Abstract: Aging is a complex process mainly categorized by a decline in tissue, cells and organ function and an increased risk of mortality. Recent studies have provided evidence that suggests a strong association between epigenetic mechanisms throughout an organism's lifespan and age-related disease progression. Epigenetics is considered an evolving field and regulates the genetic code at several levels. Among these are DNA changes, which include modifications to DNA methylation state, histone changes, which include modifications of methylation, acetylation, ubiquitination and phosphorylation of histones, and non-coding RNA changes. As a result, these epigenetic modifications are vital targets for potential therapeutic interventions against age-related deterioration and disease progression. Dietary polyphenols play a key role in modulating these modifications thereby delaying aging and extending longevity. In this review, we summarize recent advancements linking epigenetics, polyphenols and aging as well as critical findings related to the various dietary polyphenols in different fruits and vegetables. In addition, we cover studies that relate polyphenols and their epigenetic effects to various aging-related diseases such as cardiovascular diseases, neurodegenerative diseases, autoimmune disorders, diabetes, osteoporosis and cancer.

Keywords: aging; DNA methylation; histone modifications; non-coding RNAs and polyphenols

1. Introduction

Aging is an intricate biological process that causes changes in the normal function of an organism throughout its lifetime [1–3]. Both genetic and non-genetic factors, which include environmental factors, are implicated in aging by causing structural and molecular modifications at cellular, tissue, and organ levels [4,5]. Numerous animal models have served as a baseline to identify mutations in key genes and the pathways which thereby contribute to aging. For instance, studies have identified that genetic factors such as mutations in mitochondrial DNA cause a decline in somatic stem cell function and lead to mammalian aging [6]. A role of mitochondrial aging was reported in Caenorhabditis elegans (free-living transparent nematode living in temperate soil environment and about 1 mm in length) wherein decreased activity of the electron transport chain and adenosine 5'-triphosphate (ATP) synthase resulted into both reduction in body size and increased lifespan [7]. Another biochemical process, oxidative stress/damage (OS) plays a critical role in mammalian aging. Experiments on mouse
(Mus musculus) found advantageous effects of dietary-based caloric restriction (CR) on brain function and lifespan based on its ability to reduce OS levels [8]. OS arises due to various environmental factors such as metabolic processing of consumed food products with high caloric intake [9] and natural toxic chemicals found in plants [10]. During the process of aging, reactive oxygen species (ROS) produced inside the biotic system induces changes in cellular activities such cell survival thereby inducing OS and inflammatory responses [11,12]. Therefore, increased ROS production and proper functioning of antioxidant defense mechanisms protecting the cells from oxidative damage are endogenous mechanisms in aging-related diseases [13]. Other non-genetic elements such as an unhealthy diet, smoking, alcohol or drug abuse and exposure to noxious chemicals also contribute to ROS mediated aging [14]. In the past, studies have emphasized on numerous health benefits related to the consumption of bioactive compounds on an organism’s health in extending the lifespan and delaying aging.

For instance, studies have examined the effect of dietary polyphenols such as green tea polyphenols (GTPs) on damage to neuronal biomolecules associated with OS and ROS, which are generated during metabolism in neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) [15]. Polyphenols are secondary metabolites of plants found in fruits, vegetables, and certain beverages which possess strong antioxidant properties and protect against various pathogens [16]. Polyphenols-associated studies are primarily based on their ability to affect critical regulatory molecules involved in various diseases such as cancer [17]. Specifically, dietary polyphenols possess an ability to modulate biological states associated with OS and chronic inflammation that may be primary contributors to different types of cancers including cervical, ovarian and breast cancer. Various studies have also demonstrated the dynamic role of polyphenols in the suppression of inflammation related to cancer development [18]. For instance, a study in Mus musculus showed the beneficiary effects of GTPs such as epigallocatechin gallate (EGCG) on ultraviolet based (UVB) induced skin tumors. Additionally, the administration of EGCG in wild type mice led to a decline in levels of inflammation markers such as cyclooxygenase-2 (COX-2) and prostaglandin-E2 associated with tumor development [19].

In addition, other nutrients and bioactive polyphenols such as resveratrol (RES), curcumin (CUR) and quercetin also have a substantial impact on the aging process in different organisms [20]. Figure 1 illustrates numerous aging-related diseases such as cancer [21], neurodegenerative diseases [22], nephrosclerosis, arthritis and cardiovascular diseases [23] caused by a number of genetic and non-genetic factors.

Although aging and age-related diseases are associated with profound changes in epigenetic patterns, less is known about the role of dietary polyphenols in extending lifespan through alterations in epigenetics machinery. Therefore, understanding the epigenetic link between polyphenols and aging is a growing area of research and will provide deeper insight into the development of novel approaches influencing longevity and aging. Hence, this review will focus on understanding the influence of dietary polyphenols on epigenetic modulations and how these changes in-turn impact aging and longevity. Additionally, this review will also provide aggregate information on various studies related to influence of dietary polyphenols and epigenetic modifications in age-related diseases. In this review, the term epigenetics will be used broadly, highlighting the genomic alterations contributing to DNA methylation patterns, histone modifications and non-coding RNAs (ncRNAs).
2. Dietary Polyphenols

Depending on their number of classes of phenolic rings, polyphenols are classified into distinctive groups which comprise structural elements that allow these rings to bind to each another. Phenolic acids, flavonoids, stilbenoids and lignans are principal classes of polyphenols [24]. Phenolic acids are found in vegetables, fruits, cereals, olives, legumes and beverages such as coffee and tea. Phenolic acids are classified into two major classes based on benzoic acid byproducts (such as gallic acid and egallic acid) and cinnamic acid byproducts (such as caffeic acid and ferulic acid). Due to their wide availability in different sources, phenolic acid exhibits various antioxidant [25], anti-inflammatory [26] and anti-cancerous properties [27].

Flavonoids, another classes of polyphenols, are comprised of 2 aromatic rings that are bound together by 3 carbon atoms and are sub-categorized into flavonols, flavones, flavanones, isoflavones, anthocyanidins and flavanols [28]. Flavanones are widely distributed in citrus fruits (such as orange and lemon) and possess positive cardioactive properties [29]. Flavanols are another class of flavonoids that are widely distributed in different fruits and vegetables such as onions, tea, grapes skin, apple, blueberries and wine [30]. Unlike flavonoids, flavones are less abundant and mainly found in celery [31] and parsley [32]. Additionally, flavanones are mainly found in high concentrations in tomatoes [33] and citrus fruits [34]. Overall, flavonoids exhibit various antioxidant [35], anti-inflammatory [36] and anti-cancerous properties [37]. For instance, myricetin, a plant based flavonoid beholds antioxidant, anti-inflammatory and anti-cancerous properties against numerous diseases such as cardiovascular diseases and cancer [38]. A study reported that the anti-oxidative property of myricetin reacted 28-times faster with oxygen-centered galvinoxyl radicals in comparison to d-α-tocopherol (ATF), a lipid-soluble antioxidant found in biological membranes. However, the compound was incapable of preventing vitamin E-deficient microsomes from lipid peroxidation [39]. Investigations have also reported that administration of myricetin in combination with other antioxidants such as vitamins C or E in murine melanoma B16F10 cells can induce increased catalase (CAT) activity and decrease superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities [40].
Stilbenoids are another class of polyphenols which are often found in various plant families such as dipterocarpaceae, gnetaceae and fabaceae [41]. RES, pterostilbene (PTER), piceatannol and gnetol are major stilbenoids which exhibit various protective properties against cardiovascular diseases, cancer, atherosclerosis and diabetes by [42]. Besides stilbenoids, lignans are another class of polyphenols, mainly found in tea, coffee and olive oil that also possess anti-cancerous, and antioxidant properties [43–45]. Table 1 summarizes various classifications of polyphenols, their major sources, their relative content within these sources, and proposed molecular functions [46].

Table 1. List of different classes of polyphenols, primary sources, their content based on weight and serving and their respective molecular functions.

| Polyphenols | Polyphenol Source | Polyphenol Content Based on Weight or Volume (mg/kg wt or mg/L) | Molecular Functions | References |
|-------------|-------------------|-------------------------------------------------------------|-------------------|-----------|
| Phenolic acids/Hydroxybenzoic acids | | | | |
| Gallic acid | Berries, pineapples, bananas, lemons and wines | 40–130 | Anti-oxidative, pro-oxidative, anti-inflammatory, antibacterial, antiviral, anti-melanogenic, anti-invasive and anti-proliferative | [47–51] |
| Ellagic acid | Berries, pomegranate, walnuts and pecans | | Anti-oxidative, anti-inflammatory, anti-angiogenic, antimeetastatic, anti-proliferative and anti-invasive | [47,52,53] |
| Phenolic acids/Hydroxycinnamic acids | | | | |
| Caffeic acid | Kiwifruit | 600–1000 | Anti-diabetic, anti-carcinogenic, protective effects against UVB-induced skin damage, interleukin-10 and activation of mitogen-activated protein kinase (MAPK) | [54–56] |
| Rosmarinic acid | Herbs | | Anti-oxidative, reduction of HCA formation and modulation of epigenetic changes | [47,53,57] |
| Ferulic acid | Aubergine | 600–660 | Anti-oxidative, anti-inflammatory, antibacterial, antimicrobial, anti-allergic, hepatoprotective and antiviral | [58] |
| Chlorogenic acid | Cherry | 180–1150 | Anti-oxidative, antimicrobial, anti-inflammatory, analgesic and antipyretic | [59,60] |
| Flavonoids | | | | |
| Myricetin | Broccoli | 40–100 | Anti-oxidative, anti-inflammatory, anti-allergic, analgesic, hepatoprotective and hypouricemic activities, anti-diabetic and anti-obesity properties | [61–65] |
| EGCG | Tea, apples, grapes, berries, red wine and chocolate | | Anti-oxidative, anti-proliferative, suppression of growth and invasion, antiangiogenic, anti-inflammatory, inhibition of telomerase activity and lipid peroxidation and modulation of estrogen activity | [66–71] |
| Apigenin | Grapefruit, parsley, onion, orange, tea and wheat | 20–140 | Anti-oxidative, anti-mutagenic, anti-inflammatory, anti-viral, inhibition of tumor growth, anti-invasive, and anti-proliferative | [48,72–74] |
| Quercetin | Onions, broccoli, apples, apricots, berries, nuts, seeds, tea, wine and coca | | Anti-oxidative, tumor inhibition, anti-proliferative, antimetastatic, anti-angiogenic and inhibition of lipid peroxidation | [67,70–72,75–77] |
| Genistein | Miso | 250–900 | Anti-oxidative, anti-invasive, anti-inflammatory, anti-metastatic, delay/repression of tumor development/growth and anti-proliferative | [67,70–72] |
| Stilbenes | | | | |
| RES | Red wine, grapes, berries and peanuts | | Anti-oxidative, anti-inflammatory, anti-proliferative and anti-estrogenic | [75,77,78,80–82] |
| PTER | | | Anti-oxidative, anti-inflammatory, anti-proliferative and modulation of lipid metabolism | [75,77,78,80–82] |

EGCG—Epigallocatechin gallate, RES—Resveratrol, PTER—Pterostilbene.
3. The Link between Epigenetics and Aging

The term epigenetics is associated with specific gene expression patterns observed during heritable changes due to mitotic and meiotic activities which affect multiple processes such as cell development, cell differentiation and X-chromosome inactivation. The key reason for understanding and defining epigenetics is to illuminate specific epigenetics changes that occur during aging and to also comprehend whether the changes depend on genetic, environmental or stochastic factors [83]. Epigenetic modifications are comprised of DNA methylation, histone post-transcriptional modifications such as methylation, acetylation, ubiquitination and phosphorylation and ncRNAs. These alterations play a vital role in the healthy development of an organism as they are crucial for various biological processes such as transcription, cell division, DNA replication and many others. Therefore, the overall stability of epigenetic mechanisms is crucial for maintenance of proper molecular activity, which reduces the possibility of various diseases and further delays the aging process [84].

3.1. DNA Methylation and Aging

Methylation at cytosine residues serves as a pivotal epigenetic factor that modulates gene expression in various organisms. These changes occur as a result of de novo DNA methyltransferases (DNMTs) enzymes activity which are primarily responsible for transferring methyl group to 5 carbon position of cytosine [85]. Numerous experiments have revealed that there is a significant decrease in global 5-methylcytosine (5mC) during ontogenesis. For instance, in 1967, it was discovered that an overall reduction of 5mC level occurs during ontogenesis at different stages in humpback salmon [86]. One study in humans (Homo sapiens) identified aging-associated DNA methylation changes at CpG sites (DNA regions wherein cytosine nucleotide is followed by guanine nucleotide in a linear sequence of bases in the 5’ → 3’ direction) in different tissues such as blood, brain and kidney. The study reported that tissue-specific age-associated CpGs (ageCGs) decreased methylation and are localized outside CpG islands. Unlike, tissue-specific ageCGs, common ageCGs induces increased methylation and are primarily situated inside the CpG islands [87].

Currently, DNA methylation during aging occurs due to two contradicting phenomena consisting of epigenetic drift and the epigenetic clock. The epigenetic clock is built based on supervised machine learning methods which aim to identify epigenetic methylation changes that are closely related to chronological age. The supervised machine learning approach helps to determine informative CpGs for age prediction thereby associating DNA methylation (DNAm) levels to age estimates [88,89]. The age estimators, also known as “clock CpGs”, are associated with a mathematical algorithm based on a Pearson correlation coefficient (r) referring to “age correlation” and median error that calculates the absolute difference between the chronological age and biological age. These coefficients surpass a confidence interval (CI) of 95% within multiple tissues for individuals with their ages within 0-100 years [90]. The age estimator evaluates the DNAm age (also known as epigenetic age) within cells and tissues. Epigenetic age is also known as DNAm age which emphasizes crucial facets of genetic age and further reveals a strong correlation with age-related conditions, thereby predicting an individual’s age. This phenomenon relates to a wide range of aging-related changes which contribute to various diseases such as cancer [91]. In the past, studies have provided strong evidence suggesting the importance of polyphenols-associated changes in DNA methylation as enumerative measures of long-term dietary exposure to certain stilbenoids such as RES and pterostilbene (PTER) in nutritional epidemiology and clinical experiments. The study demonstrated that treatment of MCF10A human mammary epithelial cells with RES and PTER at 15 µM for 9 days led to subtle alterations thereby suggesting remodelling of DNA methylaton patterns at eight CpG sites located within KCNJ4, RNF169, BCHE, DAOA, HOXA, RUNX3, KRTAP2-1 and TAGAP [92].

Epigenetic drift refers to progressive deviation in DNA methylation levels during aging, which begins immediately after birth and becomes more prevalent during pre-puberty. Epigenetic drift can also be affected by various genetic factors and environmental factors, thereby evolving as a potential biomarker for different biological factors affecting aging and leading to disease progression. Therefore,
it is quite crucial to understand the mechanism for these fluctuations [93]. These findings indicate that alterations in DNA methylation could potentially influence various transcription factors at specific sites, eventually contributing to the dysregulation of gene expression during aging. Table 2 lists different proteins that contribute to DNA methylation and their function at the molecular and biological levels.

Table 2. List of proteins that play a vital role in DNA methylation with their molecular activity and biological function.

| DNA Methylation Enzymes | Molecular Activity | Biological Function | References |
|-------------------------|--------------------|---------------------|------------|
| DNMT1                   | Replication of methylation patterns in the new strand after DNA replication | Embryonic development, Heterochromatin formation, Gene silencing | [94,95] |
|                         | Crucial for genomic imprinting | X chromosome inactivation, Protein binding | |
|                         | Maintenance of DNA methylation during mitosis | RNA binding, Methyl-CpG binding | |
| DNMT3a and DNMT3b       | Catalyze cytidine methylation at 5-Carbon | Crucial for de novo methylation in the genome, Gene silencing | [5,96–98] |
|                         | Maintenance of DNA methylation | Heterochromatin formation | |

DNMT1—DNA methyltransferase 1, DNMT3a—DNA methyltransferase 3 alpha, DNMT3b—DNA methyltransferase 3 beta.

3.2. Histone Modifications and Aging

The histone machinery of chromatin is linked to a wide variety of translational and post-translational modifications. Histone modifications are primarily comprised of acetylation, methylation, phosphorylation and adenonsine diphosphate (ADP) ribosylation. Histone modifications are known to either interrupt the chromatin organization or offer new binding surfaces for the deployment of various proteins in a specific region of chromatin [99]. Histone acetyltransferases (HATs), histone deacetylases (HDACs) and histone methyltransferases (HMTs) are key enzymes that influence transcriptional machinery by chemical modifications of histones. For example, a study in *Saccharomyces cerevisiae* (baker’s yeast) demonstrated that decrease in Silencing Information Regulator 2 (Sir2) protein, which is responsible for maintaining silencing in yeast hetrochromatin telomeric regions, and increased levels of histone 4 on lysine 16 acetylation (H4K16Ac) delayed aging and extended the lifespan [100]. Another study in *S. cerevisiae* reported that deletion of the histone acetylase RPD3 gene extended the lifespan by enhancing silencing at three hetrochromatin regions of the genome; silent mating type (HM), subtelomeric region and ribosomal DNA (rDNA) [101].

Besides HDACs, HMTs also play a critical role in regulating transcriptional activities. An investigation in *S. cerevisiae* demonstrated a role for histone 3 lysine 36 (H3K36) methylation in promoting longevity by increasing transcription fidelity. The study demonstrated that the deletion of the K36me2/3 demethylase Rph1 gene led to increasing levels of H3K36me3 further extending the lifespan [102]. Additionally, studies in *C. elegans* have also suggested that the inactivation of somatic Set-26 domain caused a robust extension of lifespan and changes in the levels of histone 3 on lysine 9 trimethylation (H3K9me3) and histone 3 on lysine 27 trimethylation (H3K27me3) thereby inducing chromatin structure restoration and promotion of longevity [103]. Therefore, based on these results, the process of histone modification is complex and can have a positive or negative impact on transcriptional machinery, eventually extending the lifespan. Table 3 demonstrates histone modification activities of HATs, HDACs and HMTs enzymes with their exact molecular events and biological function.
Table 3. List of proteins that play a vital role in histone acetylation and methylation with their molecular activity and biological functions.

| Histone Modifications | Molecular Activity | Biological Function | References |
|-----------------------|--------------------|---------------------|------------|
| HDACs                 | Zinc-dependent amidohydrolases | DNA replication, DNA repair, Heterochromatin silencing, Gene transcription | [104–106] |
| HATs                  | Utilizes acetyl-CoA for acetylation reaction | Transcriptional activation, DNA repair, Gene expression profiling leading to disease progression | [107] |
| HMTs                  | Methylation of lysine residues | Gene transcription activation, Gene transcription suppression, DNA repair, Heterochromatin formation | [108] |

HDACs—Histone deacetylases, HATs—Histone acetyltransferases, HMTs—Histone methyltransferases.

3.3. Non-Coding RNAs and Aging

Besides DNA methylation and histone modifications, ncRNAs also play a vital role in maintaining genomic stability by regulating gene expression. Primary research on various organisms, such as *H. sapiens*, explains that ncRNAs-related regulatory processes contribute to the pathogenesis of various aging-related diseases. NcRNAs regulates a wide range of key cellular processes such as translation and gene expression profiling. Among different types of ncRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) play a central role in maintaining the healthy lifespan of organisms. Table 4 provides a list of different ncRNAs and their aging-associated molecular activity and related biological functions.

Table 4. List of ncRNAs, their related molecular activity, and biological functions contributing to aging-related diseases.

| Non-Coding RNAs | Molecular Activity | Biological Function | References |
|-----------------|--------------------|---------------------|------------|
| siRNAs          | Controls pre-messenger RNA and regulate levels of Positive transcription elongation factor (P-TEFB) | Ribosomal synthesis, Alternative splicing, OS | [109] |
| miRNAs          | Degradation of mRNA Genomic stability Chromatin modification left | Cell cycle regulation, Cell proliferation, Tumor suppression, Apoptosis | [110–112] |
| lncRNAs         | Expressed in intergenic regions or the promoter regions of mRNAs. Facilitates ubiquitination | Genome localization, Regulates gene expression, Recruitment of chromatin-modification factors, Nuclear compartmentalization | [113] |

siRNAs—small interfering RNAs, miRNAs—microRNAs, lncRNAs—long non-coding RNAs.
One of the critical factors during the aging process is genomic instability which can be stimulated in part by changes in miRNAs, and many have reported the role of various miRNAs in modulating lifespan and regulating tissue aging. The best-characterized examples of miRNAs functions during aging are derived from C. elegans investigations. A study conducted in C. elegans emphasized the modulating effects of miRNA lin-4 and lin-14 thus regulating the insulin/insulin-like growth factor-1 pathway. As a result, reducing of activity of lin-4 reduced the lifespan and improved tissue aging. Furthermore, overexpression of lin-4 and reduced expression of lin-14 extended the life span [114]. Besides miRNAs, molecular mechanisms of lncRNAs associated with transcriptional, translational and post-translational activity can affect aging-related pathways [115]. A study in Drosophila melanogaster (common fruit fly) demonstrated lncRNAs-mediated regulation of aging-associated pathways at 7 days and 42 days during CR and well-fed conditions thereby prolonging the lifespan. As a result, 1406 differentially expressed coding genes and 102 differentially expressed lncRNAs were identified. A recent aging study using fruit flies revealed that both short-term and long-term CR diets had intriguing impact on novel lncRNAs expression in addition to their well-studied transcriptional effects. Consequently, Gene ontology (GO) and KEGG (Kyoto encyclopedia of genes and genomes) analysis identified novel aging-associated pathways during CR such as protein processing pathways, hippo signaling pathway-fly and phototransduction-fly. Furthermore, novel lncRNAs XLOC_092363 and XLOC_166557 positioned in a 10 kb upstream regions of the hairy and ems promoters were also identified. The study also reported that lncRNA XLOC_076307 silencing induced growth arrest and DNA damage inducible alpha (Gadd45A) associated expression levels changes [116]. Altogether, these studies suggest that ncRNAs could serve as a useful resource for understanding aging and aging-related diseases.

4. Effects of Dietary Polyphenols the Epigenetic Machinery and Aging

Even though OS and CR play a pivotal role in aging, it is also imperative to understand the underlying mechanism by which different bioactive compounds imitate the effects of CR and further reduce the risks associated with CR side effects. A plethora of studies have demonstrated the positive effects of polyphenolic compounds such as apigenin, CUR, EGCG, genistein (GES), PTER and RES on aging-related phenomena by facilitating anti-cancer and anti-inflammatory effects as discussed below. The influence of an environmental factor such as exercise and diet on gene expression and longevity in different organisms has been a topic of great interest [117]. Diet plays a key role in regulating epigenetic modifications such as DNA methylation, DNA demethylation and histone modifications regulated through HDACs, HATs and HMTs enzymes [118,119]. For instance, a study demonstrated the effects of RA and sodium butyrate (BUT) on gene expression and HDAC activity in human RA-resistant A375 and RA-responsive S91 murine melanoma cell lines. As a result, BUT treatment resulted in both RARβ and p21^{wafl/cip1} mRNA being expressed in A375 cells, and only p21^{wafl/cip1} mRNA expression being expressed in S91 cells. Moreover, combined administration of RA and BUT caused synergistic activation of RA-responsive reporter gene in S91 cells but not in RA-resistant A375 cells. Treatment with BUT increased histone H4-acetylation levels in both RA-resistant A375 and RA-responsive S91 cell lines [120]. Another study revealed the effect of diallyl disulfide (DADS), an organosulfur compound primarily found in garlic, on HDAC activity and gene expression changes in human colon tumor Caco-2 and HT-29 cell lines. Treatment with DADS led to increasing histone H3 acetylation in both Caco-2 and HT-29 cell lines and histone H4 hyperacetylation at lysine 12 and lysine 26 in Caco-2 cell lines. Furthermore, treatment with DADS also enhanced the expression of p21^{wafl/cip1} at mRNA and protein levels in both Caco-2 and HT-29 cell lines [121]. Either of these studies provides strong evidence implicating the role of dietary polyphenols and their impact on aging-associated histone modifications. Therefore, it is vital to understand histone modifications as a molecular target mechanism linking diet related changes and longevity.
4.1. Apigenin

Apigenin is a plant-based flavone with anti-oxidative properties. Studies have demonstrated the protective effects of apigenin on aging-related diseases such as colon cancer, skin cancer and many others. A study investigated protective effects of apigenin where mice were administered continuously for 9 weeks with D-galactose subcutaneously. As a result, dietary treatment with apigenin resulted in improved aging-related changes such as behavioral deterioration, decreased organic index, histopathological injury, increased senescence-associated activity of β-galactosidase (SAβ-gal), enriched glycation product (AGE) level and decreased levels of MDA. Furthermore, treatment with apigenin also caused up-regulation of HO-1 and NQO-1, downstream gene targets for the Nrf2 pathway, eventually delaying the process of aging [122]. Another study on skin showed that apigenin reinstated the viability of human dermal fibroblasts (nHDFs) which decreased after exposure to ultraviolet (UV) radiation. Additionally, apigenin treatment also reduced collagenase and matrix metalloproteinase (MMP)-1 expression in nHDFs irradiated by UVA [123]. The study also demonstrated the beneficial effects of apigenin on texture of the skin, moisture and the depletion of transepidermal water (TEWL). In addition, consistent use of apigenin-containing cream increased skin evenness, moisture content and TEWL. As a consequence, apigenin-containing cream increased wrinkle length and further boosted dermal density and dermal elasticity. In another study, HT-29 and HCT-15 cell lines of colorectal cancer were treated with apigenin, which resulted in anti-proliferative and apoptotic effects by inducing biochemical and morphological changes. Treatment with apigenin led to increasing production of free radical species, inhibition of retinoblastoma phosphorylation and up-regulation of p21, eventually suppressing cyclin D1 and E activity [124]. These changes attributed to dietary treatment with apigenin suggest that it is a potent dietary phytochemical in chemoprevention and aging-related studies.

4.2. Curcumin (CUR)

CUR is another potent polyphenolic compound that is mainly found in vegetables and primarily known for its anti-oxidative properties influencing chronological and replicative aging. In the past, studies have explained the anti-aging properties of CUR in the context of adipose tissue-derived mesenchymal stem cells (rADSCs) by TERT gene expression in rats. rADSCs were isolated from adipose tissues and treated with CUR in a dose-dependent manner (1 µM–20 µM). As a result, dietary treatment with CUR resulted in considerable proliferation of rADSCs after 48 h of treatment at 1 µM and 5 µM CUR concentrations, thereby lessening population multiplying time and rADSCs aging at different cell passages. Moreover, SA-β-gal staining results indicated that CUR significantly decreased the number of senescent cells in different passages (five and seven cell passages) and also increased the expression of TERT gene at 1 µM and 5 µM CUR concentrations [125]. Additionally, a study in rats (Rattus rattus) investigated the beneficial effects of CUR on muscle force characteristics in aging rats. 32 weeks old F344xBN rats were administered with purified diet of CUR (AIN-93M) for 4 months. First group was administered with control ad libitum diet (CON, n = 5), second group was administered with purified CUR diet (CUR, n = 4) and third group, pair fed (PAIR, n = 4), received a purified diet in the quantity equal to group 2 (CUR). Body mass, muscle mass and contractive characteristics were evaluated using independent sample t-tests. As a result, PAIR group exhibited lower muscle mass unlike CUR group which had identical muscle mass. The study also reported that peak tetanic tension was higher in CUR group in comparison to PAIR group.

In addition, CUR also posses anti-inflammatory, anti-proliferative and anti-cancerous properties [126,127]. For instance, CUR inhibited DNMT1 activity in human breast cancer MCF-7 cell lines. Additionally, treatment with CUR also led to reactivation of Ras-associated domain family protein 1A (RASSF1A) and further decreased cell proliferation and tumor growth [128]. In addition, a study in human lung cancer A549 cell lines reported that treatment with CUR increased RA receptor beta (RARβ) gene expression, decreased tumor growth and DNMT3b activity [129]. To better understand the association of dietary polyphenols and DNA methylation, it is critical to gain a better
understanding of underlying mechanisms between DNA methylation, gene expression and various aging-related diseases.

### 4.3. Epigallocatechin-3-Gallate (EGCG)

EGCG is the primary bioactive compound found in green tea. EGCG is widely studied for its demethylating properties through its action as a DNMT inhibitor in various lung cancer, leukemia, breast cancer as well as other neurodegenerative disorders. A study was conducted in human lung adenocarcinoma A549 cell lines wherein an A549/DDP cell line model was designed by treating A549 cells with a higher concentration of cisplatin (DDP). The investigation determined that the administration of EGCG in A549/DDP cell lines resulted in inhibition of cell proliferation, cell cycle arrest in the G1 phase and increased apoptotic activity. Furthermore, EGCG treatment led to inhibition of DNMT and HDAC activity and down-regulation of Growth arrest specific 1 (GAS1), TIMP metalloproteinase inhibitor 4 (TIMP4) and Intracellular adhesion molecule 1 (ICAM1) genes [130].

Another study indicated that the administration of EGCG in human breast cancer MCF-7 and leukemia HL60 cell lines resulted in decreased cell proliferation and also induced apoptosis in both the cell lines. Additionally, EGCG treatment in MCF-7 cells caused a decrease in hTERT promoter methylation and inhibition of histone 3 lysine 9 (H3K9) acetylation. As a result, EGCG was identified as a pivotal polyphenol possessing anti-oxidative properties, altering epigenetic mechanisms and eventually causing cell death in both MCF-7 and HL60 cell lines [131]. Subsequently, another investigation demonstrated that administration of EGCG in adult hippocampal neural progenitor cell (NPC) cultures and in denote gyrus of adult mice improved spatial cognition thereby promoting adult neurogenesis. EGCG treatment caused a significant increase in the total number of 5-Bromo-2′-deoxyuridine (BrdU)-labeled cells and increased expression of the Ssh mRNA receptor as well as Gli1, a downstream transcriptional target for Ssh [132].

Another report indicated that EGCG extracted from green tea decreased 5mC, mRNA and protein levels of DNMT1, DNMT3a and DNMT3b in human epidermoid carcinoma A431 cells. Furthermore, treatment with EGCG also decreased histone deacetylase activity and increased acetylation of lysine 9 and 14 on histone H3 [133]. Another study also suggested that EGCG inhibits DNMT activity and reactivates methylation-silenced genes in HT-29 cell lines of human colon cancer, KYSE-150 cell lines of esophageal cancer and PC3 cell lines of prostate cancer [134]. These results together suggest that the beneficial properties of EGCG are numerous with respect to aging.

### 4.4. Genistein (GES)

Besides apigenin and CUR, GES is another polyphenol that is associated with aging. GES is mainly found in olives, soybeans, fava beans and is known for its wound healing properties and photoprotective properties. GES also possess inhibitory properties for tyrosine kinases by controlling glycosaminoglycan (GAG) synthesis and increase stability against UV-light exposure. A study in UVB-irradiated human skin fibroblast BJ-5ta cells suggested that combinatorial administration of GES with daidzein led to a decrease expression of the Ssh mRNA receptor as well as Gli1, a downstream transcriptional target for Ssh [135]. Another report indicated that EGCG extracted from green tea decreased 5mC, mRNA and protein levels of DNMT1, DNMT3a and DNMT3b in human epidermoid carcinoma A431 cells. Furthermore, treatment with EGCG also decreased histone deacetylase activity and increased acetylation of lysine 9 and 14 on histone H3 [133]. Another study also suggested that EGCG inhibits DNMT activity and reactivates methylation-silenced genes in HT-29 cell lines of human colon cancer, KYSE-150 cell lines of esophageal cancer and PC3 cell lines of prostate cancer [134]. These results together suggest that the beneficial properties of EGCG are numerous with respect to aging.
LC3-II levels and decreasing p62, p-mTOR and p-P70S6K levels [138]. Therefore, administration of GES in a dose-dependent manner could be helpful in establishing specific concentrations for clinical efficacy and further delaying aging.

4.5. Pterostilbene (PTER)

PTER, a natural trans-3,5-dimethyl ether, is another class of polyphenolic compound that is frequently found in grapes, berries, peanuts and wine. PTER is known for its towering pharmacokinetics and pharmacodynamics properties. Multiple studies have indicated that the administration of PTER induces chemopreventive effects by targeting metastasis-associated protein 1 (MTA1) in human prostate cancer. MTA1 is deemed to be a critical upstream regulator of tumorigenesis and targets for c-Myc and Akt, which are key genes in prostate cancer progression. The study reported that administration of PTER led to inhibition of MTA1, resulting in decreased cell proliferation as well as increased apoptosis and angiogenesis [139]. An additional report explained the antioxidant and myocardial protection property of PTER in the C57BL/6 mice model and H9c2 cell lines. C57BL/6 mice were administered with 20 mg/kg of doxorubicin (DOX), and H9c2 cells were treated with 1 µM DOX. As a result, dietary treatment with PTER led to the reduction of OS thereby improving AMP-activated protein kinase (AMPK) and SIRT1 signaling pathways. The administration of PTER inhibited OS induced by DOX and mitochondrial morphological disorder by up-regulation of peroxisome proliferator-activated receptor-gamma co-activator 1alpha (PGC-1α), thereby activating AMPK and SIRT1 activity by enhancing SIRT1 [140]. Another study examined the combinatorial impact of RES and PTER by altering DNA damage response and their effect on SIRT1 and DNMT expression activity. The results demonstrated that a synergistic combination of RES and PTER induced inhibition of triple-negative breast cancer (TNBC) by reducing cell proliferation, increasing apoptosis, and upregulating cell cycle arrest in HCC1806 and MDA-MB-157 breast cancer cells. Furthermore, combinatorial treatment of RES and PTER also resulted in the down-regulation of DNMT enzyme expression in HCC1806 cells with no effect on DNMT enzyme expression in breast MCF10A control cell lines [141]. These studies suggest that the administration of PTER, along with other polyphenols such as RES, may serve as a therapeutic target for novel treatments of various diseases such as breast cancer.

4.6. Resveratrol (RES)

RES, a polyphenol found in almonds, blueberries, and grapes, also possesses potential anti-aging and antidiabetogenic properties. Researchers have studied the metabolic effects of RES results due to inhibition of cAMP-degrading phosphodiesterases eventually causing increased cAMP levels in Mus musculus. As a result, treatment with RES induced Epac1 activation, which increased intracellular Ca^{2+} levels and further triggered the CamKKβ-AMPK pathway by controlling phospholipase C and ryanodine receptor Ca^{2+} release channel. Additionally, treatment with RES also increased NAD^+ and Sirt1 activity, thus, preventing diet-induced obesity and enhancing mitochondrial function, physical stamina, and glucose tolerance in mice [142]. An investigation conducted on Mus musculus reported that a low dosage of RES imitated CR effects and also hindered aging parameters in mice. A control diet and a lower dose of RES [4.9 mg kg^{-1}day^{-1}] and CR diet was administered to mice aged 14 months (middle aged) and 30 months (old age). As a result, RES dietary treatment simulated CR properties by inhibiting gene expression in heart, skeletal muscle and brain tissues, eventually preventing cardiac dysfunction [143]. Another study assessed the effect of RES on physiological changes in middle aged, high-calorie diet mice in comparison to those on a standard diet. Dietary administration of RES extended the lifespan by increasing AMPK and PGC-1α activity, increasing mitochondrial number and further decreasing insulin-like growth factor-1 (IGF-I) levels [144]. These results suggest that RES possesses beneficial properties in treating obesity-related disorders as well as aging-related diseases.
4.7. Quercetin

Quercetin is another flavonoid mainly found in vegetables, fruits and actively responsible for maintaining cellular ROS levels. A study in a Podospora anserine (a filamentous ascomycete fungus) model demonstrated the role of S-adenosylmethionine-dependent O-methyltransferase PaMTH1 wherein the treatment with quercetin induced longevity. Administration of quercetin extended the lifespan in wild type P. anserine but not in a mutant with PaMTH1 deletion. Additionally, treatment with quercetin also increased mitochondrial respiration and respiratory complexes along with increased release of superoxide anion [145]. Another investigation reported the effect of quercetin in declining the oocyte quality during post-ovulatory aging of mouse oocytes by modulating SIRT expression and MPF activity. As a result, treatment with quercetin repressed aging-associated changes in organization of spindles and distribution of mitochondria. In addition, quercetin treatment prevented overall decrease in SIRT expression and maturation-promoting factor (MPF) activity, and further delayed apoptosis onset during post-ovulatory aging. Moreover, treatment with quercetin during post-ovulatory aging also enhanced the early development of the embryo [146]. These studies suggest that quercetin plays a pivotal role in extending the lifespan in different organisms.

These polyphenols and many others provide evidence that polyphenol-rich diets may provide benefits to an organism’s health and display strong anti-aging properties as well as attenuate the effects of various diseases. Table 5 summarizes the epigenetic and aging-related activity, aging patterns, and their target molecular activity of dietary polyphenols.

Table 5. Polyphenols and their specific aging-related activities across different organisms.

| Polyphenols | Epigenetic and Aging-Related Activity | Aging Pattern | Target Genes/Proteins | Species | References |
|-------------|--------------------------------------|---------------|-----------------------|---------|------------|
| Apigenin    | Antioxidant activity, Behavioral impairment, Histopathological changes | Cellular senescence | Nrf2, HO-1 and NQO1, MMP-1, ↓ p53, ↑ p21, ↓ Cyclins D1 and ↑ Cyclins E | Mus musculus, Homo sapiens | [122–124] |
| CUR         | ↓ OS, DNA repair mechanisms, Hormesis, Muscle mass function, ↑ Anti-oxidative properties, ↓ Anti-oxidative properties | Cellular senescence | SOD1, SOD2 and RAD52, TERT, rADSCs and SA-β-gal | Saccharomyces cerevisiae, Rattus rattus | [125,147,148] |
| EGCG        | ↑ Apoptosis, ↓ Cellular proliferation, ↓ DNMT activity, ↓ HDAC activity, Telomerase inhibition | Organismal | GAS1, TIMP4, ICAM1, WISP2 and hTERT | Homo sapiens | [130–132] |
| GES         | ↑ DNA repair, ↓ UV-radiation exposure, ↓ Tyrosine kinase activity | Cellular senescence | COX-2, hTERT, p66Shc, ↑ p16, ↓ p21, SIRT1, LKB1, AMPK, ↓ p62, ↓ p-m-TOR and p-70S6K | Homo sapiens, Mus musculus | [135–138] |
| PTER        | ↑ OS, ↓ Mitochondrial morphological disorder, ↑ Declarative memory, ↑ Working memory | Organismal | ↑ AMPK, ↑ SIRT1 and PGC-1α, ↑ REST, ↑ PSD-95 and ↑ mitochondrial porin-1 | Homo sapiens, Mus musculus | [140,149] |
Table 5. Cont.

| Polyphenols | Epigenetic and Aging-Related Activity | Aging Pattern | Target Genes/Proteins | Species | References |
|-------------|-------------------------------------|---------------|------------------------|---------|------------|
| RES         | ↑ Myocardial performance index  
↓ HDAC activity  
↓ Inflammatory cytokines  
↓ Cognitive defects  
Reversal of aging-associated learning and cognitive impairment | Organismal     | ↓ IGF-1, ↑ AMPK and ↑ PGC-1α | Mus musculus | [142,143,150] |
| Quercetin   | ↑ Apoptosis  
↓ H3K9me3 activity  
Delaying down-regulation of SIRT activity | Organismal     | ↓ MPF activity and ↑ PaMTH1 | Podospora anserina | [145,146] |

↓—decreased, ↑—increased, CUR—Curcumin, EGCG—Epigallocatechin-3-gallate, GES—Genistein, PTER—Pterostilbene and RES—Resveratrol.

5. Conclusions

Epigenetic alterations such as DNA methylation, histone modifications, and ncRNAs play significant roles not only as hallmarks of aging-related diseases, but also as important molecular processes that underlie the basis of aging. The main cellular consequences of epigenetic dysregulation are variations in transcriptional activation, transcriptional repression, changes in genomic stability and specific disease-associated morphological changes. A significant challenge in the field of epigenetics and aging-associated diseases is to identify the exact molecular mechanisms that are expected to result in these diseases. Therefore, it is necessary to understand the precise causes behind these changes.

High-throughput studies along with various transcriptomics analysis, have also provided a wealth of information about epigenetic modifications. Furthermore, understanding the significance of dietary polyphenols to an organism’s health provides a deeper understanding of diverse molecular activities related to aging. Evidence suggests that various dietary polyphenols may a lead to an increasing cell proliferation, a decrease in tumor incidence, an increase in tumor latency and modulation of multiple signaling pathways. Although epigenetics alterations related to aging are not fully understood, this review highlights various studies towards understanding these mechanisms and their association with aging.

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Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| AD           | Alzheimer’s Disease |
| ADP          | Adenosine Di Phosphate |
| AgeCpGs      | Age-associated CpGs |
| AMPK         | AMP-activated protein kinases |
| ATP          | Adenosine Tri Phosphate |
| BUT          | Sodium Butyrate |
| CAT          | Catalase |
CI  Confidence interval
CUR  Curcumin
COX-2  Cyclooxygenase-2
DADS  Diallyl disulfide
DDP  Cisplatin
DNA  Deoxyribonucleic acid
DNMTs  DNA methyltransferases
DNMT1  DNA methyltransferase 1
DNMT3a  DNA methyltransferase 3 alpha
DNMT3b  DNA methyltransferase 3 beta
DNAm  DNA methylation
DOX  Doxorubicin
EGCG  Epigallocatechin-3-gallate
EGFR  Epidermal growth factors
ER  Endoplasmic reticulum
Gadd45A  Growth arrest and DNA damage inducible alpha
GAS1  Growth arrest specific 1
GES  Genistin
GAG  Glycosaminoglycan
GPx  Glutathione peroxidase
GTPs  Green tea polyphenols
HAT  Histone acetyltransferase
HDAC  Histone deacetylase
HMT  Histone methyltransferase
HDM  Histone demethylase
HIF-1α  Hypoxia inducible factor-1α
HP1  Heterochromatin protein 1
HDFs  Human dermal fibroblasts
HUVECs  Human umbilical vein endothelial cells
H3-K27  Histone H3 on lysine 27
H3-K9  Histone H3 on lysine 9
H4-K16  Histone H4 on lysine 16
H4-K36  Histone H4 on lysine 36
ICAM1  Intracellular adhesion molecule 1
IFNγ  Interferon gamma
LCs  Langerhans cells
IncRNAs  Long non-coding RNAs
miRNAs  microRNAs
MBDs  Methyl-CpG binding domains
MPF  Maturation promoting factor
NPC  Neural progenitor cell
ncRNAs  Non-coding RNAs
OS  Oxidative stress
PGC-1α  Proliferator-activated receptor-gamma coactivator 1 alpha
PD  Parkinson’s disease
PTER  Pterostilbene
rDNA  Ribosomal DNA
RAR β  Retinoic acid receptor beta
RASSF1A  Ras-associated domain family protein 1A
RES  Resveratrol
ROS  Reactive oxygen species
SAbβ-gal  Senescence-associated beta-galactosidase
Sir  Silent information regulator
siRNAs  Small interfering RNAs
SOD  Superoxide dismutase
TERT  Telomerase reverse transcriptase
TNBC  Triple negative breast cancer
TIMP 4  TIMP metallopeptidase inhibitor 1
T2D  Type 2 Diabetes
BrdU  5-Bromo-2′-deoxyuridine
5mC  5-methylcytosine

References
1. Di Giulio, C.; Antosiewicz, J.; Walski, M.; Petruccelli, G.; Verratti, V.; Bianchi, G.; Pokorski, M. Physiological carotid body denervation during aging. In Arterial Chemoreceptors; Springer: Berlin/Heidelberg, Germany, 2009; pp. 257–263.
2. Wagner, W.; Bork, S.; Horn, P.; Krunic, D.; Walenda, T.; Diehlmann, A.; Benes, V.; Blake, J.; Huber, F.-X.; Eckstein, V. Aging and replicative senescence have related effects on human stem and progenitor cells. PLoS ONE 2009, 4, e5846. [CrossRef] [PubMed]
3. Weinberg, E.J.; Schoen, F.J.; Mofrad, M.R. A computational model of aging and calcification in the aortic heart valve. PLoS ONE 2009, 4, e5846. [CrossRef] [PubMed]
4. Fraga, M.F.; Agrelo, R.; Esteller, M. Cross-talk between aging and cancer: The epigenetic language. Ann. N. Y. Acad. Sci. 2007, 1100, 60–74. [CrossRef]
5. Fraga, M.F.; Esteller, M. Epigenetics and aging: The targets and the marks. Trends Genet. 2007, 23, 413–418. [CrossRef] [PubMed]
6. Sharpless, N.E.; DePinho, R.A. How stem cells age and why this makes us grow old. Nat. Rev. Mol. Cell Biol. 2007, 8, 703–713. [CrossRef] [PubMed]
7. Dilin, A.; Hsu, A.-L.; Arantes-Oliveira, N.; Lehrer-Graiwer, J.; Hsin, H.; Fraser, A.G.; Kamath, R.S.; Ahringer, J.; Kenyon, C. Rates of behavior and aging specified by mitochondrial function during development. Science 2002, 298, 2398–2401. [CrossRef] [PubMed]
8. Dubey, A.; Forster, M.J.; Lal, H.; Sohal, R.S. Effect of age and caloric intake on protein oxidation in different brain regions and on behavioral functions of the mouse. Arch. Biochem. Biophys. 1996, 333, 189–197. [CrossRef]
9. Valenzuela, R.; Das, U.N.; Videla, L.A.; Llorente, C.G. Nutrients and Diet: A Relationship between Oxidative Stress, Aging, Obesity, and Related Noncommunicable Diseases. Oxidative Med. Cell. Longev. 2018. [CrossRef]
10. Ligouri, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; Della-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D. Oxidative stress, aging, and diseases. Clin. Intern. Aging 2018, 13, 757. [CrossRef]
11. He, F.; Zuo, L. Redox roles of reactive oxygen species in cardiovascular diseases. Int. J. Mol. Sci. 2015, 16, 27770–27780. [CrossRef]
12. Zhang, X.; Wang, X.; Wu, T.; Li, B.; Liu, T.; Wang, R.; Liu, Q.; Liu, Z.; Gong, Y.; Shao, C. Isoliensinine induces apoptosis in triple-negative human breast cancer cells through ROS generation and p38 MAPK/JNK activation. Sci. Rep. 2015, 5, 12579. [CrossRef] [PubMed]
13. López-Otin, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The hallmarks of aging. Cell 2013, 153, 1194–1217. [CrossRef] [PubMed]
14. World Health Organization. Health and Ageing: A discussion Paper; World Health Organization: Geneva, Switzerland, 2001.
15. Weinreb, O.; Mandel, S.; Amit, T.; Youdim, M.B. Neurological mechanisms of green tea polyphenols in Alzheimer’s and Parkinson’s diseases. J. Nutr. Biochem. 2004, 15, 506–516. [CrossRef] [PubMed]
16. Scalbert, A.; Williamson, G. Dietary intake and bioavailability of polyphenols. J. Nutr. 2000, 130, 2073S–2085S. [CrossRef] [PubMed]
17. Angeloni, C.; Maraldi, T.; Milenkovic, D.; Vauzour, D. Dietary polyphenols and their effects on cell biochemistry and pathophysiology 2014. Oxidative Med. Cell. Longev. 2015, 2015, 782424. [CrossRef]
18. Silva, G.Á.F.; Nunes, R.A.L.; Moreira, M.G.; Boccardo, E.; Aguayo, F.; Termini, L. Oxidative stress: Therapeutic approaches for cervical cancer treatment. Clinics 2018, 73, e548s. [CrossRef]
19. Meeran, S.M.; Akhtar, S.; Katiyar, S.K. Inhibition of UVB-induced skin tumor development by drinking green tea polyphenols is mediated through DNA repair and subsequent inhibition of inflammation. J. Investig. Dermatol. 2009, 129, 1258–1270. [CrossRef]
20. Cherniack, E.P. The potential influence of plant polyphenols on the aging process. *Complement. Med. Res.* 2010, 17, 181–187. [CrossRef]

21. Anisimov, V.N.; Sikora, E.; Pawelec, G. Relationships between cancer and aging: A multilevel approach. *Biogerontology* 2009, 10, 323. [CrossRef]

22. Albers, D.S.; Beal, M.F. Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease. In *Advances in Dementia Research*; Springer: Berlin/Heidelberg, Germany, 2000; pp. 133–154.

23. North, B.J.; Sinclair, D.A. The intersection between aging and cardiovascular disease. *Circ. Res.* 2012, 110, 1097–1108. [CrossRef]

24. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.* 2004, 79, 727–747. [CrossRef] [PubMed]

25. Kasprzak, K.; Oniszczuk, T.; Wójtowicz, A.; Waksmandzka-Hajnos, M.; Olech, M.; Nowak, R.; Polak, R.; Oniszczuk, A. Phenolic acid content and antioxidant properties of extruded corn snacks enriched with kale. *J. Anal. Methods Chem.* 2018, 2018. [CrossRef] [PubMed]

26. Kang, J.; Thakali, K.M.; Jensen, G.S.; Wu, X. Phenolic acids of the two major blueberry species in the US Market and their antioxidant and anti-inflammatory activities. *Plant Foods Hum. Nutr.* 2015, 70, 56–62. [CrossRef]

27. Huang, W.-Y.; Cai, Y.-Z.; Zhang, Y. Natural phenolic compounds from medicinal herbs and dietary plants: Potential use for cancer prevention. *Nutr. Cancer* 2009, 62, 1–20. [CrossRef] [PubMed]

28. Beecher, G.R. Overview of dietary flavonoids: Nomenclature, occurrence and intake. *J. Nutr.* 2003, 133, 3248S–3254S. [CrossRef]

29. Cassidy, A.; Rimm, E.B.; O’Reilly, K.; Logroscino, G.; Kay, C.; Chiuve, S.E.; Rexrode, K.M. Dietary flavonoids and risk of stroke in women. *Stroke* 2012, 43, 946–951. [CrossRef]

30. Horbowicz, M. Occurrence, biosynthesis and biological properties of the flavonols. *Postepy Nauk Rol.* 2000, 2, 3–18.

31. Qi, X. Extraction and determination of flavones from celery. *Food Sci. Technol.* 2006, 7.

32. Sutter, A.; Poulton, J.; Grisebach, H. Oxidation of flavanone to flavone with cell-free extracts from young parsley leaves. *Arch. Biochem. Biophys.* 1975, 170, 547–556. [CrossRef]

33. Bovy, A.; Schijlen, E.; Hall, R.D. Metabolic engineering of flavonoids in tomato (Solanum lycopersicum): The potential for metabolomics. *Metabolomics* 2007, 3, 399. [CrossRef]

34. Mir, I.A.; Tiku, A.B. Chemopreventive and therapeutic potential of “naringenin”, a flavanone present in citrus fruits. *Nutr. Cancer* 2015, 67, 27–42. [CrossRef] [PubMed]

35. Korkina, L.G.; Afanas’ev, I.B. Antioxidant and chelating properties of flavonoids. In *Advances in Pharmacology*; Elsevier: Amsterdam, The Netherlands, 1996; Volume 38, pp. 151–163.

36. Guardia, T.; Rotelli, A.E.; Juarez, A.O.; Pelzer, L.E. Anti-inflammatory properties of plant flavonoids. *Eur. J. Pharmacol.* 2012, 683–687. [CrossRef]

37. Le Marchand, L. Cancer preventive effects of flavonoids—A review. *Biomed. Pharmacother.* 2002, 56, 296–301. [CrossRef]

38. Ong, K.C.; Khoo, H.-E. Biological effects of myricetin. *Gen. Pharmacol.* 1997, 29, 121–126. [CrossRef]

39. Bennett, C.J.; Caldwell, S.T.; McPhail, D.B.; Morrice, P.C.; Duthie, G.G.; Hartley, R.C. Potential therapeutic antioxidants that combine the radical scavenging ability of myricetin and the lipophilic chain of vitamin E to effectively inhibit microsomal lipid peroxidation. *Bioorg. Med. Chem.* 2004, 12, 2079–2098. [CrossRef]

40. Yu, J.-S.; Kim, A.-K. Effect of myricetin combined with vitamin C or vitamin E on antioxidant enzyme system in murine melanoma cells. *Korean J. Pharmacogn.* 2004, 35, 357–363.

41. Rivière, C.; Pawlus, A.D.; Merillon, J.-M. Natural stilbenoids: Distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. *Nat. Prod. Rep.* 2012, 29, 1317–1333. [CrossRef]

42. Akinwumi, B.C.; Bordun, K.-A.M.; Anderson, H.D. Biological activities of stilbenoids. *Int. J. Mol. Sci.* 2018, 19, 792. [CrossRef]

43. Maeda, S.; MASUDA, H.; Tokoroyama, T. Studies on the preparation of bioactive lignans by oxidative coupling reaction. III. Synthesis of polyphenolic benzofuran and coumestan derivatives by oxidative coupling reaction of methyl (E)-3-(4-Hydroxy-2-methoxyphenyl) propenoate and their inhibitory effect on liquid peroxidation. *Chem. Pharm. Bull.* 1994, 42, 2536–2545.
44. Mazur, W.; Wähläl, K.; Rasku, S.; Salakka, A.; Hase, T.; Adlercreutz, H. Lignan and isoflavonoid concentrations in tea and coffee. Br. J. Nutr. 1998, 79, 37–45. [CrossRef]

45. Menendez, J.A.; Vazquez-Martín, A.; Oliveras-Ferraros, C.; García-Villalba, R.; Carrasco-Pancorbo, A.; Fernandez-Gutierrez, A.; Segura-Carretero, A. Extra-virgin olive oil polyphenols inhibit HER2 (erbB-2)-induced malignant transformation in human breast epithelial cells: Relationship between the chemical structures of extra-virgin olive oil secoiridoids and lignans and their inhibitory activities on the tyrosine kinase activity of HER2. Int. J. Oncol. 2009, 34, 43–51. [PubMed]

46. Macheix, J.-J. Fruit Phenolics; CRC Press: Boca Raton, FL, USA, 2018.

47. Kerbstadt, S.; Eliasson, L.; Mustafa, A.; Ahmé, L. Effect of novel drying techniques on the extraction of anthocyanins from bilberry press cake using supercritical carbon dioxide. Innov. Food Sci. Emerg. Technol. 2015, 29, 209–214. [CrossRef]

48. Lall, R.K.; Syed, D.N.; Adhami, V.M.; Khan, M.I.; Mukhtar, H. Dietary polyphenols in prevention and treatment of prostate cancer. Int. J. Mol. Sci. 2015, 16, 3350–3376. [CrossRef] [PubMed]

49. Santos, I.S.; Ponte, B.M.; Boonme, P.; Silva, A.M.; Souto, E.B. Nanoencapsulation of polyphenols for protective effects against colon–rectal cancer. Biotechnol. Adv. 2013, 31, 514–523. [CrossRef]

50. Stoner, G.D.; Mukhtar, H. Polyphenols as cancer chemopreventive agents. Nutr. Food Res. 2008, 52, 467–471. [CrossRef]

51. Verma, S.; Singh, A.; Mishra, A. Gallic acid: Molecular rival of cancer. Environ. Toxicol. Pharmacol. 2013, 35, 473–485. [CrossRef]

52. Ramos, S. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. Mol. Nutr. Food Res. 2008, 52, 507–526. [CrossRef]

53. Smith, J.; Ameri, F.; Gadgil, P. Effect of marinades on the formation of heterocyclic amines in grilled beef steaks. J. Food Sci. 2008, 73, T100–T105. [CrossRef]

54. Higdon, J.V.; Frei, B. Coffee and health: A review of recent human research. Crit. Rev. Food Sci. Nutr. 2006, 46, 101–123. [CrossRef]

55. Kasai, H.; Fukada, S.; Yamaizumi, Z.; Sugie, S.; Mori, H. Action of chlorogenic acid in vegetables and fruits as an inhibitor of 8-hydroxydeoxyguanosine formation in vitro and in a rat carcinosogenesis model. Food Chem. Toxicol. 2000, 38, 467–471. [CrossRef]

56. Staniforth, V.; Chiu, L.-T.; Yang, N.-S. Caffeic acid suppresses UVB radiation-induced expression of interleukin-10 and activation of mitogen-activated protein kinases in mouse. Carcinogenesis 2006, 27, 1803–1811. [CrossRef] [PubMed]

57. Link, A.; Balaguer, F.; Goel, A. Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. Biochem. Pharmacol. 2010, 80, 1771–1792. [CrossRef] [PubMed]

58. Kumar, N.; Pruthi, V. Potential applications of ferulic acid from natural sources. Biotechnol. Rep. 2014, 4, 86–93. [CrossRef]

59. Dos Santos, M.D.; Almeida, M.C.; Lopes, N.P.; De Souza, G.E.P. Evaluation of the anti-inflammatory, analgesic and antipyretic activities of the natural polyphenol chlorogenic acid. Boil. Pharm. Bull. 2006, 29, 2236–2240. [CrossRef]

60. Lou, Z.; Wang, H.; Zhu, S.; Ma, C.; Wang, Z. Antibacterial activity and mechanism of action of chlorogenic acid. J. Food Sci. 2011, 76, M398–M403. [CrossRef] [PubMed]

61. Hagenacker, T.; Hillebrand, I.; Wissmann, A.; Büsselberg, D.; Schäfers, M. Anti-allodynic effect of the flavonoid myricetin in a rat model of neuropathic pain: Involvement of p38 and protein kinase C mediated modulation of Ca²⁺ channels. Eur. J. Pain 2010, 14, 992–998. [CrossRef] [PubMed]

62. Matić, S.; Stanić, S.; Bogojević, D.; Vidaković, M.; Grdović, N.; Đinić, S.; Solujić, S.; Mladenović, M.; Stanković, N.; Mihailović, M. Methanol extract from the stem of Cotinus coggygria Scop., and its major bioactive phytochemical constituent myricetin modulate pyrogallol-induced DNA damage and liver injury. Mutat. Res. Toxicol. Environ. Mutagen. 2013, 755, 81–89. [CrossRef]

63. Ong, K.C.; Khoo, H.-E. Effects of myricetin on glycemia and glycogen metabolism in diabetic rats. Life Sci. 2000, 67, 1695–1705. [CrossRef]

64. Tzeng, T.-F.; Liou, S.-S.; Liu, I.-M. Myricetin ameliorates defective post-receptor insulin signaling via β-endorphin signaling in the skeletal muscles of fructose-fed rats. Evidence-Based Complement. Altern. Med. 2011, 2011. [CrossRef]
65. Wang, Z.H.; Kang, K.A.; Zhang, R.; Piao, M.J.; Jo, S.H.; Kim, J.S.; Kang, S.S.; Lee, J.S.; Park, D.H.; Hyun, J.W. Myricetin suppresses oxidative stress-induced cell damage via both direct and indirect antioxidant action. Environ. Toxicol. Pharmacol. 2010, 29, 12–18. [CrossRef]

66. Fantini, M.; Benvenuto, M.; Masuelli, L.; Frajese, G.V.; Tresoldi, I.; Modesti, A.; Bei, R. In vitro and in vivo antitumoral effects of combinations of polyphenols, or polyphenols and anticancer drugs: Perspectives on cancer treatment. Int. J. Mol. Sci. 2015, 16, 9236–9282. [CrossRef] [PubMed]

67. Khan, N.; Afaq, F.; Mukhtar, H. Cancer chemoprevention through dietary antioxidants: Progress and promise. Antioxid. Redox Signal. 2008, 10, 475–510. [CrossRef] [PubMed]

68. Khan, N.; Mukhtar, H. Multitargeted therapy of cancer by green tea polyphenols. Cancer Lett. 2008, 269, 269–280. [CrossRef] [PubMed]

69. Lambert, J.D.; Hong, J.; Yang, G.-y.; Liao, J.; Yang, C.S. Inhibition of carcinogenesis by polyphenols: Evidence from laboratory investigations. Am. J. Clin. Nutr. 2005, 81, 284S–291S. [CrossRef] [PubMed]

70. Lee, K.W.; Lee, H.J. The roles of polyphenols in cancer chemoprevention. Biofactors 2006, 26, 105–121. [CrossRef]

71. Surh, Y.-J. Cancer chemoprevention with dietary phytochemicals. Nat. Rev. Cancer 2003, 3, 768–780. [CrossRef]

72. Asensi, M.; Ortega, A.; Mena, S.; Feddi, F; Estrela, J.M. Natural polyphenols in cancer therapy. Crit. Rev. Clin. Lab. Sci. 2011, 48, 197–216. [CrossRef]

73. Manthey, J.A.; Guthrie, N.; Grohmann, K. Biological properties of citrus flavonoids pertaining to cancer and inflammation. Curr. Med. Chem. 2001, 8, 135–153. [CrossRef]

74. Stalikas, C.D. Extraction, separation, and detection methods for phenolic acids and flavonoids. Curr. Med. Chem. 2007, 30, 3268–3295. [CrossRef]

75. Jiang, Y.-L.; Liu, Z.-P. Natural products as anti-invasive and anti-metastatic agents. Curr. Med. Chem. 2011, 18, 808–829. [CrossRef]

76. Kris-Etherton, P.M.; Hecker, K.D.; Bonanome, A.; Coval, S.M.; Binkoski, A.E.; Hilpert, K.F.; Griel, A.E.; Etherton, T.D. Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer. Am. J. Med. 2002, 113, 71–88. [CrossRef]

77. Park, E.-J.; Pezzuto, J.M. The pharmacology of resveratrol in animals and humans. Biochim. Biophys. Acta (BBA) Mol. Basis Dis. 2015, 1852, 1071–1113. [CrossRef] [PubMed]

78. Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.; Fong, H.H.; Farnsworth, N.R.; Kinghorn, A.D.; Mehta, R.G. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997, 275, 218–220. [CrossRef] [PubMed]

79. Scheers, I.; Palermo, J.; Freedman, S.; Wilschanski, M.; Shah, U.; Abu-El-Hajia, M.; Barth, B.; Fishman, D.; Gariépy, C.; Giefer, M. NCBINCBI Logo Skip to main content Skip to navigation Resources How To About NCBI Accesskeys Sign in to NCBI PubMed US National Library of Medicine National Institutes of Health Search database Search term Clear input Advanced Help Result Filters Format: Abstract Send to J Pediatr Gastroenterol Nutr. J. Pediatr. Gastroenterol. Nutr. 2018.

80. Seyed, M.A.; Jantan, I.; Bukhari, S.N.A.; Vijayaraghavan, K. A comprehensive review on the chemotherapeutic potential of piceatannol for cancer treatment, with mechanistic insights. J. Agric. Food Chem. 2016, 64, 725–737. [CrossRef]

81. Siddiqui, I.A.; Sanna, V.; Ahmad, N.; Sechi, M.; Mukhtar, H. Resveratrol nanoformulation for cancer prevention and therapy. Ann. N. Y. Acad. Sci. 2015, 1348, 20–31. [CrossRef]

82. Soural, I.; Vrchotová, N.; Tříská, J.; Balík, J.; Horník, Š.; Čuřínová, P.; Sýkora, J. Various extraction methods for obtaining stilbenes from grape cane of Vitis vinifera L. Molecules 2015, 20, 6093–6112. [CrossRef]

83. Calvanese, V.; Lara, E.; Kahn, A.; Fraga, M.F. The role of epigenetics in aging and age-related diseases. Ageing Res. Rev. 2009, 8, 268–276. [CrossRef]

84. Pal, S.; Tyler, J.K. Epigenetics and aging. Sci. Adv. 2016, 2, e1600584. [CrossRef]

85. Johnson, A.A.; Akman, K.; Callimport, S.R.; Wuttke, D.; Stolzing, A.; De Magalhaes, J.P. The role of DNA methylation in aging, rejuvenation, and age-related disease. Rejuvenation Res. 2012, 15, 483–494. [CrossRef]

86. Berdyshev, G.; Korotaev, G.; Boiarshikh, G.; Vanuushin, B. Nucleotide composition of DNA and RNA from somatic tissues of humpback and its changes during spawning. Biokhimia 1967, 32, 988. [PubMed]
87. Day, K.; Waite, L.L.; Thalacker-Mercer, A.; West, A.; Bamman, M.M.; Brooks, J.D.; Myers, R.M.; Absher, D. Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. Genome Biol. 2013, 14, R102. [CrossRef] [PubMed]

88. Friedman, J.; Hastie, T.; Tibshirani, R. Regularization paths for generalized linear models via coordinate descent. J. Stat. Softw. 2010, 33, 1. [CrossRef] [PubMed]

89. Hochschild, R. Validating biomarkers of aging—mathematical approaches and results of a 2462-person study. In Practical Handbook of Human Biological Age Determination; CRC Press: Boca Raton, FL, USA, 1994; pp. 93–144.

90. Horvath, S.; Raj, K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. J. Stat. Softw. 2018, 19, 371. [CrossRef] [PubMed]

91. Horvath, S. DNA methylation age of human tissues and cell types. Genome Biol. 2013, 14, 3156. [CrossRef]

92. Beetch, M.; Lubecka, K.; Kristofzski, H.; Suderman, M.; Stefanska, B. Subtle alterations in DNA methylation patterns in normal cells in response to dietary stilbenoids. Mol. Nutr. Food Res. 2018, 62, 1800193. [CrossRef]

93. Zheng, S.C.; Widschwendter, M.; Teschendorff, A.E. Epigenetic drift, epigenetic clocks and cancer risk. Epigenomics 2016, 8, 705–719. [CrossRef]

94. Fatemi, M.; Hermann, A.; Gowher, H.; Jeltsch, A. Dnmt3a and Dnmt1 functionally cooperate during de novo methylation of DNA. Eur. J. Biochem. 2002, 269, 4981–4984. [CrossRef]

95. Sugiyama, Y.; Hatano, N.; Sueyoshi, N.; Sueetake, I.; Tajima, S.; Kinoshita, E.; Kinoshita-Kikuta, E.; Koike, T.; Kameshita, I. The DNA-binding activity of mouse DNA methyltransferase 1 is regulated by phosphorylation with casein kinase 1ε. Biochem. J. 2010, 427, 489–497. [CrossRef]

96. Casillas, M.A.; Lopatina, N.; Andrews, L.G.; Tollefsbol, T.O. Transcriptional control of the DNA methyltransferases is altered in aging and neoplastically-transformed human fibroblasts. Mol. Cell. Biochem. 2003, 252, 33–43. [CrossRef]

97. Okano, M.; Bell, D.W.; Haber, D.A.; Li, E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell 1999, 99, 247–257. [CrossRef]

98. Okano, M.; Xie, S.; Li, E. Cloning and characterization of a family of novel mammalian DNA (cytosine-5) methyltransferases. Nat. Genet. 1998, 19, 219–220. [CrossRef] [PubMed]

99. Bannister, A.J.; Kouzarides, T. Regulation of chromatin by histone modifications. Cell Res. 2011, 21, 381–395. [CrossRef]

100. Dang, W.; Steffen, K.K.; Perry, R.; Dorsey, J.A.; Johnson, F.B.; Shilatifard, A.; Kaeberlein, M.; Kennedy, B.K.; Berger, S.L. Histone H4 lysine 16 acetylation regulates cellular lifespan. Nature 2009, 459, 802. [CrossRef] [PubMed]

101. Kim, S.; Benguria, A.; Lai, C.-Y.; Jazwinski, S.M. Modulation of life-span by histone deacetylase genes in Saccharomyces cerevisiae. Mol. Biol. Cell 1999, 10, 3125–3136. [CrossRef] [PubMed]

102. Sen, P.; Dang, W.; Donahue, G.; Dai, J.; Dorsey, J.; Cao, X.; Liu, W.; Cao, K.; Perry, R.; Lee, J.Y. H3K36 methylation promotes longevity by enhancing transcriptional fidelity. Genes Dev. 2015, 29, 1362–1376. [CrossRef]

103. Ni, Z.; Ebata, A.; Alipanahiramandi, E.; Lee, S.S. Two SET domain containing genes link epigenetic changes and aging in Caenorhabditis elegans. Aging Cell 2012, 11, 315–325. [CrossRef]

104. Delcuve, G.P.; Khan, D.H.; Davie, J.R. Roles of histone deacetylases in epigenetic regulation: Emerging paradigms from studies with inhibitors. Clin. Epigenetics 2012, 4, 5. [CrossRef]

105. Feser, J.; Truong, D.; Das, C.; Carson, J.J.; Kieft, J.; Harkness, T.; Tyler, J.K. Elevated histone expression promotes life span extension. Mol. Cell 2010, 39, 724–735. [CrossRef]

106. Hu, Z.; Chen, K.; Xia, Z.; Chavez, M.; Pal, S.; Seol, J.-H.; Chen, C.-C.; Li, W.; Tyler, J.K. Nucleosome loss leads to global transcriptional up-regulation and genomic instability during yeast aging. Genes Dev. 2014, 28, 396–408. [CrossRef]

107. Wade, P.A.; Pruss, D.; Wolfe, A.P. Histone acetylation: Chromatin in action. Trends Biochem. Sci. 1997, 22, 128–132. [CrossRef]

108. Teperino, R.; Schoonjans, K.; Auwerx, J. Histone methyl transferases and demethylases; can they link metabolism and transcription? Cell Metab. 2010, 12, 321–327. [CrossRef] [PubMed]

109. Frías-Lasserre, D.; Villagra, C.A. The importance of ncRNAs as epigenetic mechanisms in phenotypic variation and organic evolution. Front. Microbiol. 2017, 8, 2483. [CrossRef]

110. Friedman, R.C.; Farh, K.K.-H.; Burge, C.B.; Bartel, D.P. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009, 19, 92–105. [CrossRef] [PubMed]
111. Grillari, J.; Grillari-Voglauer, R. Novel modulators of senescence, aging, and longevity: Small non-coding RNAs enter the stage. *Exp. Gerontol.* 2010, 45, 302–311. [CrossRef]

112. He, L.; Hannon, G.J. MicroRNAs: Small RNAs with a big role in gene regulation. *Nat. Rev. Genet.* 2004, 5, 522–531. [CrossRef]

113. Grammatikakis, I.; Panda, A.C.; Abdelmohsen, K.; Gorospe, M. Long noncoding RNAs (IncRNAs) and the molecular hallmarks of aging. *Aging* 2014, 6, 992. [CrossRef]

114. Boehm, M.; Slack, F. A developmental timing microRNA and its target regulate life span in *C. elegans*. *Science* 2005, 310, 1954–1957. [CrossRef]

115. He, J.; Tu, C.; Liu, Y. Role of IncRNAs in aging and age-related diseases. *Aging Med.* 2018, 1, 158–175. [CrossRef] [PubMed]

116. Yang, D.; Lian, T.; Tu, J.; Gaur, U.; Mao, X.; Fan, X.; Li, D.; Li, Y.; Yang, M. LncRNA mediated regulation of cellular mechanisms contribute to telomerase inhibition by EGCG. *Carcinogenesis* 2004, 25, 1227–1236. [CrossRef]

117. Denham, J.; Marques, F.Z.; O’Brien, B.J.; Charchar, F.J. Exercise: Putting action into our epigenome. *Sports Med.* 2014, 44, 189–209. [CrossRef] [PubMed]

118. Donohoe, D.R.; Bultman, S.J. Metaboloepigenetics: Interrelationships between energy metabolism and epigenetic control of gene expression. *J. Cell. Physiol.* 2012, 227, 3169–3177. [CrossRef] [PubMed]

119. Ribarič, S. Diet and aging. *Aging Med.* 2010, 3, 627–634. [CrossRef] [PubMed]

120. Du, L.; Xie, Z.; Wu, L.-c.; Chiu, M.; Lin, J.; Chan, K.K.; Liu, S.; Liu, Z. Reactivation of RASSF1A in breast cancer cells by curcumin. *Nutr. Cancer* 2012, 64, 1228–1235. [CrossRef] [PubMed]

121. Berletch, J.B.; Liu, C.; Love, W.K.; Andrews, L.G.; Katiyar, S.K.; Tollefsbol, T.O. Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *J. Cell. Biochem.* 2008, 103, 509–519. [CrossRef]

122. Sang, Y.; Zhang, F.; Wang, H.; Yao, J.; Chen, R.; Zhou, Z.; Yang, K.; Xie, Y.; Wan, T.; Ding, H. Apigenin exhibits anti-invasive effects in a mouse model of d-galactose-induced aging via activating the Nrf2 pathway. *Food Funct.* 2017, 8, 2331–2340. [CrossRef]

123. Choi, S.; Youn, J.; Kim, K.; Joo, D.H.; Shin, S.; Lee, J.; Lee, H.K.; An, I.-S.; Kwon, S.; Youn, H.J. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. *Int. J. Mol. Med.* 2016, 38, 627–634. [CrossRef]

124. Banerjee, K.; Mandal, M. Oxidative stress triggered by naturally occurring flavone apigenin results in senescence and chemotherapeutic effect in human colorectal cancer cells. *Redox Biol.* 2015, 5, 153–162. [CrossRef]

125. Pirmoradi, S.; Fathi, E.; Farahzadi, R.; Pilehvar-Soltanahmadi, Y.; Zarghami, N. Curcumin affects adipose tissue-derived mesenchymal stem cell aging through TERT gene expression. *Drug Res.* 2018, 68, 213–221. [CrossRef]

126. Henning, S.M.; Wang, P.; Said, J.; Magyar, C.; Castor, B.; Doan, N.; Tosity, C.; Moro, A.; Gao, K.; Li, L. Polyphenols in brewed green tea inhibit prostate tumor xenograft growth by localizing to the tumor and decreasing oxidative stress and angiogenesis. *J. Nutr. Biochem.* 2014, 25, 189–209. [CrossRef] [PubMed]

127. Kim, Y.-H.; Lee, D.-H.; Jeong, J.-H.; Guo, Z.S.; Lee, Y.J. Quercetin augments TRAIL-induced apoptotic death: Involvement of the ERK signal transduction pathway. *Biochem. Pharmacol.* 2008, 75, 1946–1958. [CrossRef] [PubMed]

128. Yang, D.; Lian, T.; Tu, J.; Gaur, U.; Mao, X.; Fan, X.; Li, D.; Li, Y.; Yang, M. LncRNA mediated regulation of cellular mechanisms contribute to telomerase inhibition by EGCG. *Carcinogenesis* 2004, 25, 1227–1236. [CrossRef] [PubMed]

129. Berletch, J.B.; Liu, C.; Love, W.K.; Andrews, L.G.; Katiyar, S.K.; Tollefsbol, T.O. Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *J. Cell. Biochem.* 2008, 103, 509–519. [CrossRef]

130. Zhang, Y.; Wang, X.; Han, L.; Zhou, Y.; Sun, S. Green tea polyphenol EGCG reverse cisplatin resistance of A549/DDP cell line through candidate genes demethylation. *Biomed. Pharmacother.* 2015, 69, 285–290. [CrossRef] [PubMed]

131. Berletch, J.B.; Liu, C.; Love, W.K.; Andrews, L.G.; Katiyar, S.K.; Tollefsbol, T.O. Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *J. Cell. Biochem.* 2008, 103, 509–519. [CrossRef]

132. Wang, Y.; Li, M.; Xu, X.; Song, M.; Tao, H.; Bai, Y. Green tea epigallocatechin-3-gallate (EGCG) promotes neural progenitor cell proliferation and sonic hedgehog pathway activation during adult hippocampal neurogenesis. *Mol. Nutr. Food Res.* 2012, 56, 1292–1303. [CrossRef]
Li, Y.; Chen, F.; Wei, A.; Bi, F.; Zhu, X.; Yin, S.; Lin, W.; Cao, W. Klotho recovery by genistein via promoter.

Fang, M.Z.; Wang, Y.; Ai, N.; Hou, Z.; Sun, Y.; Lu, H.; Welsh, W.; Yang, C.S. Tea polyphenol.

Nandakumar, V.; Vaid, M.; Katiyar, S.K. (-)-Epigallocatechin-3-gallate reactivates silenced tumor suppressor genes, Cip1/p21 and p 16 INK4a, by reducing DNA methylation and increasing histones acetylation in human skin cancer cells. Carcinogenesis 2011, 32, 537–544. [CrossRef]

Fang, M.Z.; Wang, Y.; Ai, N.; Hou, Z.; Sun, Y.; Lu, H.; Welsh, W.; Yang, C.S. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res. 2003, 63, 7563–7570.

Iovine, B.; Iannella, M.L.; Gasparri, F.; Monfrecola, G.; Bevilacqua, M.A. Synergistic effect of genistein and daidzein on UVB-induced DNA damage: An effective photoprotective combination. BioMed. Res. Int. 2011, 2011, 8. [CrossRef]

Isoherranen, K.; Punnonen, K.; Jansen, C.; Uotila, P. Ultraviolet irradiation induces cyclooxygenase-2 expression in keratinocytes. Br. J. Dermatol. 1999, 140, 1017–1022. [CrossRef]

Li, Y.; Chen, F.; Wei, A.; Bi, F.; Zhu, Y.; Yin, S.; Lin, W.; Cao, W. Klotho recovery by genistein via promoter.

Liu, D.; Ma, Z.; Xu, L.; Zhang, X.; Qiao, S.; Yuan, J. PGC1α expression in keratinocytes.

Zhang, H.; Yang, X.; Pang, X.; Zhao, Z.; Yu, H.; Zhou, H. Genistein protects against ox-LDL-induced senescence through enhancing SIRT1/LKB1/AMPK-mediated autophagy flux in HUVECs. Mol. Cell. Biochem. 2019, 455, 127–134. [CrossRef] [PubMed]

Dhar, S.; Kumar, A.; Zhang, L.; Rimando, A.M.; Lage, J.M.; Lewin, J.R.; Atfi, A.; Zhang, X.; Levenson, A.S. Dietary pterostilbene is a novel MTA1-targeted chemopreventive and therapeutic agent in prostate cancer. Oncotarget 2016, 7, 18469. [CrossRef] [PubMed]

Liu, D.; Ma, Z.; Xu, L.; Zhang, X.; Qiao, S.; Yuan, J. PGC1α activation by pterostilbene ameliorates acute doxorubicin cardiotoxicity by reducing oxidative stress via enhancing AMPK and SIRT1 cascades. Aging 2019, 11, 10061. [CrossRef]

Kala, R.; Shah, H.N.; Martin, S.L.; Tollefsbol, T.O. Epigenetic-based combinatorial resveratrol and pterostilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-dependent γ-H2AX and telomerase regulation in triple-negative breast cancer. BMC Cancer 2015, 15, 672. [CrossRef]

Park, S.-J.; Ahmad, F.; Philp, A.; Baar, K.; Williams, T.; Luo, H.; Ke, H.; Rehmann, H.; Tsuassig, R.; Brown, A.L. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. Cell 2012, 148, 421–433. [CrossRef]

Barger, J.L.; Kayo, T.; Vann, J.M.; Arias, E.B.; Wang, J.; Hacker, T.A.; Wang, Y.; Raederstorff, D.; Morrow, J.D.; Leeuwenburgh, C. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PLoS ONE 2008, 3. [CrossRef]

Baur, J.A.; Pearson, K.J.; Price, N.L.; Jamieson, H.A.; Jerin, C.; Kalra, A.; Prabhhu, V.V.; Allard, J.S.; Lopez-Lluch, G.; Lewis, K. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006, 444, 337–342. [CrossRef]

Warnsman, V.; Haimbuch, S.; Osiewacz, H.D. Quercetin-induced lifespan extension in Podospora anserina requires methylation of the flavonoid by the O-methyltransferase PaMTH1. Front. Genet. 2018, 9, 160. [CrossRef]

Wang, H.; Jo, Y.-J.; Oh, J.S.; Kim, N.-H. Quercetin delays postovulatory aging of mouse oocytes by regulating SIRT expression and MPF activity. Oncotarget 2017, 8, 38631. [CrossRef]

Receno, C.N.; Liang, C.; Korol, D.L.; DeRuisseau, K.C. Curcumin supplementation effects on aging skeletal muscle. FASEB J. 2017, 31, 1021–1022.

Stepier, K.; Wojdyla, D.; Nowak, K.; Motori, M. Impact of curcumin on replicative and chronological aging in the Saccharomyces cerevisiae yeast. Biogerontology 2020, 21, 109–123. [CrossRef] [PubMed]

La Spina, M.; Sansevero, G.; Biasutto, L.; Zoratti, M.; Peruozz, R.; Berardi, N.; Sale, A.; Azzolini, M. Pterostilbene Improves Cognitive Performance in Aged Rats: An in Vivo Study. Cell Physiol. Biochem. 2019, 52, 232–239. [PubMed]

Abharzanjani, F.; Afshar, M.; Hemmati, M.; Moossavi, M. Short-term high dose of quercetin and resveratrol alters aging markers in human kidney cells. Int. J. Prev. Med. 2017, 8, 64. [CrossRef]