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Review

Dietary Polyphenols and Their Biological Significance

Xiuzhen Han, Tao Shen and Hongxiang Lou*

Department of Natural Product Chemistry, School of Pharmaceutical Sciences, Shandong University, 44 West Wenhua Road, Jinan 250012, P. R. China; E-mails: xzyhan@sina.com (X. Han); v.shentao@yahoo.com.cn (T. Shen)

* Author to whom correspondence should be addressed; E-mail: louhongxiang@sdu.edu.cn; Tel.: (+86)-531-88382012; Fax: (+86)-531-88382019

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Abstract: Dietary polyphenols represent a wide variety of compounds that occur in fruits, vegetables, wine, tea, extra virgin olive oil, chocolate and other cocoa products. They are mostly derivatives and/or isomers of flavones, isoflavones, flavonols, catechins and phenolic acids, and possess diverse biological properties such as antioxidant, antiapoptosis, anti-aging, anticarcinogen, anti-inflammation, anti-atherosclerosis, cardiovascular protection, improvement of the endothelial function, as well as inhibition of angiogenesis and cell proliferation activity. Most of these biological actions have been attributed to their intrinsic reducing capabilities. They may also offer indirect protection by activating endogenous defense systems and by modulating cellular signaling processes such as nuclear factor-kappa B (NF-κB) activation, activator protein-1(AP-1) DNA binding, glutathione biosynthesis, phosphoinositide 3 (PI3)-kinase/protein kinase B (Akt) pathway, mitogen-activated protein kinase (MAPK) proteins [extracellular signal-regulated protein kinase (ERK), c-jun N-terminal kinase (JNK) and P38] activation, and the translocation into the nucleus of nuclear factor erythroid 2 related factor 2 (Nrf2). This paper covers the most recent literature on the subject, and describes the biological mechanisms of action and protective effects of dietary polyphenols.

Keywords: Polyphenols; antioxidant; anticarcinogen; antiapoptosis; cardiovascular protection; Nrf2; NF-κB; biological properties.

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1. Introduction

Oxidative stress results in oxidative alteration of biological macromolecules such as lipids, proteins and nucleic acids. It is considered to play a pivotal role in the pathogenesis of aging and degenerative diseases [1-3]. In order to cope with an excess of free radicals produced upon oxidative stress, human bodies have developed sophisticated mechanisms for maintaining redox homeostasis. These protective mechanisms include scavenging or detoxification of reactive oxygen species (ROS), blocking ROS production, sequestration of transition metals, as well as enzymatic and nonenzymatic antioxidant defenses produced in the body, that is, endogenous [4,5], and others supplied with the diet, namely, exogenous ones. Among them, dietary polyphenols have been widely studied for their strong antioxidant capacities and other properties by which cell functions are regulated [6,7].

Dietary polyphenols represent a group of secondary metabolites which widely occur in fruits, vegetables, wine, tea, extra virgin olive oil, chocolate and other cocoa products. They are mostly derivatives, and/or isomers of flavones, isoflavones, flavonols, catechins, and phenolic acids. Dietary polyphenols exhibit many biologically significant functions, such as protection against oxidative stress, and degenerative diseases. Experimental data indicate that most of these biological actions can be attributed to their intrinsic antioxidant capabilities. Dietary polyphenols may offer an indirect protection by activating endogenous defense systems and by modulating cellular signaling processes such as NF-κB activation, AP-1 DNA binding, glutathione biosynthesis, PI3-kinase/Akt pathway, MAPK proteins (ERK, JNK and P38) activation, and the translocation into the nucleus of Nrf2 [8-10].

2. Classification and occurrence of dietary polyphenols

Dietary polyphenols are the most abundant antioxidants in human diets. With over 8,000 structural variants, they are secondary metabolites of plants and denote many substances with aromatic ring(s) bearing one or more hydroxyl moieties. They are subdivided into groups (Figure 1) by the number of phenolic rings and of the structural elements that link these rings [11]: (1) The phenolic acids with the subclasses derived from hydroxybenzoic acids such as gallic acid and from hydroxycinnamic acid, containing caffeic, ferulic, and coumaric acid; (2) the large flavonoid subclass, which includes the flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols; (3) the stilbenes; and (4) the lignans and the polymeric lignins.

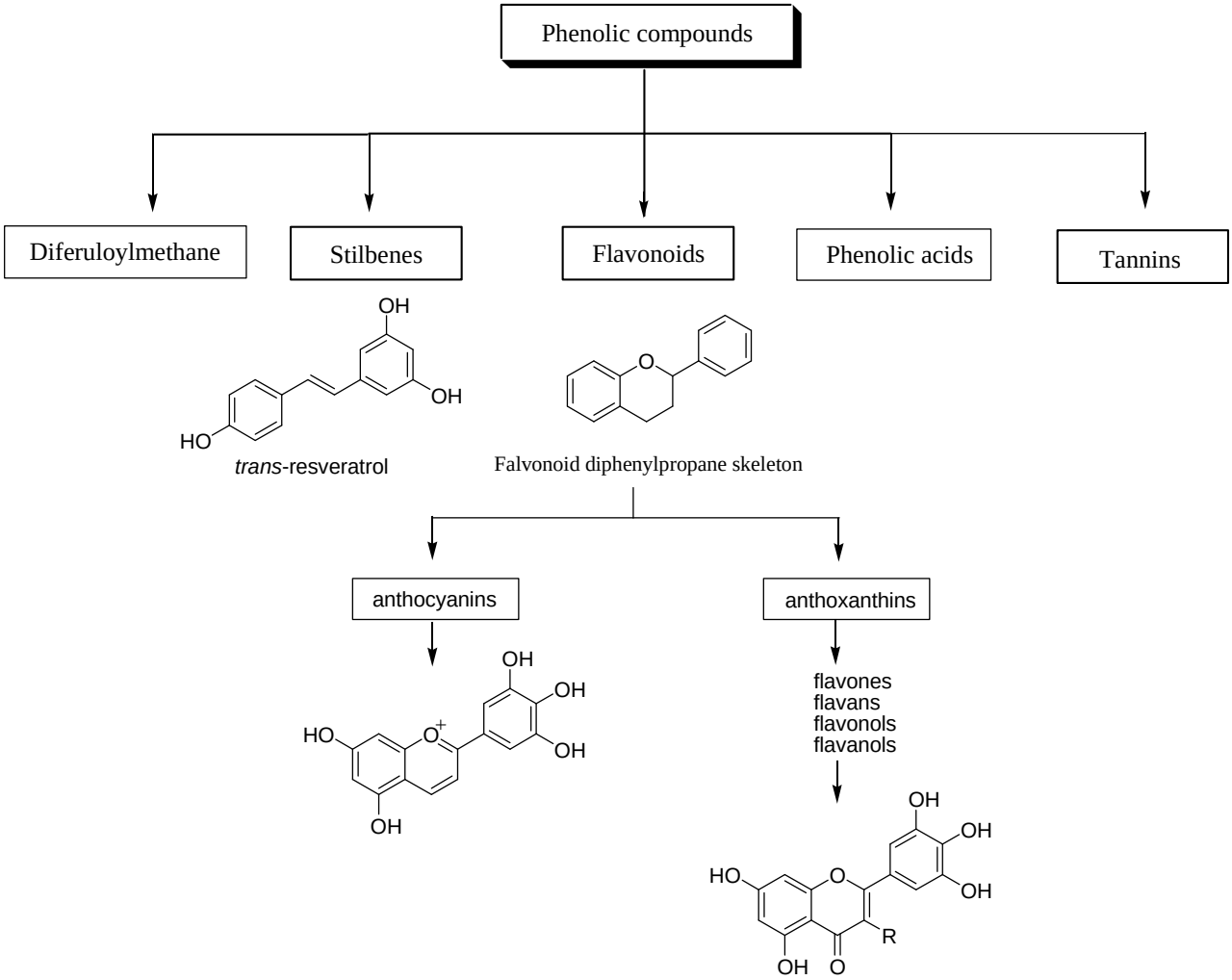
The main dietary sources of polyphenols include some common fruits, vegetables and beverages. Phenolic acids account for about one third of the total intake and flavonoids account for the remaining two thirds. The most abundant flavonoids in the diet are flavanols (catechins plus proanthocyanidins), anthocyanins and their oxidation products. The main polyphenol dietary sources are fruit and beverages (fruit juice, wine, tea, coffee, chocolate and beer) and, to a lesser extent vegetables, dry legumes and cereals. Most of dietary polyphenols and their sources in our diets were shown in Table 1.

2.1 Phenolic acids

A major class within the phenolic compounds is the hydroxycinnamic acids, which are widely distributed in plant kingdom. The major hydroxycinnamic acid is caffeic acid, which occurs in foods mainly as an ester with quinic acid called chlorogenic acid (5-caffeoylquinic acid). Chlorogenic acid

and caffeic acid are antioxidants *in vitro* and they might inhibit the formation of mutagenic and carcinogenic *N*-nitroso compounds for the inhibitory effect on the *N*-nitrosation reaction *in vitro*.

Figure 1. Classification of dietary polyphenols.



2.2 Flavonoids

Flavonoids are the most abundant polyphenols in human diets, and are mainly divided into: (a) anthocyanins, glycosylated derivative of anthocyanidin, present in colorful flowers and fruits; (b) anthoxanthins, a group of colorless compounds further divided in several categories, including flavones, flavans, flavonols, flavanols, isoflavones, and their glycosides. Flavonols are mainly represented by myricetin, fisetin, quercetin and kaempferol.

2.3 Stilbenes

Stibenes are structurally characterized by the presence of a 1,2-diphenylethylene nucleus with hydroxyls substitued on the aromatic rings, and exist in the form of monomers or oligomers. The best known compound is trans-resveratrol, possessing a trihydroxystilbene skelelton.

2.4 Tannins

Tannins are a group of water-soluble polyphenols having molecular weights from 500 to 3,000 which are subdivided into condensed and hydrolisable tannins, and commonly found complexed with alkaloids, polysaccharides and proteins, particularly the latter. On the basis of structural characteristics there are two groups, gallotannins and ellagitannins of hydrolysable tannins.

2.5 Diferuloylmethanes

Diferuloylmethanes are a small group of phenolic compounds with two aromatic rings substitued with hydroxyls, and linked by aliphatic chain containing carbonyl groups. There are also some other polyphenols such as hydroxytyrosol, a simple polyphenol presenting in olive fruits and olive oil [12,13].

Table 1. Classification and sources of dietary polyphenols

Class and subclass	**Dietary polyphenol**	**Foods or beverages**	**Ref**
Flavonoids			
Anthocyanidins	Cyanidin 3-galactoside Cyanidin 3-glucoside Cyanidin 3-arabinoside Cyanidin 3-xyloside Malvidin Delphinidin Pelargonidin	**Fruits**: blackberries,black currant,blueberries, black grape, elderberries,strawberries, cherries, plums, cranberry, pomegranate juice, raspberry **Others**: red wine	6 14 15 16
Anthoxanthins			
Flavonols	Myricetin Fisetin Quercetin Kaempferol Isorhamnetin	**Vegetables**: capers, celery, chives, onions, red onions, dock leaves, fennel, hot peppers,cherry tomatoes, spinach, sweet potato leaves, lettuce, celery, broccoli, Hartwort leaves, kale **Cereal**: buckwheat, beans(green/yellow) **Fruits**: apples, apricots, grapes, plums, bilberries, blackberries, blueberries, cranberries, olive elderberries, currants, cherries, black currant juice, apple juice, ginkgo biloba **Spices and herbs**: dill weed **Others**: red wine, tea (green, black), tea (black beverage), cocoa powder, turnip (green), endive, leek	7 17 14
Flavanones	Naringenin Eriodictyol Hesperetin	**Citrus fruits and juices**: lemon, lemon juice, lime juice, orange, orange juice, grapefruit, tangerine juice **Spices and herbs**: peppermint	18 19 20
Flavones	Apigenin Luteolin	**Fruits**: celery, olives **Vegetables**: hot peppers, celery hearts, fresh parsley **Spices and herbs**: oregano, rosemary, dry parsley, thyme	14 21 22

Table 1. Cont.

Flavanols (Flavan-3-ols)	(+)-Catechin (-)-Epicatechin (-)-Epicatechin 3-gallate Morin (-)-Epigallocatechin (-)-Epigallocatechin-3-gallate (+)-Gallocatechin Procyanidins Prodelphinidins	**Fruits**: apples, apricots, grapes, peaches, nectarines, pears,plums, raisins, raspberries, cherries, blackberries, blueberries, cranberries **Others**: red wine, tea (green, black), chocolate (dark, milk), white wine, cocoa	23 24
Isoflavones (Flavans)	Genistein Daidzein Equol	**Fruits**: grape seed/skin **Others**: soybean, soy nuts, soy flour/bread, tofu, miso, soy milk, tofu yogurt, soy cheese/sauce/hot dog	25
Flavonoid glycoside	Rutin Hesperidin Naringin	**Fruits**: lemon, orange, orange juice, grapefruit, tangerine juice	26
Phenolic acids Hydroxycinnamic acids	Caffeic acid Chlorogenic acid Ferulic acid Neochlorogenic acid P-coumaric acid Sinapic acid Caftaric acids	**Fruits**: bluberry, cranberry, pear, cherry(sweet), apple, orange, grapefruit, cherry juice,apple juice, lemon, peach, **Vegetables**: potato, lettuce, spinach **Others**: coffee beans, tea, coffee, cider	27
Hydroxybenzoic acids	Ellagic acid Gallic acid Corilagin	**Fruits**: strawberry, raspberry grape juice(black/green), longan seed, pomegranate juice	28 29
Trihydroxy-stilbenes	Resveratrol Trans-resveratrol	**Fruits**: grapes, peanuts, **Others**: red wine	30 31
Tannins	Catechin polymers Epicatechin polymers Ellagitannins Proanthocyanidins Casuarictin Sanguin H6 Tannic acids	**Fruits**: grape (dark/light) seed/skin, apple juice, strawberries, longan, raspberries, pomegranate, walnuts, muscadine grape, muscadine grape, peach, blackberry (juices/jams/jellies), olive, plum, **Vegetables**: chick pea, black-eyed peas, lentils, **Cereal**: haricot bean, **Others**: red wine, white wine, cocoa, chocolate, oak-aged red wine, tea, cider, tea, coffee, immature fruits	14 29 32
Diferuloylmethane	Curcumin	herbal remedy, dietary spice turmeric	33

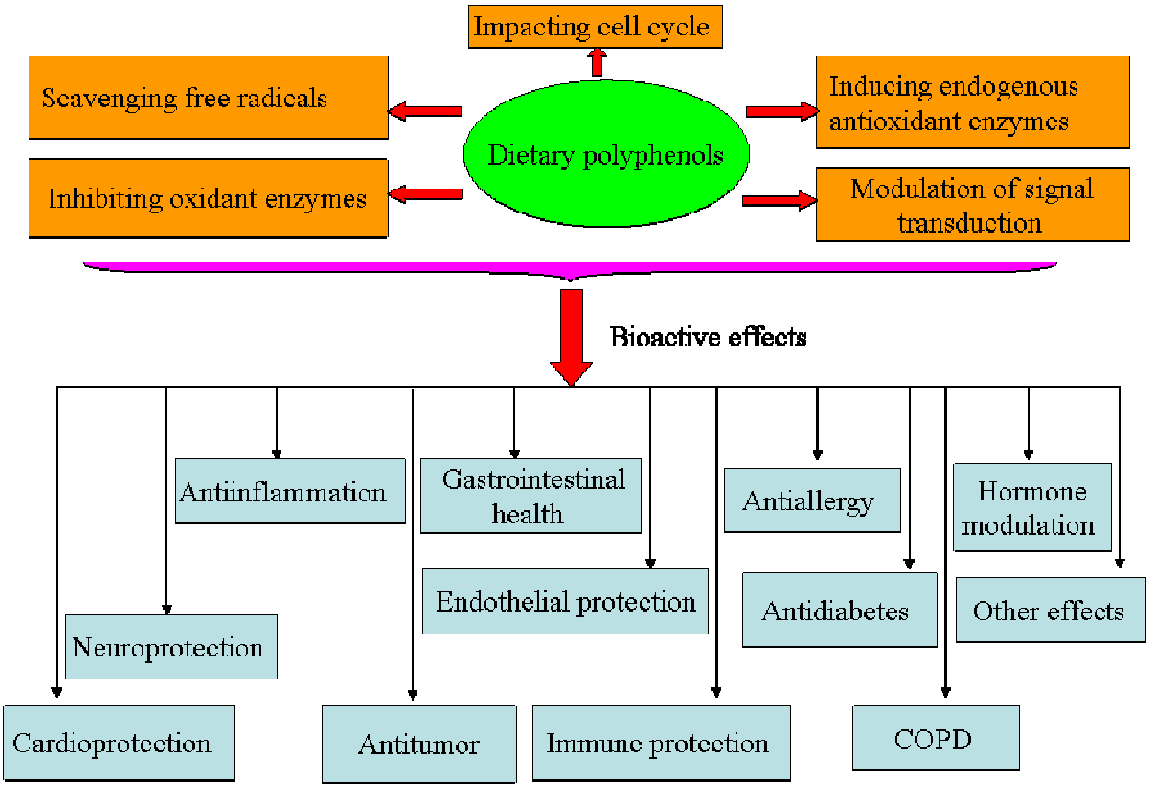
3. Bioactivities of dietary polyphenols

Oxidative stress is considered to play a pivotal role in the pathogenesis of aging and several degenerative diseases, such as atherosclerosis, cardiovascular disease, type II diabetes and cancer [1-3]. In order to cope with an excess of free radicals produced upon oxidative stress, humans have developed endogenous and exogenous mechanisms in order to maintain redox homeostasis. Among these, dietary polyphenols have been largely studied for their strong antioxidant capacities and other properties by which cell activities are regulated (Figures 2 and 3).

3.1 Antioxidant and free radical scavenging properties

In order to combat and neutralize the deleterious effects of ROS, various antioxidant strategies have evolved either by increasing the endogenous antioxidant enzyme defenses or by enhancing the non-enzymatic defenses through dietary or pharmacological means (Table 2). Dietary polyphenols have been reported to possess potent antioxidant activity by endogenous and exogenous mechanisms.

Figure 2. Bioactivities of dietary polyphenols.



Dihydrocaffeic acid was able to scavenge free radicals (superoxide anion, hydroxyl and peroxyl radicals) in human EA.hy926 endothelial cells [42]. Curcumin and quercetin increased several antioxidant enzyme activities such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) or glutathione reductase (GR) *in vivo* and *in vitro* [8,9,44], and activated endogenous defense systems *in vitro* [40,45]. Hydroxytyrosol could increase CAT and SOD activities in rats fed a cholesterol-rich diet [35].

The transcription factor Nrf2 regulates the basal and inducible expression of numerous detoxifying and antioxidant genes. The Nrf2–Kelch-like ECH-associated protein 1 (Keap1)-ARE system is now recognized as one of the major cellular defence mechanisms against oxidative and xenobiotic stresses [46]. (⁻)-Epigallochatechin gallate (EGCG) and (⁻)-epichatechin gallate (ECG) induced ARE-mediated gene expression through the activation of MAPK proteins (ERK, JNK and p38) in HepG2-ARE-C8 cell [10]. Tanigawa *et al.* reported that quercetin-induced ARE activity involves upregulation of Nrf2 through the regulation of both transcription and posttranscription sites and repression of Keap1 by affecting the posttranscription site in HepG2 cells [48]. Curcumin could increase the expression of glutathione S-transferase P1 (GSTP1) by activing ARE and Nrf2 in HepG2 cells [40].

Figure 3. Mechanisms of the biological effects of dietary polyphenols.

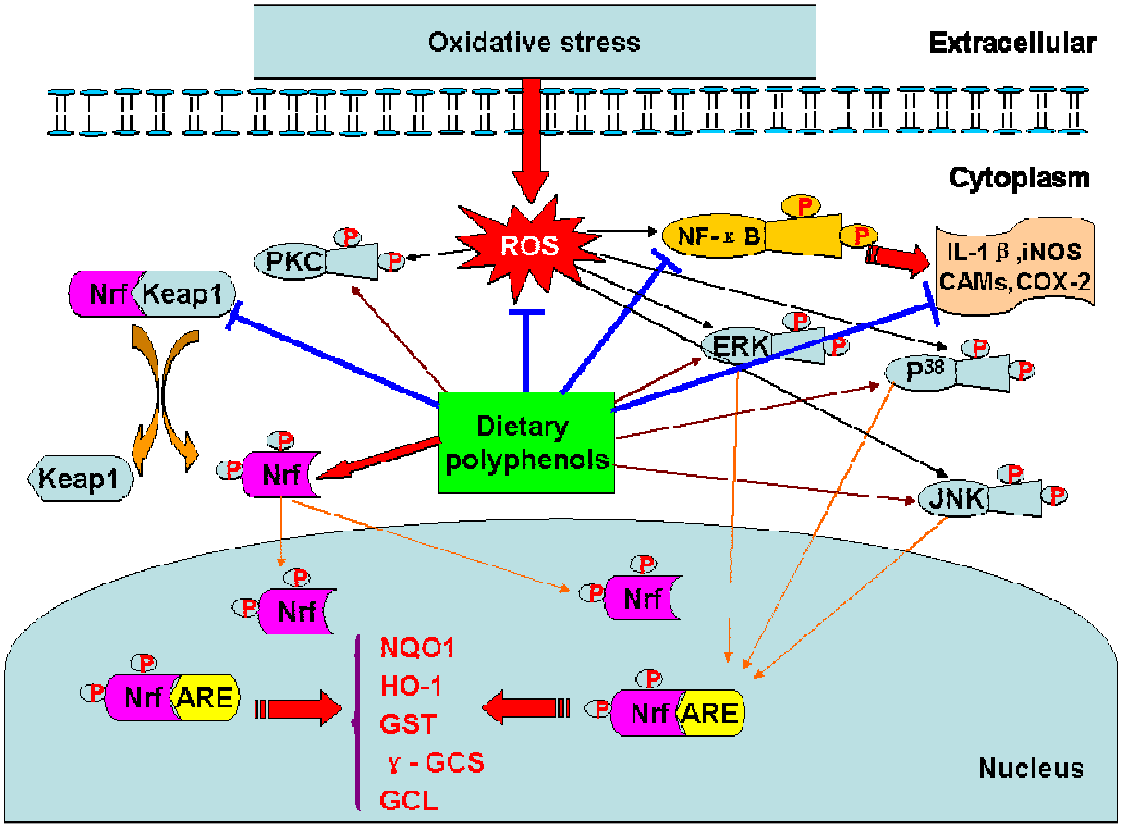


Table 2. Antioxidant and free radical scavenging properties of dietary polyphenols.

Dietary polyphenols	Protective effects and mechanisms	Conditions	Levels	Ref
Epigallocatechin, EGCG, ECG	Inhibiting lipoxygenase and cyclooxygenase	In human colon mucosa and colon tumor tissues	*In vitro*	34
EGCG ECG	Inducing ARE-mediated gene expression through the activation of MAPK proteins (ERK, JNK and p38)	In HepG2-ARE-C8 cell	*In vitro*	10
Hydroxytyrosol	Increasing CAT and SOD activities	In rats fed a cholesterol-rich diet	*In vivo*	35
	Inhibiting the activities of 12-lipoxygenase and 5-lipoxygenase Reducing leukotriene B4 production	In rat platelets and rat polymorphonuclear leukocytes (PMNL)	*In vitro*	36

Table 2. Cont.

Catechin Proanthocyanidin B4	Increasing CAT, glutathione S-transferase (GST) and SOD activities Elevating cellular GSH content	In cardiac H9C2 cells	*In vitro*	37
Curcumin	Inhibiting CYP1A2, CYP3A4, CYP2B6, CYP2D6, and CYP2C9	The plasmids with human cytochrome P450 NADPH reductase	*In vitro*	38
	Inhibiting mitochondrial proton F0F1-ATPase/ATP synthase	Rat brain F0F1-ATPase	*In vitro*	39
	Increasing the expression of GSTP1 by activing ARE and Nrf2	In HepG2 cells	*In vivo*	40
	Increasing CAT, SOD activity and heat shock proteins 70 expression Decreasing the activity of iNOS Decreasing malondialdehyde (MDA), NO(2)(-) + NO(3)(-) and myeloperoxidase (MPO) level and serum transaminase concentration	In rat model	*In vivo*	8
Kaempferol-3-O-galactoside	Inhibiting human recombinant synovial phospholipase A2 (PLA2)	In mice	*In vivo*	41
EGCG, Quercetin, Kaempferol Morin, Apigenin, Daidzein, ECG	Inhibiting mitochondrial proton F0F1-ATPase/ATP synthase	Rat brain F0F1-ATPase	*In vitro*	39
Ellagic acid Gallic acid Corilagin	Inhibiting tyrosinase, xanthine oxidase, and the formation of superoxide radical	In substrate of L-tyrosine	*In vitro*	29
Dihydrocaffeic acid	Enhancing eNOS activity and protein expression Scavenging intracellular ROS	In human EA.hy926 endothelial cells	*In vitro*	42
Caffeic acid (+)-catechin	Inhibiting peroxynitrite-mediated oxidation of dopamine	In dopamine	*In vitro*	43
Quercetin	Preventing lactate dehydrogenase (LDH) leakage Increasing SOD, CAT, GSH, GPx, and GR activity	In mouse liver	*In vivo*	9
	Decreasing MDA and lipoperoxidation Increasing Cu/Zn SOD and GPx mRNA	In HepG2 cells	*In vitro*	44
	Increasing the expression and activity of NADPH:quinone oxidoreductase-1(NQO1)	In the MCF-7 human breast carcinoma cellse	*In vitro*	45
	Enhancing γ-glutamylcysteine synthetase（γ-GCS)	In HepG2 cells	*In vitro*	47
	Enhancing the ARE binding activity and Nrf2-mediated transcription activity Upregulating and stabilizing Nrf2 Reducing the level of Keap1 protein	In HepG2 cells	*In vitro*	48

Table 2. Cont.

Resveratrol	Inhibiting O-acetyltransferase and sulfotransferase activities Preventing the oxidative DNA damage	In male Wistar rats treated with potassium bromate	*In vivo*	49
	Inhibiting the production of H_2O_2 and MPO activity Increasing GSH levels and SOD activities Decreasing the levels of MPO and oxidized GR	In mouse skin	*Ex vivo*	50
	Reducing PhIP-DNA-adduct formation by O-acetyltransferase and sulfotransferase catalysis	In primary cultures of human mammary epithelial cells	*In vitro*	51
	Inhibiting the expression and activity of CYP 1A1/1A2	In microsomes and intact HepG2 cells	*In vitro*	52
	Inhibiting mitochondrial proton F0F1-ATPase/ATP synthase	Rat brain and liver F0F1-ATPase	*In vitro*	39
	Suppressing CYP1A1 and IL-1 β transcription by blocking aryl hydrocarbon receptor		*Ex vivo* *In vivo*	53
(-)-Epicatechin Procyanidin EGCG, ECG	Inhibiting recombinant human platelet 12-lipoxygenase and 15-lipoxygenase	In rabbit smooth muscle cells and in J774A.1 cells	*In vitro*	54

3.2. Anti-atherosclerosis and cardioprotection

Studies have shown that some of dietary polyphenols exerted anti-atherosclerosis and cardioprotection (Table 3). Oleuropein inhibited the oxidation of low density lipoprotein (LDL) *in vitro* [61]. Quercetin decreased lipid peroxidation, upregulated the expression of serum high density lipoprotein (HDL)-associated paraoxonase 1(PON-1) in the HuH7 human hepatoma cell line [66], inhibited oxidized LDL (oxLDL)-triggered apoptosis, and increased intracellular glutathione (GSH) downregulation in COS-1 cells [68].

Proanthocyanidin could significantly reduce cardiomyocyte apoptosis by inhibiting ischemia/reperfusion-induced activation of JNK-1 and c-Jun in Male Sprague Dawley rats [74]. Furthermore, proanthocyanidin could regulate the levels of CD36 mRNA and protein in oxLDL treated peripheral blood mononuclear cells [73]. Resveratrol showed that in vitro it could decrease the expression of vascular cell adhesion molecule-1 (VCAM-1) [64], cyclooxygenase-2 (COX-2) [55], and matrix metalloproteinase-9 (MMP-9) mRNA [56] through suppression of activation of nuclear factor AP-1 [55]. Hydroxytyrosol could not only lower serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), but also slow the lipid peroxidation process in rats fed a cholesterol-rich diet [35].

Table 3. Anti-atherosclerosis and cardioprotection of dietary polyphenols.

Dietary polyphenols	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Resveratrol	Suppresing the expression and activity of COX-2 Suppresing activation of AP-1	In human mammary epithelial cells	*In vitro*	55
	Inhibiting the activity and expression of MMP-9	In U937 cells	*In vitro*	56
	Enhancing myocardial angiogenesis by induction of VEGF, thioredoxin-1 (Trx-1), and HO-1	In male Sprague Dawley rats	*In vivo*	57
	Inhibiting the expression and binding activity of the monocyte chemotactic protein-1 (MCP-1) receptor, CC-chemokine receptor-2（CCR2)	on THP-1 monocytes	*In vitro*	58
	Increasing NO and NOS levels Increasing intracellular cyclc GMP (cGMP) level and decreasing atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels	In cultured rat cardiac fibroblasts	*In vitro*	59
(-)-Epicatechin	Inhibiting 7β-OH-cholesterol formation	In endothelial cells	*In vitro*	60
Hydroxytyrosol	Preventing platelet aggregation and eicosanoid formation Inhibiting thromboxane B2 production	In platelet rich plasma	*In vitro*	61
	Inhibit thromboxane B2 production	In patients with uncomplicated type I diabetes	*In vivo*	62
Hydroxytyrosol Oleuropein Caffeic acid	Inhibiting leukotriene B4 generation Inhibiting 5-lipoxygenase	In rat peritoneal leukocytes	*In vitro*	63
Oleuropein Hydroxytyrosol Resveratrol	Reducing monocytoid cell adhesion to stimulated endothelium Decreasing VCAM-1 mRNA and protein	In human umbilical vein endothelial cells (HUVECs)	*In vitro*	64
Oleuropein	Decreasing creatine kinase and GSH release	In the isolated rat heart	*Ex vivo*	65
Quercetin	Upregulating the expression of serum HDL-associated PON-1	In the HuH7 human hepatoma cell line	*In vitro*	66
Kaempferol Apigenin	Inducing interferon-gamma (IFN-γ) gene expression Downregulating IL-4 gene expression	In peripheral blood mononuclear cells	*In vitro*	67
	Increasing the intracellular GSH and activating γ-GCS heavy subunit (GCS(h)) promoter	In COS-1 cells	*In vitro*	68
EGCG and ECG	Inhibiting rat VSMCs adhesion on collagen and laminin Interference with VSMC's integrin β1 receptor and binding to extracellular matrix (ECM) proteins	In rat VSMCs	*In vitro*	69
Genistein	Decreasing hydroxyproline concentrations Suppressing the progression of myocardial fibrosis	In Long-Evans Tokushima Otsuka non-diabetic rats	*In vivo*	70
Genistein Daidzein	Incorporating into LDLs, increasing their oxidation resistance and antiproliferative efficacy	In cultured U937 cells	*Ex vivo*	71

Table 3. Cont.

Procyanidins	Decreasing leukotriene-prostacyclin ratio in plasma	In humans and human aortic endothelial cells	*In vivo* *In vitro*	72
Proanthocyanidin	Inhibiting CD36 mRNA expression	In peripheral blood mononuclear cell	*In vitro*	73
Proanthocyanidin	Reducing cardiomyocyte apoptosis by inhibiting ischemia–reperfusion-induced activation of JNK-1 and c-Jun	In Male Sprague Dawley rats	*In vivo*	74
Hydroxytyrosol	Lowering serum TC and LDL-C Slowing the lipid peroxidation process	In rats fed a cholesterol-rich diet	*In vivo*	35

3.3 Neuroprotective effects on anti-aging and neurodegenerative diseases

Recently, there has been considerable interest in the neuroprotective effects of dietary polyphenols (Table 4), especially in the context of their modes of action as antioxidants [6]. Resveratrol had an impact on cognitive deficits by activating the phosphorylation of protein kinase C (PKC), secreting transthyretin to prevent Aβ aggregation in cultured rat hippocampal cells [77], and stimulating AMP kinase activity in Neuro2a cells and primary neurons [75]. EGCG stimulated the deacetylase activity of recombinant silent information regulator two ortholog 1 (SIRT1) protein in human HT29 cells [80]. Curcumin could disrupt existing plaques and restore distorted neurites in an Alzheimer mouse model [84]. They had been considered as therapeutic agents for altering brain aging processes, and as possible neuroprotective agents in progressive neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.

Table 4. Neuroprotective effects of dietary polyphenols.

Dietary polyphenols	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Hydroxytyrosol	Attenuating Fe^{2+}- and NO-induced cytotoxicity Increasing cellular ATP Reducing lipid peroxidation Hyperpolarizing basal mitochondrial membrane potential	In murine-dissociated brain cells and mice	*In vitro* *Ex vivo*	12
Resveratrol	Stimulating AMP kinase activity	In Neuro2a cells and primary neurons	*In vitro*	75
	Preventing fibrosis, NF-κB activation and TGF-β increases induced by chronic CCl(4) treatment	In rats	*In vivo*	76
	Activating the phosphorylation of PKC Secreting transthyretin to prevent Aβ aggregation	In cultured rat hippocampal cells	*In vitro*	77
	Protecting dopaminergic neurons Activating sirtuin family of NAD-dependent histone deacetylases	In organotypic midbrain slice culture	*In vitro*	78

Table 4. Cont.

EGCG ECG Myricetin	Inhibiting IL-6, IL-8, VEGF and prostaglandin E2 (PGE2) production Attenuating the expression of COX-2 and activation of NF-κB Inducing the expression of MAPK phosphatase-1 Suppressing the phosphorylation of MAPK (p38 and JNK)	In human astrocytoma U373MG cells	*In vitro*	79
	Attenuating disruption of mitochondrial membrane potential and release of cytochrome c Decreasing the activities of caspase-9 and caspase-3 and increase in the Bax to Bcl-2 ratio	In rat PC12 cells	*In vitro*	115
	Stimulating the deacetylase activity of recombinant SIRT1 protein	In human HT29 cells	*In vitro*	80
	Increasing the activities of PKC and ERK1/2 Decreasing the expression of Bax, Bad, and Mdm2 Increasing the expression of Bcl-2, Bcl-w, and Bcl-xL	In human neuroblastoma SH-SY5Y cell	*In vitro*	81
Catechin Quercetin Genestein Naringenin	Attenuating the apoptotic injury induced *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium hydrochloride (MPP+)	In mesencephalic dopamine neurones	*In vivo*	82
Epicatechin Kaempferol	Protecting neurons from oxLDL-induced apoptosis by inhibiting the activation of JNK, c-Jun and caspase-3	In cultured primary neurons	*In vitro*	83
Curcumin	Disrupting existing plaques and restoring distorted neurites Crossing the blood-brain barrier and labels senile plaques and cerebrovascular amyloid angiopathy	In an Alzheimer mouse model In APPswe/PS1dE9 mice	*In vivo*	84

3.4 Anti-inflammatory properties

Oxidative stress induced inflammation is mediated by the activation of NF-kB and AP-1. It affects a wide variety of cellular signaling processes leading to generation of inflammatory mediators and chromatin remodeling [95,96]. The latter allows expression of pro-inflammatory genes such as interleukin-1beta (IL-1β), IL-8, tumor necrotic factor alpha (TNF-a), and inducible nitric oxide synthase (iNOS). The undesired effects of oxidative stress have been found to be controlled by the antioxidant and/or anti-inflammatory effects of dietary polyphenols such as curcumin and resveratrol *in vivo* and *in vitro* [88-90,95,97] (Table 5). Resveratrol inhibited pro-inflammatory gene expression via inhibition of inhibitory κB (IκB), thus inhibiting NF-κB transactivation, as well as restoring transrepressive pathways through the activation of histone deacetylases in RAW 264.7 cells [89].

Table 5. Anti-inflammatory effects of dietary polyphenols.

Dietary polyphenols	Protective effects and mechanisms	Conditions	Levels	Ref
Procyanidins	Inhibiting transcription and secretion of IL-1β	In peripheral blood mononuclear cells	*In vitro*	85
EGCG ECG	Inducing apoptosis by activating caspases 3, 8, and 9	In Isolated peripheral blood monocytes	*In vitro*	86
	Downregulating CD11b expression Attenuating adhesion and migration of peripheral blood CD8+T cells	In peripheral blood CD8+ T cells	*In vitro*	87
Resveratrol	Inhibiting stimulation of caspase-3 and cleavage of PARP induced by IL-1β	In human articular chondrocytes	*In vitro*	88
	Suppressing the expression of iNOS mRNA and protein by inhibiting the activation of NF-κB Inhibiting NO generation	In RAW 264.7 cells	*In vitro*	89
	Upregulating MAP kinase phosphatase-5	In prostate cells	*In vitro*	90
Apigenin Luteolin Quercetin	Blocking the expression of intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin Inhibiting prostaglandin synthesis and IL-6, 8 production	In human endothelial cells	*In vitro*	91
	Inhibiting the upregulation of THP-1 adhesion and VCAM-1 expression Inhibiting the activity of the NF-κB	In HUVECs	*In vitro*	92
	Inhibiting NO production and iNOS protein expression	In NR8383 macrophages	*In vitro*	93
Anthocyanins Hydroxy-cinnamic acids	Localizing into endothelial cells Reducing the upregulation of IL-8, MCP-1, and ICAM-1	In human microvascular endothelial cells	*In vitro*	94
Curcumin	Decreasing MPO activity and TNF-α on chronic colitis Reducing nitrites levels and the activation of p38 MAPK Downregulating COX-2 and iNOS expression	In rats	*In vivo*	95
	Upregulating MAP kinase phosphatase-5	In prostate cells	*In vitro*	90
	Suppressing the induction of COX-2 and iNOS Inhibiting the expression of ICAM-1 and MCP-1 Suppressing the Janus kinase (JAK)-STAT via activation of Src homology 2 domain-containing protein tyrosine phosphatases (SHP-2)	In both rat primary microglia and murine BV2 microglial cells	*In vitro*	97

On the other hand, to counter the effects of oxidative stress, the cells also concomitantly express protective antioxidants such as glutamate cysteine ligase (GCL), manganese superoxide dismutase

(MnSOD), and heme oxygenase-1(HO-1). In addition, expression of these antioxidant genes via modulation of MAPK-ARE-Nrf2 pathway is upregulated by EGCG and ECG in HepG2-ARE-C8 cell [10]. Apigenin, luteolin and quercetin had also been reported to inhibit inflammatory responses by downregulating the expression of iNOS and adhesion molecules in NR8383 macrophages and human endothelial cells [91-93].

3.5 Antimutagenic/anticarcinogenic properties

Dietary polyphenols could modulate diverse biochemical processes involved in carcinogenesis (Table 6). Curcumin exerted antitumor activities by inhibition of cellular proliferation and angiogenesis, blockade of tumor cell cycle progression, and induction of programmed cell death in vivo and in vitro [109,110]. Cellular signaling cascades mediated by NF-κB or AP-1 acted as a centerplay in regulating many of aforementioned biochemical processes [102,110].

Table 6. Antimutagenic/anticarcinogenic properties of dietary polyphenols.

Dietary polyphenols	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Hydroxytyrosol	Inhibiting cell proliferation Inducing apoptosis by arresting the cells in the G0/G1 phase with a concomitant decrease in the cell percentage in the S and G2/M phases	In human promyelocytic leukaemia cells HL60	*In vitro*	98
Resveratrol	Inhibiting cell proliferation and downregulating telomerase activity	In human colon tumor cells	*In vitro*	99
	Inducing apoptosis mediated by p53-dependent pathway	In HepG2 cells	*In vitro*	100
	Inhibiting cell proliferation by interfering with an estrogen receptor-α (ERα)-associated PI3K pathway	In estrogen-responsive MCF-7 human breast cancer cells	*In vitro*	101
	Suppressing COX-2 expression by blocking the activation of MAPKs and AP-1	In dorsal skin of female ICR mice	*In vitro*	102
	Decreasing the expression of COX-1, COX-2, c-myc, c-fos, c-jun, transforming growth factor-beta1 (TGF-β1) and TNF-α	In mouse skin	*Ex vivo*	50
	Inhibiting oncogenic disease through the inhibition of protein kinase CKII activity	In HeLa cell lysates	*In vitro*	103
	Inhibiting the Ca(2+)-dependent activities of PKCα and PKCβI	On the activities of PKC isozymes	*In vitro*	104
	Inhibiting nitrobenzene(NB)-DNA adducts and NB–Hb adducts	In male Kunming mice	*In vivo*	105
Chlorogenic acid	Inhibiting the formation of DNA single strand breaks	In supercoiled pBR322 DNA	*In vitro*	106
Quercetin Luteolin	Blocking EGFR tyrosine kinase activity	In MiaPaCa-2 cancer cells	*In vitro*	107

Table 6. Cont.

Myricetin Apigenin Quercetin Kaempferol	Inhibiting human CYP1A1 activities Inhibiting the formation of diolepoxide 2(DE2) and B[a]P activation	On 7-ethoxyresorufin O-deethylation	*In vitro*	26
Silymarin Hesperetin Quercetin Daidzein	Interacting with P-glycoprotein and modulating the activity of ATP-binding cassette transporter, breast cancer resistance protein (BCRP/ABCG2)	In two separate BCRP-overexpressing cell lines	*In vitro*	108
EGCG	Inhibiting telomerase	In human cancer cells In nude mice models	*In vitro* *In vivo*	114
Curcumin	Suppressing proliferation and angiogenesis Inhibiting NF-κB-regulated gene products (cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, COX-2, MMP, and VEGF)	In various pancreatic cancer cell lines and nude mice	*In vitro* *In vivo*	109
	Inducing apoptosis by sustained phosphorylation of JNK and p38 MAPK Inhibitiing NF-κB transcriptional activity Inducing phosphorylation of c-jun and stimulation of AP-1 transcriptional activity	In HCT116 cells	*In vitro*	110
	Inducing apoptosis through activation of caspase-8, BID cleavage and cytochrome c release Suppressing ectopic expression of Bcl-2 and Bcl-xl	In human acute myelogenous leukemia HL-60 cells	*In vitro*	111
	Inhibiting the Akt/mTOR/p70S6K pathway and activating the ERK1/2 pathway Inhibiting tumor growth and inducing autophagy	In U87-MG and U373-MG malignant glioma cells In the subcutaneous xenograft model of U87-MG cells	*In vitro* *In vivo*	112

Resveratrol could block the activation of MAPKs and AP-1 in the skin of mice [102]. Consumption of berries and red fruits rich in polyphenols contributed to the reduction of cancer through many mechanisms such as in vitro inhibiting human cytochrome P450-dependent monooxygenases 1A1 (CYP1A1) activities [26], blocking the epidermal growth factor receptor (EGFR) tyrosine kinase activity [107], and decreasing protein kinase CKII activity [103].

3.6 Maintenance of gastrointestinal health and effects on digestive enzymes

It had been reported that digestive enzymes such as lipase, α-amylase, and α-glucosidase, were inhibited by proanthocyanidins and tannins in young chicks, which decreased the digestibility of protein, starch and lipid [119, 120]. Resveratrol could inhibit pancreatic bile salt-dependent lipase (BSDL) activity, expression and secretion in the rat pancreatic AR4-2J cells [121]. Cyanidin-3α-O-rhamnoside and quercetin-3α-O-rhamnoside could inhibit α-glucosidase and advanced glycation end product (AGE) formation *in vitro* [123]. The inhibition of digestive enzymes by dietary polyphenols

may represent an under-reported mechanism for delivering some of the health benefits attributed to a diet rich in fruit and vegetables.

3.7 Modulation of signal transduction pathways

Table 7. Effects of dietary polyphenols on signal transduction pathways.

Dietary polyphenols	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Curcumin	Inhibiting both myeloid differential factor 88 (MyD88)-and TIR domain-containing adapter inducing IFN-β (TRIF)-dependent pathways Inhibiting homodimerization of Toll-like receptor 4(TLR4) Suppressing the activation of NF-κB by inhibiting IκB kinase β activity in MyD88-dependent pathway Inhibiting IFN-regulatory factor 3 (IRF3) activation	In 293T cells	*In vitro*	124
	Inhibiting the level of NOS mRNA and protein Suppressing NF-κB activation through inhibitory of IκB kinase activity	In macrophages	*In vitro*	125
	Suppressing COX-2 expression by inhibiting AP-1 and NF-κB	In BV2 microglial cells	*In vitro*	126
	Inhibiting IL-6-inducible STAT3 phosphorylation and nuclear translocation	In human multiple myeloma cells	*In vitro*	118
	Upregulating CYP3A4 via pregnane X receptor (PXR) activation Activating the electrophile responsive element (EpRE) of HO-1 and enhancing the gastrointestinal (GI)-GPx activity	In HepG2 cells	*In vitro*	127
	Suppressing JAK-STAT inflammatory signaling through activation of SHP-2	In both rat primary microglia and murine BV2 microglial cells	*In vitro*	97
Proanthocyanidins	Promoting apoptosis through alterations in Cdki-Cdk-cyclin cascade, and caspase-3 activation via loss of mitochondrial membrane potential	In human epidermoid carcinoma A431 cells	*In vitro*	128
Proanthocyanidins	Inhibiting the phosphorylation of ERK1/2, JNK and p38 Inhibiting the activation of NF-κB/p65 through inhibition of degradation of IκBα and activation of IκB kinase α	In SKH-1 hairless mice	*In vivo*	129

Table 7. Effects

Caffeic acid	Modulating ceramide-induced signal transduction pathway and NF-κB activation Inhibiting protein tyrosine kinase activity	In U937 cells	In vitro	113
Quercetin	Inhibiting phosphorylation of JNK and p38 MAPK on ROS-mediated signaling	In HUVECs	In vitro	117
	Modulating Akt/PKB and ERK1/2 signalling cascades on neuronal viability	In primary cortical neurons	In vitro In vivo	130
Equol	Mediating rapid vascular relaxation by Ca2+-independent activation of eNOS/Hsp90 involving ERK1/2 and Akt phosphorylation	In human endothelial cells	In vitro	131
Resveratrol	Inhibiting monocyte CCR2 binding activity in an NO-, MAPK- and PI3K-dependent manner Inhibiting CCR2 mRNA in an NO- and MAPK-independent, PI3K-dependent manner	on THP-1 monocytes	In vitro	58
	Inhibiting proliferation of cardiac fibroblasts by NO-cGMP signaling pathway	In cultured rat cardiac fibroblasts	In vitro	59
	Inducing phase II genes by regulating ARE/EpRE activation Modifying the capability of Keap1 in sequestering Nrf2	In PC12 cells	In vitro	132

Dietary polyphenols may not merely exert their diverse biological effects as free radical scavengers, but may also modulate cellular signaling processes by affecting signal transduction pathways [122] (Table 7). Studies have been reported that curcumin could in vitro modulate NF-κB activation [124], AP-1 DNA binding [126], signal transducer and activator of transcription-3 (STAT3) phosphorylation [118]. Resveratrol exerted protection in vitro through PI3-kinase/Akt pathway, MAPK proteins (ERK, JNK and P38) activation [58], and the translocation into the nucleus of Nrf2 [132]. Resveratrol could also upregulate the expressions of GCL, MnSOD, and HO-1 against oxidative stress via MAPK-ARE-Nrf2 pathway in PC12 cells [132].

3.8 Improvement of endothelium functions

Several studies have indicated that red wine polyphenolic compounds (RWPCs) were able to inhibit proliferation and migration of vascular cells (Table 8). RWPCs induced nitric oxide (NO)-mediated endothelium-dependent relaxations in isolated arteries. The activation of endothelial NO synthase (eNOS) was due to two distinct mechanisms: (a) an increase in [Ca2+] i and (b) a phosphorylation of eNOS by the PI3-kinase/Akt pathway [137]. In addition, RWPCs caused endothelium-derived hyperpolarizing factor (EDHF)-mediated relaxations of isolated arteries consecutively to a localized and controlled formation of superoxide anions leading to the activation of the PI3-kinase/Akt pathway [136]. RWPCs also increased endothelial prostacyclin release and inhibited the synthesis and the effects of endothelin-1 in endothelial cell [139,141].

Table 8. Protective effects of dietary polyphenols on endothelial cells and blood vessels

Dietary polyphenols	Protective effects and mechanisms	Conditions	Levels	Ref
EGCG Quercetin	Inhibiting apoptosis through modulation of Bcl-2 and Bax Inhibiting nuclear transactivation of p53 Decreasing the activity of caspase-3 Blocking JNK- and p38 MAPK-related signaling	In HUVECs	*In vitro*	117
RWPCs	Inhibiting the expression of VEGF mRNA and protein Preventing the activation of the p38 MAPK pathway	In VSMCs	*In vitro*	133
	Inhibiting the invasion and migration of VSMCs Inhibiting pro-MMP-2 expression and its activation via inhibition of membrane type 1-MMP (MT1-MMP) activity	In VSMCs	*In vitro*	134
	Inhibiting VSMCs migration through inhibiting the PI3K activity and p38 MAPK phosphorylation Inhibiting the phosphorylation of MKK3/6	In cultured VSMCs	*In vitro*	135
	Inducing EDHF-mediated relaxations through activation of the PI3-kinase/Akt pathway	In porcine coronary arteries	*In vivo*	136
	Increasing intracellular Ca^{2+} and activate tyrosine kinases Increasing NO production	In bovine aortic endothelial cells	*In vitro*	137
	Inhibiting NADPH oxidase activity and/or reducing endothelin-1(ET-1) release	In Twelve-week-old male Wistar rats	*In vivo*	138
	Inhibiting the synthesis of ET-1	In cultured bovine aortic endothelial cells	*In vitro*	139
	Elevating NO and prostacyclin (PGI2)	In rats	*In vivo*	140
	Ehancing PGI2 release	In endothelial cell	*In vitro*	141
Cy3G	Enhancing eNOS activity and expression Inducing NO production Regulating phosphorylation of eNOS and Akt Increasing cGMP production	In bovine vascular endothelial cells	*In vitro*	142
EGCG	Having endothelial-dependent vasodilator actions Activatiing phosphatidylinositol 3-kinase, Akt, and eNOS	In bovine aortic endothelial cells	*In vitro*	143
	Increasing eNOS activity Inducing a sustained activation of Akt, ERK1/2, and eNOS Ser1179 phosphorylation	In bovine aortic endothelial cells	*In vitro*	144
Catechins	Reducing the vascularization induced by the angiogenin-like protein on chicken CAM	In chichen	*In vitro*	145
Activin	Reducing ICAM-1, VCAM-1 and E-selectin	In systemic sclerosis	*In vivo*	146
Proanthocyanidin	Downregulating VCAM-1 expression; Decreasing TNFα-induced adherence of T-cells to HUVECs	In primary HUVECs	*In vitro*	147
Procyanidins Flavan-3-ols	Inhibiting angiotensin I converting enzyme (ACE) activity	In two substrates	*In vitro*	148

RWPCs could prevent matrix metalloproteinases-2 (MMP-2) activation and vascular endothelial growth factor (VEGF) expression in vascular smooth muscle cells (VSMCs) [133,134]. All these mechanisms might contribute to explain the vasodilatory, vasoprotective and anti-hypertensive effects of polyphenols in vivo.

Cyanidin-3-glucoside (Cy3G) and EGCG could enhance vascular eNOS activity and improve vascular endothelial function in bovine vascular endothelial cells [142]. Catechins had anti-angiogenic effects by reducing the vascularization on the chicken chorioallantoic membrane (CAM) [145].

3.9 Protective effect on immune cell functions

Dietary polyphenols appear to have a protective effect on immune cell functions. Alvarez *et al.* showed that leukocyte functions were improved in prematurely aging mice after five weeks of diet supplementation with polyphenol-rich cereals [149]. They could increase macrophage chemotaxis, phagocytosis, microbicidal activity, and natural killer function, and increase lymphoproliferation and IL-2 release in response to concanavalin A and lipopolysaccharide.

Curcumin could prevent tumor-induced T cell apoptosis by downregulating Bax level and augmenting Bcl-2 expression and restore cytokine-dependent Jak-3/Stat-5a signaling pathway in T cells of tumor bearer [150]. Caffeic acid, ellagic acid, and ferulic acid could inhibit apoptosis through the Bcl-2 independent mechanism in normal human peripheral blood mononuclear cells [116]. Thus, regular intake of these compounds will protect and improve quality of life.

3.10 Antiallergic activity

The incidence of type I allergic disorders have been increasing worldwide, particularly, the hypersensitivity to food. Akiyama and his coworkers reported that the apple condensed tannins intake would inhibit the development of the oral sensitization, and the inhibition could correlate with the rise in the population of TCRγδ-T cells in the intestinal intraepithelial lymphocytes [151]. Moreover, the apple condensed tannins could inhibit the release of histamine from rat basophilic leukemia (RBL-2H3) cells stimulated by the antigen-stimulation and from rat peritoneal mast cells stimulated by compound 48/80. They also inhibited hyaluronidase activity and increase in intracellular free calcium concentration in RBL-2H3 cells stimulated with the antigen [152].

3.11 Antidiabetic effects

Johnston and coworkers demonstrated that glucose uptake into cells under sodium-dependent conditions was inhibited by flavonoid glycosides and non-glycosylated polyphenols in polarised Caco-2 intestinal cells [154]. Under sodium-free conditions, aglycones and non-glycosylated polyphenols inhibited glucose uptake whereas glycosides and phenolic acids were ineffective. These data suggest that aglycones inhibit facilitated glucose uptake whereas glycosides inhibit the active transport of glucose. The non-glycosylated dietary polyphenols appeared to exert their effects via steric hindrance, while EGCG, ECG and (⁻)-epigallochatechin were effective against both transporters.

More recently, Koboyashi *et al.* have shown that the green tea polyphenols EGCG and ECG also inhibited glucose transport, possibly by sodium-dependent glucose transporter 1 (SGLT1) inhibition in

the rabbit small intestine [155]. Song et al have presented evidence for quercetin-mediated inhibition of the facilitated diffusion glucose transporter 2 (GLUT2) in Chinese hamster ovary cells [156].

Anthocyanins inhibited α-glucosidase activity and reduced blood glucose levels after starch-rich meals. This is a proven clinical therapy for controlling type II diabetes [158] (Table 9).

Table 9. Antidiabetic activity of dietary polyphenols.

Dietary polyphenols	Protective effects and mechanisms	Conditions	Levels	Ref
Curcumin	Inhibiting diabetes-induced elevation in the levels of IL-1β, VEGF, and NF-κB Decreasing oxidatively modified DNA and nitrotyrosine	In streptozotocin-induced diabetic rats	*In vivo*	153
EGCG, ECG, (⁻)-epigallochatechin	Inhibiting SGLT1 and sodium-free GLUT	In polarised Caco-2 intestinal cells	*In vitro*	154
	Inhibiting SGLT1 and glucose uptake	In the rabbit small intestine	*In vivo*	155
Quercetin	Reducing blood glucose levels Inhibiting sodium-dependent vitamin C transporter 1 (SVCT1) and GLUT2	In Chinese hamster ovary cells	*In vitro*	156
Mangiferin	Inhibiting sucrase, isomaltase, and aldose reductase	In rats	*In vivo*	157
Tannins Anthocyanin	Inhibiting α-amylase and α-glucosidase	In the substrate of 2-chloro-4-nitro-phenyl-4-O-b-D-galactopyranosyl-maltoside	*In vitro*	158

3.12 Regulation of cell cycle progression

It was demonstrated that resveratrol and proanthocyanidins could regulate cell cycle progression by upregulating p21 expression, G1 phase arrest and downregulating cyclin D1/D2–Cdk6 in vitro [163-165, 170] (Table 10).

3.13 Modulation of hormonal effects and contraceptive activity

Some studies showed that dietary polyphenols could modulate the level of hormone. Resveratrol could exert mixed estrogen agonist/antagonist activities in mammary tumor models. It could affect the expression of 17β-estradiol-responsive progesterone receptor (PR) and presnelin 2 proteins in vitro and in vivo [159]. Bhat *et al.* showed that resveratrol exhibited antiestrogenic properties and inhibited the levels and activity of PR by downregulating α (1)-integrin expression in human endometrial adenocarcinoma cells [160].

Otake and his coworkers demonstrated that quercetin and resveratrol potently reduced estrogen sulfotransferase (EST) activity and inhibited sulfation of 17β-estradiol in normal human mammary epithelial cells [161]. Both of the compounds potently inhibited recombinant human EST. In fact, they could serve as substrates for EST. Gossypol, a polyphenolic compound from cotton seed, had contraceptive activity and could inhibit 11β-hydroxysteroid dehydrogenase and cause hypokalemia in some men [162].

Table 10. Regulate cell cycle progression of dietary polyphenols.

Dietary polyphenols	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Resveratrol	Upregulating p21 expression and cause G1 phase arrest	In HepG2 cells	*In vitro*	163
	Inhibiting cyclin D1/D2-cdk6, cyclin D1/D2-cdk4, and cyclin E-cdk2 complexes	In human epidermoid carcinoma A431 cells	*In vitro*	164
	Downregulatiing cyclin D1/Cdk4 complex and upregulating cyclin E and A expression	In the human colonic adenocarcinoma cell line Caco-2	*In vitro*	165
	Decreasing in the hyperphosphorylated form of pRb and increasing in hypophosphorylated pRb Downregulating the protein expression of E2F (1-5) family members of transcription factors and their heterodimeric partners DP1 and DP2 Leading to a G0/G1 arrest	In human epidermoid carcinoma A431 cells	*In vitro*	166
	Inhibiting the expression of cyclin B1, D1, A1 and β-catenin	In six human cancer cell lines (MCF7, SW480, HCE7, Seg-1, Bic-1, and HL60)	*In vitro*	167
	Arresting cell cycle in the G1-S phase	In VSMCs	*In vitro*	168
	Upregulating the expression of cyclins A, E, and B1	In human SK-Mel-28 melanoma cells	*In vitro*	169
Proanthocyanidins	Increasing G1-phase arrest Inhibiting cyclin-dependent kinases (Cdk) Cdk2, Cdk4, Cdk6 and cyclins D1, D2 and E Increasing the protein expression of cyclin-dependent kinase inhibitors (Cdki), Cip1/p21 and Kip1/p27 Enhancing the binding of Cdki-Cdk	In human epidermoid carcinoma A431 cells	*In vitro*	170

3.14 Effect in the treatment of chronic obstructive pulmonary disease (COPD)

Since a variety of oxidants and free radicals are implicated in the pathogenesis of COPD, it is possible that therapeutic administration of multiple antioxidants will be effective in the treatment of COPD. Various approaches to enhance lung antioxidant capacity and clinical trials of dietary polyphenols in COPD are discussed. Resveratrol, EGCG, and quercetin could inhibit inflammatory gene expression by controling NF-κB activation and regulate GSH biosynthesis and chromatin remodel in human airway epithelial A549 cells [171,172]. Curcumin could decrease protein/mRNA expressions of pulmonary type I collagen (Col-I) and TGF-β1 in rats [173].

3.15 Other bioactive effects

It has been demonstrated that dietary polyphenols have other bioactive effects (Table 11), such as antibacterial activity of Gnemonol B and gnetin E [174], anti-HIV effect of proanthocyanidins [176], hepatoprotective ability of a novel proanthocyanidins IH636 [178], and angiogenesis effect of proanthocyanidins [177].

Table 11. Other bioactive effects of dietary polyphenols.

Type of Activity	**Dietary polyphenols**	**Protective effects and mechanisms**	**Conditions**	**Levels**	**Ref**
Antibacterial activity	Gnemonol B and gnetin E	Exhibiting strong antibacterial activities against vancomycin-resistant Enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA)	In Enterococci and Staphylococcus aureus	*In vitro*	174
	Hydroxytyrosol	Antimycoplasmal activity against M. pneumoniae, *M. hominis*, and *M. fermentans*	In *Mycoplasma*	*In vitro*	175
Anti-HIV effects	Proanthocyanidins	Downregulating the expression of the HIV-1 entry co-receptors, CCR2b, CCR3 and CCR5	In normal peripheral blood mononuclear cells	*In vitro*	176
Angiogenesis effect	Proanthocyanidins Resveratrol	Upregulating VEGF expression	In cultured keratinocytes	*In vitro*	177
Hepato-protective ability	A novel Proanthocyanidins IH636	Increasing the expression of Bcl-xL Attenuating acetaminophen-induced hepatic DNA damage, apoptotic and necrotic cell death of liver cells	In male ICR mice	*In vivo*	178
	Daidzein	Ameliorating the d-galactosamine-induced increase in malondialdehyde-protein adducts and cytosolic SOD activities	In the rat liver	*In vivo*	179
	Genistein	Reducing experimental liver damage caused by CCl(4) by preventing lipid peroxidation and strengthening antioxidant systems	In rats	*In vitro*	180

4. Prooxidant activity and cellular effects of the phenoxyl radicals of dietary polyphenols

Dietary polyphenols have beneficial antioxidant, anti-inflammatory and anticancer effects. However, at higher doses or under certain conditions these compounds may exert toxic prooxidant activities [181]. Galati *et al.* [182] have observed that dietary polyphenols with phenol rings were metabolized by peroxidase to form prooxidant phenoxyl radicals which, in some cases were sufficiently reactive to cooxidize GSH or NADH accompanied by extensive oxygen uptake and reactive oxygen species formation. Polyphenols with catechol rings also cooxidized ascorbate, likely mediated by semiquinone radicals. Incubation of hepatocytes with dietary polyphenols containing

phenol rings was found to partially oxidize hepatocyte GSH to GSSG while polyphenols with a catechol ring were found to deplete GSH through formation of GSH conjugates.

Dietary polyphenols with phenol rings also oxidized human erythrocyte oxyhemoglobin and caused erythrocyte hemolysis more readily than polyphenols with catechol rings. It is concluded that polyphenols containing a phenol ring are generally more prooxidant than polyphenols containing a catechol ring. Subsequent studies revealed that [183] B-ring catechol-type flavonoids showed swift formation of their two electron oxidized quinone type metabolites, even upon their one electron oxidation by peroxidases. Enzymatic and/or chemical (auto) oxidation of the flavonoid generates the flavonoid semiquinone radical, which may be scavenged by GSH, thereby regenerating the flavonoid and generating the thiyl radical of glutathione. This thiyl radical may react with GSH to generate a disulfide radical anion which rapidly reduces molecular oxygen to superoxide anion radicals.

Huisman *et al*. [184] found that wine polyphenols and ethanol do not significantly scavenge superoxide nor affect endothelial nitric oxide production. Studies showed that flavonoids can induce oxidative damage and nick DNA via the production of radicals in the presence of Cu and O (2). Al, Zn, Ca, Mg and Cd have been found to stimulate phenoxyl radical-induced lipid peroxidation [185]. As a result of such enzymatic as well as non-enzymatic antioxidant reactions, phenoxyl radicals are formed as the primary oxidized products. Phenoxyl radicals can initiate lipid peroxidation. It is concluded that the prooxidant cytotoxicity of diet polyphenols is due to formation of ROS [186], role of phenoxyl radical/phenol redox couple [187], and stimulation by metals [185].

5. Bioavailability of dietary polyphenols

Polyphenols are the most abundant antioxidants in the human diet. They show a considerable structural diversity, which largely influences their bioavailability [188]. The biological properties of polyphenols depend on the amount consumed and on their bioavailability. Bioavailability appears to differ greatly between the various polyphenols, and the most abundant polyphenols in our diet are not necessarily those leading to the highest concentrations of active metabolites in target tissues [189]. Both isoflavones and phenolic acids like caffeic acid and gallic acid are the most well absorbed polyphenols, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least well-absorbed polyphenols are large molecular weight polyphenols such as the proanthocyanidins, the galloylated tea catechins, and the anthocyanins [190].

Ellagic acid was detected in human plasma at a maximum concentration (31.9 ng/mL) after 1 h postingestion [191]. Absorption of flavanols such as catechins was enhanced when tea polyphenols were administered as a green tea supplement in capsule form when consumed in the absence of food and led to a small but significant increase in plasma antioxidant activity compared with when tea polyphenols were consumed as black tea or green tea [192,193]. No differences were found in plasma EGCG concentrations and trolox equivalents determined by the trolox equivalent antioxidant capacity assay after administration as a single large dose in the form of either purified EGCG or as green tea extract (Polyphenon E) [194]. Hydroxytyrosol, the major olive oil phenolic compound, is dose-dependently absorbed from olive oil [195]. Tuck *et al.* showed that hydroxytyrosol intravenously and orally administered oil-based dosings resulted in significantly greater elimination of the phenolics in urine within 24 h than the oral, aqueous dosing method. Oral bioavailability estimates of hydroxyl-

tyrosol when administered in an olive oil solution and when dosed as an aqueous solution was 99% and 75%, respectively [13].

Once absorbed, polyphenols are conjugated to glucuronide, sulphate and methyl groups in the gut mucosa and inner tissues. Non-conjugated polyphenols are virtually absent in plasma. Such reactions facilitate their excretion and limit their potential toxicity. EGCG and ECG were present in plasma mostly as the free form, whereas epicatechin and epigallocatechin were mostly present as the glucuronide and sulfate conjugates [192]. Recent data suggest that beta-glucosidases and maybe also lactase phlorizin hydrolase (LPH) in the small intestine are capable of hydrolysing flavonoid glucosides and these compounds are thus taken up as the free aglycon and not as the intact glycosides [196]. It has been reported that around 98% of hydroxytyrosol is present in plasma and urine in conjugated forms, mainly glucuronoconjugates, suggesting an extensive first pass intestinal/ hepatic metabolism of the ingested primary forms [197-199] and the 3-*O*-glucuronide of hydroxytyrosol shows stronger activity as a radical scavenger than hydroxytyrosol itself [200]. The major metabolites identified in *in vitro* and *in vivo* studies were an Omethylated derivative of hydroxytyrosol, glucuronides of hydroxytyrosol and a novel glutathionyl conjugate of hydroxytyrosol [200,201]. It has been recently reported that hydroxytyrosol and its metabolites are capable of binding human LDL after olive oil ingestion [202].

The polyphenols reaching the colon are extensively metabolised by the microflora into a wide array of low molecular weight phenolic acids. It has been shown that the plasma concentrations of total metabolites ranged from 0 to 4 μmol/L with an intake of 50 mg aglycone equivalents, and the relative urinary excretion ranged from 0.3% to 43% of the ingested dose, depending on the polyphenol [189]. The biological properties of both conjugated derivatives and microbial metabolites will be essential to better assess the health effects of dietary polyphenols. Alternatively, some health effects of polyphenols may not require their absorption through the gut barrier. Their role as iron chelators in the gut lumen is briefly discussed. Tannic acid and catechin both interact with the gut but only catechin appears able to traverse the gut. In addition, they provide evidence for binding of tannic acid and catechin by endogenous proteins in the intestinal lumen. This may limit their absorption from the small intestine [203].

6. Conclusions

Consumption of polyphenol-rich fruits, vegetables, and beverages derived from plants, such as cocoa, red wine and tea, represents a diet beneficial to human health. Some dietary polyphenols possess antioxidative and anti-inflammatory properties, to some extent, contributing to their cancer chemopreventive potential. These phenolic substances have the ability to abrogate various biochemical processes induced or mediated by the tumor promoters. Some dietary polyphenols also induce apoptosis in premalignant or cancerous cells, and suppress growth and proliferation of various types of tumor cells via induction of apoptosis or arrest of a specific phase of the cell cycle.

However, the specific mechanism(s) by which these compounds affect human health remains unclear, despite extensive research conducted in this area in recent years. Most of that research has focused on the antioxidant properties of dietary polyphenols, which are well characterized and well established *in vitro*. The *in vitro* data often conflict with results obtained from *in vivo* studies on the antioxidant capacity of plasma or the resistance of plasma and lipoproteins to oxidation *ex vivo* after the consumption of polyphenols-rich foods by human subjects. These inconsistencies between the *in*

vitro and the *in vivo* data are likely explained by the limited bioavailability of dietary polyphenols and their extensive metabolism in humans. Most of them exert multifacet action, and any clinical applications using these substances should be based on the precise understanding of the physiologically relevant action mechanisms.

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