Hydrogen peroxide activates NF-kappa B through tyrosine phosphorylation of I kappa B alpha and serine phosphorylation of p65: evidence for the involvement of I kappa B alpha kinase and Syk protein tyrosine kinase. Journal of Biological Chemistry. 2003;278(26):24233–24241. doi: 10.1074/jbc.M212892200. [PubMed] [CrossRef] [Google Scholar]

138. Haraksh S., Diab-Assaf M., Khalfih J. C., et al. Ascorbic acid induces apoptosis in adult T-cell leukemia. Anticancer Research. 2007;27(1A):289–298. [PubMed] [Google Scholar]

139. Nakano H., Nakajima A., Sakon-Comazawa S., Piao J. H., Xue X., Okumura K. Reactive oxygen species mediate crosstalk between NF-kappaB and JNK. Cell Death and Differentiation. 2006;13(5):730–777. doi: 10.1038/sj.cdd.4401830. [PubMed] [CrossRef] [Google Scholar]

140. Belin S., Kaya F., Duist G., Giacometti S., Ciccioni J., Fontès M. Antiproliferative effect of ascorbic acid is associated with the inhibition of genes necessary to cell cycle progression. PLoS One. 2009;4(2) doi: 10.1371/journal.pone.0004409. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

141. Migliozzi J. A. Effect of ascorbic acid on tumour growth. British Journal of Cancer. 1977;35p. 448. [PMC free article] [PubMed] [Google Scholar]

142. Kishino K., Hashimoto K., Amano O., Koshi M., Liu W., Sakagami H. Tumor-specific cytotoxicity and type of cell death induced by sodium 5,6-benzylidene-l-ascorbate. Anticancer Research. 2008;28:2577–2584. [PubMed] [Google Scholar]

143. Chen Q., Espey M. G., Sun A. Y., et al. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. Proceedings of the National Academy of Science. 2008;105(32):11105–11109. doi: 10.1073/pnas.0804226105. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

144. Chen Q., Espey M. G., Sun A. Y., et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. Proceedings of the National Academy of Science. 2007;104(21):8749–8754. doi: 10.1073/pnas.0702865104. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

145. Richardson D. R., Ponka P. The molecular mechanisms of the metabolism and transport of iron in normal and neoplastic cells. Biochimica et Biophysica Acta. 1997;1331(1):1–40. [PubMed] [CrossRef] [Google Scholar]

146. Hann H. W., Evans A. E., Siegel S. E., et al. Prognostic importance of serum ferritin in patients with stages III and IV neuroblastoma: the Children's Cancer Study Group experience. Cancer Research. 1985;45(6):2843–2848. [PubMed] [Google Scholar]

147. Shen L., Zhao H. Y., Dui J., Wang F. Anti-tumor activities of four chelating agents against human neuroblastoma cells. In Vivo. 2005;19(1):233–236. [PubMed] [Google Scholar]

148. Chen Q., Espey M. G., Krishna M. C., et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. Proceedings of the National Academy of Science. 2005;102(38):13604–13609. doi: 10.1073/pnas.0506390102. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
149. Bhat S. H., Azmi A. S., Harif S., Hadi S. M. Ascorbic acid mobilizes endogenous copper in human peripheral lymphocytes leading to oxidative DNA breakage: a putative mechanism for anticancer properties. *International Journal of Biochemistry and Cell Biology.* 2006;38:2074–2081. doi: 10.1016/j.biocel.2006.05.017. [PubMed] [CrossRef] [Google Scholar]

150. Kinoshita N., Yamamura T., Teranuma H., et al. Interaction between dental metals and antioxidants assessed by cytotoxicity assay and ESR spectroscopy. *Anticancer Research.* 2002;22:4017–4022. [PubMed] [Google Scholar]

151. Sakagami H., Arakawa H., Haeda M., et al. Production of hydrogen peroxide and methionine sulfoxide by epigallocatechin gallate and antioxidants. *Anticancer Research.* 2001;21:2633–2642. [PubMed] [Google Scholar]

152. Vojdani A., Bazargan M., Vojdani E., Wright J. New evidence for antioxidant properties of vitamin C. *Cancer Detection and Prevention.* 2000;24(6):508–523. [PubMed] [Google Scholar]

153. Kelley E. E., Domann F. E., Buettner G. R., Oberley L. W., Patrick Burns C. Increased efficiency of in vitro Photofrin photosensitization of human oral squamous cell carcinoma by iron and ascorbate. *Journal of Photochemistry and Photobiology B: Biology.* 1997;40:273–277. [PubMed] [Google Scholar]

154. Noto V., Taper H. S., Jiang Y.-H., Janssens J., Bonte J., De Loecker W. Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. 1. Synergism of combined vitamin C and K3 action. *Cancer.* 1989;63:901–906. [PubMed] [Google Scholar]

155. Leveille C. R., Schwartz E. R. Effect of ascorbate on lysosomal enzyme activities in guinea pig cartilage and adrenals. *International Journal for Vitamin and Nutrition Research.* 1982;52:436–441. [PubMed] [Google Scholar]

156. Harada T., Enomoto A., Kitazawa T., Maita K., Shirasu Y. Oral leukoplakia and costochondral hyperplasia induced by diethylaminoethylamine in hamsters exposed to cigarette smoke with or without dietary vitamin C. *Veterinary Pathology.* 1987;24.p. 257. doi: 10.1177/03009858702400310. [PubMed] [CrossRef] [Google Scholar]

157. Prochazkova D., Bousova L., Wilhelmina N. Antioxidant and prooxidant properties of flavonoids. *Fitoterapia.* 2011;82:513–523. doi: 10.1016/j.fitote.2011.01.018. [PubMed] [CrossRef] [Google Scholar]

158. Park E. J., Pezzuto J. M. Flavonoids in cancer prevention. *Anti-Cancer Agents in Medicinal Chemistry.* 2012;12:836–851. [PubMed] [Google Scholar]

159. Hodnick W. F., Milosavljevic E. B., Nelson J. H., Pardini R. S. Electrochemistry of flavonoids. Relationships between redox potentials, inhibition of mitochondrial respiration, and production of oxygen radicals by flavonoids. *Biochemical Pharmacology.* 1988;37:2607–2611. [PubMed] [Google Scholar]

160. Choi S. I., Jeong C. S., Cho S. Y., Lee Y. S. Mechanism of apoptosis induced by apigenin in HepG2 human hepatoma cells: involvement of reactive oxygen species generated by NADPH oxidase. *Archives of Pharmacal Research.* 2007;30:1328–1335. [PubMed] [Google Scholar]

161. Lee Y. S. Role of NADPH oxidase-mediated generation of reactive oxygen species in the mechanism of apoptosis induced by phenolic acids in HepG2 human hepatoma cells. *Archives of Pharmacal Research.* 2005;28:1183–1189. [PubMed] [Google Scholar]

162. Alhosin M., Leon-Gonzalez A. J., Dandache I., et al. Bilberry extract (Antho 50) selectively induces redox-sensitive caspase 3-related apoptosis in differentiated counterparts. *Journal of Asian Natural Products Research.* 2010;12:158–168. doi: 10.1080/10286020903427336. [PubMed] [CrossRef] [Google Scholar]

163. Kim J. H., Auger C., Kurita I., et al. Aronia melanocarpa juice, a rich source of polyphenols, induces endothelium-dependent relaxations in porcine coronary arteries via the redox-sensitive activation of endothelial nitric oxide synthase. *Nitric Oxide: Biology and Chemistry.* 2013;35:54–64. doi: 10.1016/j.niox.2013.08.002. [PubMed] [CrossRef] [Google Scholar]

164. Sharif T., Stamboul M., Burrus B., et al. The polyphenolic-rich Aronia melanocarpa juice kills teratocarcinomal cancer stem-like cells, but not their differentiated counterparts. *Journal of Functional Foods.* 2013;5:1244–1252. [PubMed] [Google Scholar]

165. Wang J., Lu M. L., Dai H. L., Zhang S. P., Wang H. X., Wei N. Esculetin, a coumarin derivative, exerts in vitro and in vivo antiproliferative activity against hepatocellular carcinoma by initiating a mitochondrial-dependent apoptosis pathway. *Brazilian Journal of Medical and Biological Research.* 2015;48:245–253. doi: 10.1590/1414-431X20144074. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

166. Yang J., Xiao Y. L., He X. R., Qiu G. F., Hu X. M. Aesculetin-induced apoptosis through a ROS-mediated mitochondrial dysfunction pathway in human cervical cancer cells. *Journal of Asian Natural Products Research.* 2010;12:185–193. doi: 10.1080/10286020903427336. [PubMed] [CrossRef] [Google Scholar]

167. Liang T., Zhang X., Xue W., Zhao S., Zhang X., Pei J. Curcumin induced human gastric cancer BGC-823 s apoptosis by ROS-mediated ASK1-MKK4-JNK stress signaling pathway. *International Journal of Molecular Sciences.* 2014;15:15754–15765. doi: 10.3390/ijms150915754. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

168. Lambert J. D., Elias R. J. The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention. *Archives of Biochemistry and Biophysics.* 2010;501:65–72. doi: 10.1016/j.abb.2010.06.013. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

169. Hwang J. T., Ha J., Park I. J., et al. Apoptotic effect of EGCG in HT-29 colon cancer cells via AMPK signal pathway. *Cancer Letters.* 2007;247:115–121. doi: 10.1016/j.canlet.2006.03.030. [PubMed] [CrossRef] [Google Scholar]

170. Oikawa S., Furukawa A., Asada H., Hirakawa K., Kawanishi S. Catechins induce oxidative damage to urol and isolated DNA through the generation of reactive oxygen species. *Free Radical Research.* 2003;37:881–890. [PubMed] [Google Scholar]

171. Palit S., Kar S., Sharma G., Das P. K. Hesperetin induces apoptosis in breast carcinoma by triggering accumulation of ROS and activation of ASK1/JNK pathway. *Journal of Cellular Physiology.* 2015;230:1729–1739. doi: 10.1002/jcp.24818. [PubMed] [CrossRef] [Google Scholar]

172. Zhang Q., Cheng G., Qiu H., et al. The p53-inducible gene 3 involved in flavonoid-induced cytotoxicity through the reactive oxygen species-mediated mitochondrial apoptotic pathway in human hepatoma cells. *Food & Function.* 2015;6:1518–1525. doi: 10.1039/c5fo00142k. [PubMed] [CrossRef] [Google Scholar]

173. Kim G. T., Lee S. H., Kim Y. M. Quercetin regulates sestrin 2-AMPK-mTOR signaling pathway and induces apoptosis via increased intracellular ROS in HCT116 Colon cancer cells. *Journal of Cancer Prevention.* 2013;18:264–270. [PMC free article] [PubMed] [Google Scholar]

174. Iwasaki M., Inoue M., Otani T., et al. Plasma isoflavone level and subsequent risk of breast cancer among Japanese women: a nested case-control study from the Japan Public Health Center-based prospective study group. *Journal of Clinical Oncology.* 2008;26:1677–1683. doi: 10.1200/JCO.2007.13.9984. [PubMed] [CrossRef] [Google Scholar]

175. Jin S., Zhang Q. Y., Kang X. M., Wang J. X., Zhao W. H. Daidzein induces MCF-7 breast cancer cell apoptosis via the mitochondrial...
pathway. *Annals of Oncology*. 2010;21:263–268. doi: 10.1093/annonc/mdp499. [PubMed] [CrossRef] [Google Scholar]

176. Lo Y.-L., Wang W., Ho C. T., 7,3’-4’-[Thiroydroxyisoflavone modulates multidrug resistance transporters and induces apoptosis via production of reactive oxygen species. *Toxicology*. 2012;302:221–232. doi: 10.1016/j.tox.2012.08.003. [PubMed] [CrossRef] [Google Scholar]

177. Yang X. J., Belosay A., Hartman J. A., et al. Dietary soy isoflavones increase metastasis to lungs in an experimental model of breast cancer with bone micro-tumors. *Clinical & Experimental Metastasis*. 2015;32:323–333. doi: 10.1007/s10585-015-9709-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

178. Rakshit S., Mandal L., Fal B. C., et al. Involvement of ROS in chlorogenic acid-induced apoptosis of Bcr-Abl+ CML cells. *Biochemical Pharmacology*. 2010;80:1662–1675. doi: 10.1016/j.bcp.2010.08.013. [PubMed] [CrossRef] [Google Scholar]

179. Kim K. K., Singh A. P., Singh R. K., et al. Anti-angiogenic activity of cranberry proanthocyanidins and cytotoxic properties in ovarian cancer cells. *International Journal of Oncology*. 2012;40:227–235. doi: 10.3892/ijo.2011.1198. [PubMed] [CrossRef] [Google Scholar]

180. Luo C., Li Y., Wang H., et al. Hydroxytyrosol promotes superoxide production and defects in autophagy leading to anti-apoptosis and proliferation on human prostate cancer cells. *Current Cancer Drug Targets*. 2013;13:625–639. [PubMed] [CrossRef] [Google Scholar]

181. Sun L. J., Luo C., Liu J. K. Hydroxytyrosol induces apoptosis in human colon cancer cells through ROS generation. *Food & Function*. 2014;5:1909–1914. doi: 10.1039/c4fo00187g. [PubMed] [CrossRef] [Google Scholar]

182. Guha P., Dey A., Sen R., Chattjee M., Chattopadhyay S., Bandyopadhyay S. K. Intracellular GSH depletion triggered mitochondrial Bax translocation to accomplish resveratrol-induced apoptosis in the U937 cell line. *The Journal of Pharmacology and Experimental Therapeutics*. 2011;336:206–214. doi: 10.1124/jpet.110.171983. [PubMed] [CrossRef] [Google Scholar]

183. Alhosin M., Sharif T., Moussal M., et al. Down-regulation of UHRF1, associated with re-expression of tumor suppressor genes, is a common feature of natural compounds exhibiting anti-cancer properties. *Journal of Experimental & Clinical Cancer Research*. 2011;30: doi: 10.1186/1756-9966-30-41. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

184. Achour M., Moussi M., Alhosin M., et al. Epigallocatechin-3-gallate up-regulates tumor suppressor gene expression via a reactive oxygen species-dependent down-regulation of UHRF1. *Biochemical and Biophysical Research Communications*. 2013;430:208–212. doi: 10.1016/j.bbrc.2012.11.087. [PubMed] [CrossRef] [Google Scholar]

185. Kang J., Chen J., Shi Y., Jia J., Zhang Y. Curcumin-induced histone hypoacetylation: the role of reactive oxygen species. *Biochemical Pharmacology*. 2005;69:1205–1213. doi: 10.1016/j.bcp.2005.01.014. [PubMed] [CrossRef] [Google Scholar]

186. Rajendran P., Ho E., Williams D. E., Dashwood R. H. Dietary phytochemicals, HDAC inhibition, and DNA damage/repair defects in cancer cells. *Clinical Epigenetics*. 2011;3:4. doi: 10.1186/1688-7083-3-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

187. Remely M., Lovrecic L., de la Garza A. L., et al. Therapeutic perspectives of epigenetically active nutrients. *British Journal of Pharmacology*. 2015;159:2756–2768. doi: 10.1111/bph.12854. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

188. Vanden Berghe W. Epigenetic impact of dietary polyphenols in chemoprevention: lifelong remodeling of our epigenomes. *Pharmaceutical Research*. 2012;29:565–576. doi: 10.1007/s11095-012-0799-6. [PubMed] [CrossRef] [Google Scholar]

189. Malireddy S., Kotha S. R., Secor J. D., et al. Phytochemicals modulate mammalian uro epigenome: implications in health and disease. *Antioxidants & Redox Signaling*. 2012;17:327–339. doi: 10.1089/ars.2012.4600. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

190. Ong T. P., Moreno F. S., Ross S. A. Targeting the epigenome with bioactive food components for cancer prevention. *Journal of Nutrigenetics and Nutrigenomics*. 2011;4:275–292. doi: 10.1159/000334585. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

191. Nakazato T., Ito K., Miyakawa Y., et al. Catechin, a green tea component, rapidly induces apoptosis of myeloid leukemic cells via modulation of reactive oxygen species production in vitro and inhibits tumor growth in vivo. *Haematologica*. 2005;90:317–325. [PubMed] [CrossRef] [Google Scholar]

192. Jeong J. C., Jang S. W., Kim T. H., Kim Y. K. Mulberry fruit (Morus fructus) extracts induce human glioma cell death in vitro through ROS-dependent mitochondrial pathway and inhibits glioma tumor growth in vivo. *Nutrition and Cancer*. 2010;62:402–412. doi: 10.1080/01635580903441287. [PubMed] [CrossRef] [Google Scholar]

193. Dent P., Yacoub A., Contessa J., et al. Stress and radiation-induced activation of multiple intracellular signaling pathways. *Radiation Research*. 2003;159(3):283–300. [PubMed] [CrossRef] [Google Scholar]

194. Mladenov E., Magin S., Soni A., Ilakis G. DNA double-strand-break repair in higher eukaryotes and its role in genomic instability and cancer: cell cycle and proliferation-dependent regulation. *Seminars in Cancer Biology*. 2016;37-38:51–64. doi: 10.1016/j.semcancer.2016.03.003. [PubMed] [CrossRef] [Google Scholar]

195. Roos W. P., Thomas A. D., Kaina B. DNA damage and the balance between survival and death in cancer biology. *Nature Reviews Cancer*. 2016;16(1):20–33. doi: 10.1038/nrc.2015.2. [PubMed] [CrossRef] [Google Scholar]

196. Ward J. F. DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. *Progress in Nucleic Acid Research and Molecular Biology*. 1988;35:95–125. [PubMed] [Google Scholar]

197. O’Driscoll M., Jeggo P. A. The role of double-strand break repair—insights from human genetics. *Nature Reviews Genetics*. 2006;7(1):45–54. doi: 10.1038/ng1746. [PubMed] [CrossRef] [Google Scholar]

198. Jackson S. P., Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461(7267):1071–1078. doi: 10.1038/nature08467. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

199. Tubiana M. The role of local treatment in the cure of cancer. *European Journal of Cancer*. 1992;28A:2061–2069. [PubMed] [Google Scholar]

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