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Plant-derived bioactives and oxidative stress-related disorders: a key trend towards health and longevity promotion

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Abstract

Plants and its corresponding botanical preparations have been used for centuries due to their remarkable potentialities in both treatment and prevention of numerous affections. Hundreds of biologically active constituents are present in each whole plant matrice, working in synergism and conferring both its own protection against invaders and even providing promissory bioactive effects for human beings. The worldwide population has devoted increasing attention and preference by medicinal plants use for health promotion and disease prevention, and more recently for oxidative-stress related disorders protection. Indeed, oxidative stress-related disorders, like cardiovascular and (neuro) degenerative disorders, and even cancer have raised exponentially. Although oxidative stress is in itself intrinsic to our own metabolism, allarming sources of free radicals are daily affecting us. In fact, plant-derived bioactives present a broad spectrum of biological effects, and its antioxidant, anti-inflammatory and more recently anti-aging effects have been considered a hot topic among the medical and scientific community. Nonetheless, and although its numerous biological effects, it should not also be forgotten that some bioactive molecules are prone to oxidation and can even exert pro-oxidant effects. In this sense, the objective of the present review is to provide a detailed overview on plant-derived bioactives in oxidative stress-related disorders. Specifically, the role of phytochemicals as antioxidants and pro-oxidant agents is carefully addressed, as is its therapeutic relevance in disease prevention. Finally, an eye-opening look in overall evidence in humans is also ensured.

Keywords: Medicinal plants; Bioactive molecules; Phenolic compounds; Oxidative stress; Antioxidants; Chronic disorders; Health maintenance; Longevity.

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I. Introduction

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

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

Plants possess miraculous antioxidant effects because of their high oxygen exposure physiology. In fact, plants may have more sites of ROS generation. Therefore, they could evolve more proficient non-enzymatic antioxidant systems than humans [1,7]. Plants synthesize several enzymatic and non-enzymatic antioxidants to avoid free radicals' toxic effects, besides to synthesize and accumulate a wide variety of low and high molecular weight secondary metabolites, that play important roles in ROS metabolism and effectively avoid uncontrolled oxidation of essential biomolecules, thus, acting as antioxidants [1,7,8].

There is a broad diversity of naturally-occurring antioxidants found in plants, differing in their composition, physicochemical properties, site and mechanism of action. The major antioxidant plant secondary metabolites are phenolic compounds, and they can be divided into five general groups: phenolic acids, flavonoids, lignans, stilbenes and tannins [9–11]. Briefly, they provide protection through scavenging

numerous ROS, including hydroxyl radical, peroxyl radical, hypochlorous acids, superoxide anion and peroxynitrite [12]. Particularly, the antioxidant activity of polyphenols in cardiovascular diseases, as hepatoprotective, anti-carcinogenic, antimicrobial, antiviral and anti-inflammatory agents, has been broadly described [13,14]. In fact, anthocyanins play a key antioxidant role in plants against ROS-generated abiotic stress, such ultraviolet light and extreme temperatures [15,16], besides to inhibit chemically-induced cancer and turn-off genes involved in proliferation, inflammation, and angiogenesis [17]. Also, these secondary metabolites are known to prevent a key step in atherogenesis and are more potent antioxidants than vitamin C or synthetic antioxidants [18].

Moreover, a meta-analysis of epidemiological studies showed that carotenoids act protectively against head and neck cancer [19], while other studies have suggested that carotenoid-rich diets appear to have a protective effect against Parkinson's disease [20], and prostate [21] and breast [22] cancers. In this sense, the objective of the present review is to provide a detailed overview on plant-derived bioactives in oxidative stress-related disorders. Specifically, the role of phytochemicals as antioxidants and pro-oxidant agents is carefully addressed, as is its therapeutic relevance in disease prevention. Finally, an eye-opening look in overall evidence in humans is also ensured.

II. The role of phytochemicals in oxidative stress-related disorders

Nowadays, ROS-related research is increasing due to their involvement in a wide variety of human diseases, such as cardiovascular and neurodegenerative diseases, atherosclerosis, aging, among others [23–25]. Thus, the importance of removing excessive ROS is becoming increasingly recognized by using antioxidants.

In a broad sense, the antioxidant is defined as *"any substance that delays, prevents or removes oxidative damage to a target molecule"* [26]. Thus, oxidative stress represents an imbalance between humans' protective molecules, the antioxidants, and molecules that can damage all sorts of cellular components, the free radicals. Nonetheless, some antioxidant molecules may also play pro-oxidant effects. For instance, ascorbic acid plays an important role in ameliorating photosynthesis' oxidative stress, besides to have

several other roles in cell division and protein modification, but also act as a pro-oxidant [27]. Similarly, vitamin E also play pro-oxidant effects, when used at high concentrations. Indeed, it has been reported that vitamin E react with free radicals to become a reactive radical (pro-oxidant) in the absence of co-antioxidants [7]. On the other hand, it has also been reported that some antioxidant phytochemicals from foods, spices, herbs, and medicinal plants may also act as prooxidant agents when a transition metal is available [28].

(1) Phytochemicals as antioxidant agents

Phytochemicals exhibiting antioxidant effects are broadly categorized into alkaloids, carotenoids, coumarins, flavonoids, phenolics and terpenoids groups, among other organic compounds. However, given the focus of the present review, and based on the number of structures, they are grouped as follows (**Table 1**).

Table 1. Scaffold, structures, and corresponding bioactive phytochemicals organization.

Scaffold	Alkaloids	Betalains	Coumarins	Flavonoids	Organics	Phenolics	Steroids	Terpenoids	Xanthenones
Structures	A-1 to A-7	B-1 to B-13	C-1 to C-23	F-1 to F-130	O-1 to O-64	P-1 to P-156	S-1 to S-15	T-1 to T-61	X-1 to X-19
Table	Table 2	Table 3	Table 4	Table 5	Table 6	Table 7	Table 8	Table 9	Table 10

An extensive search in published literature was performed, defining as inclusion criteria: journals listed in Scopus and Web of Science databases, as also the isolated compounds purified and assayed for antioxidant activity. Regarding the exclusion criteria, it comprises all those compounds known to possess antioxidant effects but isolated from different plant material. Thus, given the above-established aspects and considering both the taxonomical classification and the family name listed in the plant list website, the literature search was carried out. All the obtained data are carefully organized and presented in **Tables 2-10**.

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Table 2. Alkaloids isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
A-1	(−)-boldine	*Dehaasia longipedicellata*	Lauraceae	[29]
A-2	(−)-*O*,*O*-dimethylgrisabine	*Dehaasia longipedicellata*	Lauraceae	[29]
A-3	(−)-reticuline	*Dehaasia longipedicellata*	Lauraceae	[29]
A-4	(+)-sebiferine	*Dehaasia longipedicellata*	Lauraceae	[29]
A-5	indicaxanthin	*Opuntia ficus-indica*	Cactaceae	[30]
A-6	uridine	*Aruncus dioicus*	Rosaceae	[31]
A-7	(−)-norboldine	*Dehaasia longipedicellata*	Lauraceae	[29]

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Table 3. Betalains isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
B-1	(iso)gomphrenin	*Gomphrena globosa*	Amaranthaceae	[32]
B-2	(S)-tryptophan-betaxanthin	*Celosia plumosa* (yellow)	Amaranthaceae	[32]
B-3	3-methoxytyramine-betaxanthin	*Celosia plumosa* (yellow)	Amaranthaceae	[32]
B-4	amaranthine	*Amaranthus tricolor*	Amaranthaceae	[32]
B-5	betanidin	*Beta vulgaris*	Amaranthaceae	[33]
B-6	betanin	*Opuntia ficus-indica*	Cactaceae	[30]
		Beta vulgaris	Amaranthaceae	[32]
B-7	celosianins (acylated amaranthine)	*Celosia plumosa* (yellow)	Amaranthaceae	[32]
B-8	dopamine-betaxanthin	*Celosia plumosa* (yellow)	Amaranthaceae	[32]
B-9	iresinins (acylated amaranthine)	*Iresine herbstii*	Amaranthaceae	[32]
B-10	isoamaranthine	*Amaranthus tricolor*	Amaranthaceae	[32]
B-11	isobetanin	*Beta vulgaris*	Amaranthaceae	[32]
B-12	vulgaxanthin-I	*Beta vulgaris*	Amaranthaceae	[33]
B-13	vulgaxanthin-II	*Beta vulgaris*	Amaranthaceae	[33]

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Table 4. Coumarins isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
C-1	3′-*O*-methylvaginol	*Cnidium monnieri*	Apiaceae	[34]
C-2	6,7-diacetoxy coumarin	*Tagetes lucida*	Asteraceae	[35]
C-3	6-methoxy-7-acetoxycoumarin	*Tagetes lucida*	Asteraceae	[35]
C-4	7-methoxy-6-hydroxycoumarin	*Tagetes lucida*	Asteraceae	[35]
C-5	7-hydroxycoumarin	*Durio zibethinus*	Malvaceae	[36]
C-6	7-methoxy-8-(3-methyl-2,3-epoxy-1-oxobutyl)chromen-2-one	*Cnidium monnieri*	Apiaceae	[34]
C-7	7-*O*-methylphellodenol-B	*Cnidium monnieri*	Apiaceae	[34]
C-8	cleomiscosin A	*Durio zibethinus*	Malvaceae	[36]
C-9	cleomiscosin B	*Durio zibethinus*	Malvaceae	[36]
C-10	dimethylfraxetin	*Gomortega keule*	Gomortegaceae	[37]
C-11	esculetin	*Tagetes lucida*	Asteraceae	[35]
C-12	fraxetin	*Durio zibethinus*	Malvaceae	[36]
C-13	fraxidin	*Durio zibethinus*	Malvaceae	[36]
		Gomortega keule	Gomortegaceae	[37]
C-14	hydroxydimethyl fraxetin	*Gomortega keule*	Gomortegaceae	[37]
C-15	isofraxidin	*Vitex negundo*	Verbenaceae	[38]
C-16	propacin	*Durio zibethinus*	Malvaceae	[36]
C-17	scoparone	*Gomortega keule*	Gomortegaceae	[37]
		Tagetes lucida	Asteraceae	[35]
C-18	scopoletin	*Tagetes lucida*	Asteraceae	[35]
		Durio zibethinus	Malvaceae	[36]
		Gomortega keule	Gomortegaceae	[37]
		Melicope glabra	Rutaceae	[39]
C-19	scopolin	*Gomortega keule*	Gomortegaceae	[37]
C-20	umbelliferone	*Melicope glabra*	Rutaceae	[39]
C-21	methyl brevifolincarboxylate	*Phyllanthus urinaria*	Phyllanthaceae	[40]
C-22	trimethyl-3,4-dehydrochebulate	*Phyllanthus urinaria*	Phyllanthaceae	[40]
C-23	eleocharin	*Eleocharis tuberosa*	Cyperaceae	[41]

Table 5. Flavonoids isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
F-1	(−)-epicatechin	*Hypericum triquetrifolium*	Hypericaceae	[42]
		Hypericum triquetrifolium	Hypericaceae	[43]
F-2	(−)-epigallocatechin 3-*O*-gallate	*Rhodiola sachalinensis*	Crassulaceae	[44]
F-3	(−)-eriodictyol	*Eleocharis tuberosa*	Cyperaceae	[41]
F-4	(2*R*)-eriodictyol 7,4-di-*O*-β-D-glucopyranoside	*Viscum coloratum*	Loranthaceae	[45]
F-5	(2*S*)-8-formyl-6-methylnaringenin	*Cleistocalyx operculatus*	Myrtaceae	[46]
F-6	(2*S*)-8-formyl-6-methylnaringenin 7-*O*-β-D-glucopyranoside	*Cleistocalyx operculatus*	Myrtaceae	[46]
F-7	(2*S*)-eriodictyol 7-*O*-β-D-glucopyranoside	*Viscum coloratum*	Loranthaceae	[45]
F-8	(2*S*)-homoeriodictyol 7,4-di-*O*-β-D-glucopyranoside	*Viscum coloratum*	Loranthaceae	[45]
F-9	(2*S*)-homoeriodictyol 7-*O*-β-D-glucopyranoside	*Viscum coloratum*	Loranthaceae	[45]
F-10	(2*S*)-naringenin 7-*O*-β-D-glucopyranoside	*Viscum coloratum*	Loranthaceae	[45]
F-11	3′,4′,6,7,8-pentamethoxyflavone	*Gutierrezia gayana*	Asteraceae	[35]
F-12	3′,4′,6,7,8-pentamethoxyflavone	*Parastrephia quadrangularis*	Asteraceae	[35]
F-13	3′, 4′,5,7-tetrahydroxyflavonol	*Callistemon salignus*	Myrtaceae	[47]
F-14	3-*O*-α-L-rhamnopyranosylkaempferol-7-*O*-β-D-glucopyranoside	*Ligustrum sinense*	Oleaceae	[48]
F-15	3-*O*-α-L-rhamnopyranosylkaempferol-7-*O*-α-L-rhamnopyranoside	*Ligustrum sinense*	Oleaceae	[48]
F-16	3-*O*-methylorobol	*Cudrania tricuspidata*	Moraceae	[49]
F-17	4′,5-dihydroxy-3,3′,6,7,8-pentamethoxyflavone	*Gutierrezia gayana*	Asteraceae	[35]
		Parastrephia quadrangularis	Asteraceae	[35]
F-18	4′-O-methylalpinumisoflavone	*Cudrania tricuspidata*	Moraceae	[49]
F-19	5,4′,5′-trihydroxy-3,6,7,8- tetramethoxyflavone	*Parastrephia quadrangularis*	Asteraceae	[35]
		Gutierrezia gayana	Asteraceae	[35]
F-20	5,6,4’-trihydroxy-7,3’-dimethoxyflavone	*Anisomeles ovata*	Lamiaceae	[50]
F-21	5,7-dimethoxyflavanone-4’-*O*-[5’’-O-trans-cinnamoyl-β-D-apiofuranosyl]-β-D-glucopyranoside	*Viscum album*	Loranthaceae	[51]
F-22	5-hydroxy-6,7,3’,4’-tetramethoxyflavone (HTF)	*Citrus aurantium*	Rutaceae	[52]
F-23	5-methoxy-6,7-methylene dioxy-2’-hydroxyisoflavone	*Celosia argentea*	Amaranthaceae	[53]
F-24	5-methylaureusidin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-25	5-prenylaureusidin	*Eleocharis tuberosa*	Cyperaceae	[41]

F-26	6,8-dimethylluteolin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-27	6,8-diprenyleriodictyol	*Dorstenia mannii*	Moraceae	[54]
F-28	6,8-diprenylgenistein	*Cudrania tricuspidata*	Moraceae	[49]
F-29	6-isopentenylgenistein	*Cudrania tricuspidata*	Moraceae	[49]
F-30	6-methyleriodictyol	*Eleocharis tuberosa*	Cyperaceae	[41]
F-31	6-methylluteolin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-32	6-prenylnaringenin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-33	7-methoxykaempferol 3-*O*-β-D-glucopyranoside	*Siraitia grosvenorii*	Cucurbitaceae	[55]
F-34	7-methoxykaempferol 3-*O*- α-L-rhamnopyranoside	*Siraitia grosvenorii*	Cucurbitaceae	[55]
F-35	adenodimerin A	*Myrica adenophora*	Myricaceae	[56]
F-36	afzelin	*Lindera obtusiloba*	Lauraceae	[57]
		Alnus japonica	Betulaceae	[58]
F-37	Alpinumisoflavone	*Cudrania tricuspidata*	Moraceae	[49]
F-38	apigenin	*Verbena officinalis*	Verbenaceae	[59]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Origanum vulgare	Lamiaceae	[61]
		Macaranga gigantea	Euphorbiaceae	[62]
F-39	apigenin-6,8-di-*C*-glycoside	*Sechium edule*	Cucurbitaceae	[63]
F-40	apigenin-7- glucoside	*Pyrus pyrifolia*	Rosaceae	[64]
		Cudrania tricuspidata	Moraceae	[49]
		Origanum vulgare	Lamiaceae	[61]
F-41	artocarpesin	*Cudrania tricuspidata*	Moraceae	[49]
		Cudrania tricuspidata	Moraceae	[49]
F-42	astilbin	*Smilacis Glabrae*	Smilacaceae	[65]
F-43	astragalin	*Toona sinensis*	Meliaceae	[65]
F-44	baicalin	*Smilacis Glabrae*	Smilacaceae	[65]
F-45	broussoflavonol F	*Macaranga gigantea*	Euphorbiaceae	[62]
F-46	catechin	*Cudrania tricuspidata*	Moraceae	[49]
		Benincasa hispida	Cucurbitaceae	[63]
		Momordica charantia	Cucurbitaceae	[63]
F-47	chrysoeriol	*Euterpe oleracea*	Arecaceae	[66]
F-48	cyrtominetin	*Eleocharis tuberosa*	Cyperaceae	[41]

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F-49	didymin	*Origanum vulgare*	Lamiaceae	[61]
F-50	dihydrokaempferol	*Euterpe oleracea*	Arecaceae	[66]
		Cudrania tricuspidata	Moraceae	[49]
F-51	dihydrokaempferol-7-*O*-β-D-glucopyranoside	*Abies koreana*	Pinaceae	[67]
F-52	diosmetin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-53	dorsmanin C	*Dorstenia mannii*	Moraceae	[68]
F-54	dorsmanin F	*Dorstenia mannii*	Moraceae	[68]
F-55	epicatechin	*Pyrus pyrifolia*	Rosaceae	[64]
		Momordica charantia	Cucurbitaceae	[63]
F-56	epidorsmanin F	*Dorstenia mannii*	Moraceae	[68]
F-57	eriodyctiol-7-*O*-rutinoside	*Foeniculum vulgare*	Apiaceae	[69]
F-58	fortunellin	*Citrus japonica*	Rutaceae	[70]
F-59	genistein	*Cudrania tricuspidata*	Moraceae	[49]
F-60	gerontoisoflavone	*Cudrania tricuspidata*	Moraceae	[49]
F-61	glabranin	*Melicope glabra*	Rutaceae	[39]
F-62	glyasperin A	*Macaranga gigantea*	Euphorbiaceae	[62]
F-63	gossypetin-8-*O*-β-D-xylopyranoside	*Sedum takesimense*	Crassulaceae	[71]
F-64	guangsangon H	*Morus macroura*	Moraceae	[72]
F-65	guangsangon I	*Morus macroura*	Moraceae	[72]
F-66	guangsangon F	*Morus macroura*	Moraceae	[72]
F-67	guangsangon G	*Morus macroura*	Moraceae	[72]
F-68	herbacetin-7-*O*-α-L-rhamanopyranoside	*Rhodiola sachalinensis*	Crassulaceae	[44]
F-69	hesperetin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-70	hesperidin	*Citrus reticulata* Blanco	Rutaceae	[73]
F-71	homoorientin	*Euterpe oleracea* Mart	Arecaceae	[66]
F-72	homovitexin	*Shibataea chinensis*	Poaceae	[74]
		Pleioblastus kongosanensis	Poaceae	[74]
F-73	hyperin	*Fagopyrum esculentum*	Polygonaceae	[75]
F-74	hyperoside	*Aruncus dioicus*	Rosaceae	[31]
F-75	I3,II8-biapigenin	*Hypericum triquetrifolium*	Hypericaceae	[43]
		Hypericum triquetrifolium	Hypericaceae	[42]
F-76	isoastilbin	*Smilacis Glabrae*	Smilacaceae	[65]
F-77	isohyperoside	*Alnus japonica*	Betulaceae	[58]
F-78	isoorientin	*Colocasia esculenta*	Araceae	[76]

F-79	isoorientin	*Pleioblastus kongosanensis*	Poaceae	[74]
F-80	isoorientin	*Shibataea chinensis*	Poaceae	[74]
F-81	isorhamnetin-3-methylquercetin	*Nasturtium officinale*	Brassicaceae	[77]
F-82	isorhamnetin	*Zygophyllum simplex*	Zygophyllaceae	[78]
F-83	isorhamnetin-3-*O*-β-D-glucoside	*Zygophyllum simplex*	Zygophyllaceae	[78]
F-84	isorhamnetin-3-*O*-β-D-rutinoside	*Zygophyllum simplex*	Zygophyllaceae	[78]
F-85	isovitexin	*Colocasia esculenta*	Araceae	[76]
F-86	kaempferol	*Centella asiatica*	Apiaceae	[79]
		Siraitia grosvenorii	Cucurbitaceae	[55]
		Opuntia ficus-indica	Cactaceae	[30]
		Cyclocarya paliurus	Juglangdaceae	[80]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Rhodiola sachalinensis	Crassulaceae	[44]
		Toona sinensis	Meliaceae	[81]
F-87	kaempferol 3-*O*-galactopyranoside	*Pinus densiflora*	Pinaceae	[82]
F-88	kaempferol 3-*O*-galactopyranoside 6″-acetate	*Pinus densiflora*	Pinaceae	[82]
F-89	kaempferol 3-*O*-glucoside 7-*O*-rhamnoside	*Hydrocotyle bonariensis*	Apiaceae	[79]
		Hydrocotyle bonariensis	Apiaceae	[79]
F-90	kaempferol 3-*O*-α-L-rhamnopyranoside-7-*O*-[β-D-1→2)]-α-L-rhamnopyranoside	*Siraitia grosvenorii*	Cucurbitaceae	[55]
F-91	kaempferol 3-*O*-rhamnoside	*Hydrocotyle sibthorpioides*	Araliaceae	[79]
F-92	kaempferol 7-*O*-α-L-rhamnopyranoside	*Siraitia grosvenorii*	Cucurbitaceae	[55]
		Toona sinensis	Meliaceae	[81]
F-93	kaempferol-3-*O*-glucoside	*Cyclocarya paliurus*	Juglangdaceae	[80]
		Hydrocotyle sibthorpioides	Apiaceae	[79]
		Foeniculum vulgare	Apiaceae	[69]
		Cudrania tricuspidata	Moraceae	[49]
		Hypericum triquetrifolium	Hypericaceae	[43]
		Hypericum triquetrifolium	Hypericaceae	[42]
F-94	kaempferol-3-*O*-rutinoside	*Foeniculum vulgare*	Apiaceae	[69]
F-95	kaempferol-7-*O*-α-L-rhamnoside	*Cyclocarya paliurus*	Juglangdaceae	[80]
F-96	kaempherol 7-*O*-α-L-rhamanopyranoside	*Rhodiola sachalinensis*	Crassulaceae	[44]
F-97	kampeferol diglucoside	*Spathodea campanulata*	Bignoniaceae	[83]

F-98	ledebourin A	*Ledebouria floribunda*	Asparagaceae	[84]
F-99	ledebourin B	*Ledebouria floribunda*	Asparagaceae	[84]
F-100	ledebourin C	*Ledebouria floribunda*	Asparagaceae	[84]
F-101	luteolin	*Euterpe oleracea*	Arecaceae	[66]
		Begonia trichocarpa	Begoniaceae	[85]
		Verbena officinalis	Verbenaceae	[59]
		Cudrania tricuspidata	Moraceae	[49]
		Origanum vulgare	Lamiaceae	[61]
		Sedum takesimense	Crassulaceae	[71]
F-102	luteolin 7-*O*-rutinoside	*Sechium edule*	Cucurbitaceae	[63]
F-103	luteolin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-104	luteolin-7-*O*-β-D-glucoside	*Zygophyllum simplex*	Zygophyllaceae	[78]
		Sedum takesimense	Crassulaceae	[71]
F-105	myricetin	*Sideritis congesta*	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Myrica adenophora	Myricaceae	[56]
		Sedum takesimense	Crassulaceae	[71]
		Zygophyllum simplex	Zygophyllaceae	[78]
		Myrica adenophora	Myricaceae	[56]
		Cudrania tricuspidata	Moraceae	[49]
F-106	nobiletin	*Citrus reticulate*	Rutaceae	[73]
F-107	orientin	*Euterpe oleracea*	Arecaceae	[66]
		Pleioblastus kongosanensis	Poaceae	[74]
		Shibataea chinensis	Poaceae	[74]
F-108	pedalitin	*Verbena officinalis*	Verbenaceae	[59]
F-109	pelargonidin-3-*O*-glucoside	*Cudrania tricuspidata*	Moraceae	[49]
F-110	pinoquercetin	*Eleocharis tuberosa*	Cyperaceae	[41]
F-111	poncirin	*Citrus japonica*	Rutaceae	[41]
F-112	quercetin	*Centella asiatica*	Apiaceae	[79]
		Begonia trichocarpa	Begoniaceae	[85]
		Euterpe oleracea	Arecaceae	[66]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Rosa sempervirens	Rosaceae	[86]

		Eleocharis tuberosa	Cyperaceae	[41]
		Toona sinensis	Meliaceae	[81]
		Fagopyrum esculentum	Polygonaceae	[75]
		Sedum takesimense	Crassulaceae	[71]
		Smilacis Glabrae	Smilacaceae	[65]
F-113	quercetin 3-*O*-β-D-glucuronide	*Centella asiatica*	Apiaceae	[79]
		Cyclocarya paliurus	Juglangdaceae	[80]
F-114	quercetin-3-diglucoside	*Hydrocotyle sibthorpioides*	Apiaceae	[79]
F-115	quercetin-3-galactoside	*Rosa sempervirens*	Rosaceae	[86]
		Hypericum triquetrifolium	Hypericaceae	[42]
		Foeniculum vulgare	Apiaceae	[69]
		Hypericum triquetrifolium	Hypericaceae	[43]
F-116	quercetin-3-*O*-glucoside	*Hydrocotyle bonariensis*	Apiaceae	[79]
		Hydrocotyle sibthorpioides	Apiaceae	[79]
		Foeniculum vulgare	Apiaceae	[69]
		Foeniculum vulgare	Apiaceae	[69]
F-117	quercetin-3-*O*-rhamnoside	*Hydrocotyle sibthorpioides*	Apiaceae	[79]
		Cryptocarya latifolia	Lauraceae	[87]
		Rosa sempervirens	Rosaceae	[86]
F-118	quercetin-3-*O*-rutinoside	*Foeniculum vulgare*	Apiaceae	[69]
		Nasturtium officinale	Brassicaceae	[77]
		Cudrania tricuspidata	Moraceae	[49]
F-119	quercetin-3-xyloside	*Rosa sempervirens*	Rosaceae	[86]
F-120	quercetin-rutinoside	*Hydrocotyle bonariensis*	Apiaceae	[79]
F-121	quercetrin	*Toona sinensis*	Meliaceae	[81]
		Lindera obtusiloba	Lauraceae	[57]
		Alnus japonica	Betulaceae	[58]
		Myrica adenophora	Myricaceae	[56]
		Phyllanthus urinaria	Phyllanthaceae	[40]
F-122	rhamnocitrin	*Phyllanthus urinaria*	Phyllanthaceae	[40]
F-123	rhodalidin	*Sedum takesimense*	Crassulaceae	[71]
F-124	rhodiolinin	*Rhodiola sachalinensis*	Crassulaceae	[44]
F-125	rutin	*Phyllanthus debilis*	Phyllanthaceae	[88]
		Gomortega keule	Gomortegaceae	[37]

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		Fagopyrum esculentum	Polygonaceae	[75]
		Pyrus pyrifolia	Rosaceae	[64]
		Phyllanthus urinaria	Phyllanthaceae	[40]
		Smilacis Glabrae	Smilacaceae	[65]
F-126	sanggenol B	*Cudrania tricuspidata*	Moraceae	[49]
F-127	scutellarein	*Verbena officinalis*	Verbenaceae	[59]
F-128	tangeretin	*Citrus reticulate*	Rutaceae	[73]
F-129	taxifolin	*Smilacis Glabrae*	Smilacaceae	[65]
F-130	vitexin	*Colocasia esculenta*	Araceae	[76]
		Euterpe oleracea	Arecaceae	[66]
		Sechium edule	Cucurbitaceae	[63]
		Pleioblastus kongosanensis	Poaceae	[74]
		Shibataea chinensis	Poaceae	[74]

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Table 6. Other organic compounds isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
O-1	1,10-epoxyovatifolin	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-2	1,5-anhydro-D-glucitol	*Protea magnifica* × *Protea susanne*	Proteaceae	[89]
O-3	10,11-dehydrotremetone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
		Baccharis linearis	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-4	10,11-epoxytremetone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-5	10-nonacosanol	*Aruncus dioicus*	Rosaceae	[31]
O-6	11,13-dihydroovatifolin	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-7	9,12-octadecadienoic acid	*Ricinus communis*	Euphorbiaceae	[62]
O-8	3,4-dimethoxycinnamic acid	*Lagenaria siceraria*	Cucurbitaceae	[63]
O-9	3-octanone	*Rosmarinus officinalis*	Lamiaceae	[90]
O-10	4-acetylacetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-11	4-bromoacetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-12	4-glucosylacetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-13	4-methylacetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-14	5-hexyltetrahydro-2*H*-pyran-2-one	*Cryptocarya latifolia*	Lauraceae	[87]

O-15	acetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-16	arturin	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-17	cuminaldehyde	*Bunium persicum*	Apiaceae	[91]
O-18	cuminyl acetate	*Bunium persicum*	Apiaceae	[91]
O-19	deacetylovatifolin	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-20	hypericin	*Hypericum triquetrifolium*	Hypericaceae	[42]
		Hypericum triquetrifolium	Hypericaceae	[43]
O-21	jatrocin A	*Durio zibethinus*	Malvaceae	[36]
O-22	lysoPC(16:0) (1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine)	*Cudrania tricuspidata*	Moraceae	[49]
O-23	lysoPC(18:2) (1-[(11Z)-octadecenoyl]-sn-glycero-3-phosphocholine)	*Cudrania tricuspidata*	Moraceae	[49]
O-24	methyl ricinoleate	*Ricinus communis*	Euphorbiaceae	[62]
O-25	ovatifolin	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-26	ovatifolin acetate	*Podanthus mitiqui*	Asteraceae	[35]
		Podanthus ovatifolius	Asteraceae	[35]
O-27	palmitic acid	*Aruncus dioicus*	Rosaceae	[31]
O-28	pentacosan-1-ol	*Aruncus dioicus*	Rosaceae	[31]
O-29	quinic acid	*Pyrus pyrifolia*	Rosaceae	[64]
O-30	ricinoleic acid	*Ricinus communis*	Euphorbiaceae	[62]
O-31	sesamin	*Melicope glabra*	Rutaceae	[39]
O-32	taurine	*Opuntia ficus-indica*	Cactaceae	[30]
O-33	tremetone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
O-34	2,6,10-trimethyldodec-2-en-1-oyl-1-*O*-α-L-arabinopyranosyl-(2a→1b)-2a-*O*-α-L-arabinopyranosyl-(2b→1c)-2b-*O*-α-L-arabinopyranosyl-(2c→1d)-2c-*O*-α-L-arabinopyranosyl-(2d→1e)-2d-*O*-α-L-arabinopyranosyl-(2e→1f)-2e-*O*-α-L-arabinopyranosyl-(2f→1g)-2f-*O*-α-L-arabinopyranoside	*Lycium chinense*	Solanaceae	[92]

O-35	β-D-glucopyranosyl-(2a→1b)-2a-*O*-β-L-arabinopyranosyl- (2b→1c)-2b-*O*-β-L-arabinopyranosyl-(2c→1d)-2c-*O*-β-L-arabinopyranosyl-(2d→1e)-2d-*O*-β-L-arabinopyranosyl-(2e→1f)-2e-*O*-β-L-arabinopyranoside	*Lycium chinense*	Solanaceae	[92]
O-36	(2*E*)-7-hydroxy-3,7-dimethyl-2-octenyl α-L-arabinopyranosyl (1→6)-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
O-37	(*E*)-4-(hydroxymethyl)phenyl-6-*O*-caffeoyl-β-D-glucopyranoside	*Lagenaria siceraria*	Cucurbitaceae	[63]
O-38	epiprogoitrin	Cruciferae	Brassicaceae	[94]
O-39	glucoiberin	Cruciferae	Brassicaceae	[94]
O-40	gluconapin	Cruciferae	Brassicaceae	[94]
O-41	gluconasturtiin	Cruciferae	Brassicaceae	[94]
O-42	glucoraphanin	Cruciferae	Brassicaceae	[94]
O-43	glucoraphanin	Cruciferae	Brassicaceae	[94]
O-44	prunasin	*Prunus mume*	Rosaceae	[93]
O-45	sinigrin	Cruciferae	Brassicaceae	[94]
O-46	amygdalin	*Prunus mume*	Rosaceae	[93]
O-47	benzyl-α-L-arabinofuranosyl (1→6)-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
O-48	benzyl-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
O-49	benzyl-β-D-glucopyranoside	*Prunus mume.*	Rosaceae	[93]
O-50	benzyl-β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
O-51	eleocharin C	*Eleocharis tuberosa*	Cyperaceae	[41]
O-52	glucobarbarin	Cruciferae	Brassicaceae	[94]
O-53	glucobrassicin	Cruciferae	Brassicaceae	[94]
O-54	glucocheorolin	Cruciferae	Brassicaceae	[94]
O-55	glucoerucin	Cruciferae	Brassicaceae	[94]
O-56	glucosibarin	Cruciferae	Brassicaceae	[94]
O-57	glucotropaeolin	Cruciferae	Brassicaceae	[94]
O-58	guangsangons H	*Morus macroura*	Moraceae	[72]
O-59	guangsangons H	*Morus macroura.*	Moraceae	[72]
O-60	guangsangons J	*Morus macroura*	Moraceae	[72]

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O-61	docos-9,12-dienoyl-α-D-glucopyranosyl-(2a→1b)-2a-*O*-α-D glucopyranosyl-(2b→1c)-2b-*O*-α-D-glucopyranosyl-(2c→1d)-2c-*O*-α-D-glucopyranosyl-(2d→1e)-2d-*O*-α-D-glucopyranosyl-(2e→1f)-2e-*O*-α-D-glucopyranoside	*Lycium chinense*	Solanaceae	[92]
O-62	progoitrin	Cruciferae	Brassicaceae	[94]
O-63	sanshiside-D	*Mussaenda phillipica*	Rubiaceae	[95]
O-64	3'-formyl-6',4-dihydroxy- 2'-methoxy-5'-methylchalcone 4'-*O*- β -D-glucopyranoside	*Cleistocalyx operculatus*	Myrtaceae	[46]

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Table 7. Phenols isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
P-1	(+)-myricananin D	*Myrica adenophora*	Myricaceae	[56]
P-2	(+)-myricanol	*Myrica adenophora*	Myricaceae	[56]
P-3	(+)-galeon	*Myrica adenophora*	Myricaceae	[56]
P-4	(+)-lyoniresinol	*Prunus mume*	Rosaceae	[93]
	(+)-lyoniresinol	*Vitex negundo*	Verbenaceae	[38]
P-5	(+)-medioresinol	*Prunus mume*	Rosaceae	[93]
P-6	(+)-pinoresinol	*Prunus mume*	Rosaceae	[93]
P-7	(+)-S-myricanol	*Alnus japonica*	Betulaceae	[96]
P-8	(+)-syringaresinol	*Prunus mume*	Rosaceae	[93]
P-9	1-(4-hydroxy-2- methoxybenzofuran-5-yl)-3-phenylpropane-1,3-dione	*Celosia argentea*	Amaranthaceae	[53]
P-10	2-ethoxy-4-(hydroxymethyl)phenol	*Protea magnifica* × *Protea susanne*	Proteaceae	[89]
P-11	3,4-dihydroxybenzaldehyde	*Durio zibethinus*	Malvaceae	[36]
		Fagopyrum esculentum	Polygonaceae	[75]
P-12	3,4-dihydroxybenzoic acid	*Durio zibethinus*	Malvaceae	[36]
		Origanum vulgare	Lamiaceae	[61]
P-13	3'-formyl-4',6',4-trihydroxy-2'-methoxy-5'-methylchalcone	*Cleistocalyx operculatus*	Myrtaceae	[46]
P-14	3-hydroxy-3-methoxycarbonylglutaric acid	*Prunus mume*	Rosaceae	[93]
P-15	4,4′-dihydroxstilbene	*Yucca periculosa*	Asparagaceae	[35]
P-16	4-hydroxy-3-methoxybenzoic acid	*Durio zibethinus*	Malvaceae	[36]
P-17	5-deoxymyricanone	*Myrica adenophora*	Myricaceae	[56]
P-18	5-*O*-caffeoylshikimic acid	*Smilacis Glabrae*	Smilacaceae	[65]
P-19	5-*O*-ethylhirsutanonol	*Alnus japonica*	Betulaceae	[58]
P-20	5-*O*-Methylhirusutanonol	*Alnus japonica*	Betulaceae	[58]
P-21	60-O-galloyl orbicularin	*Myrica adenophora*	Myricaceae	[56]
P-22	acrovestone	*Acronychia peduncolata*	Rutaceae	[97]
P-23	actinidione	*Myrica adenophora*	Myricaceae	[56]
P-24	aureusidin	*Eleocharis tuberosa*	Cyperaceae	[41]
P-25	caffeic acid	*Nasturtium officinale*	Brassicaceae	[77]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]

		Sedum takesimense	Crassulaceae	[71]
		Lagenaria siceraria	Cucurbitaceae	[63]
		Pleioblastus kongosanensis f. *aureostriatus*	Poaceae	[74]
		Shibataea chinensis,	Poaceae	[74]
P-26	Cardanols	*Harpephyllum caffrum*	Anacardiaceae,	[98]
P-27	carvacrol	*Thymus zygis*	Lamiaceae	[99]
		Nigella sativa	Ranunculaceae	[100]
P-28	chlorogenic acid	*Nasturtium officinale*	Brassicaceae	[77]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Gomortega keule	Gomortegaceae	[37]
		Pyrus pyrifolia	Rosaceae	[64]
		Smilacis Glabrae	Smilacaceae	[65]
		Momordica charantia	Cucurbitaceae	[63]
P-29	chlorogenic acid methyl ester	*Prunus mume*	Rosaceae	[93]
		Pleioblastus kongosanensis f. *aureostriatus*	Poaceae	[74]
		Shibataea chinensis	Poaceae	[74]
P-30	*cis*-Miyabenol	*Foeniculum vulgare*	Apiaceae	[101]
		Foeniculum vulgare	Apiaceae	[102]
P-31	corilagin	*Phyllanthus debilis*	Phyllanthaceae	[88]
P-32	dedehydrohirsutanonol	*Alnus japonica*	Betulaceae	[58]
P-33	dehydrotriferulic acid	*Hydrocotyle sibthorpioides*	Araliaceae	[79]
		Hydrocotyle sibthorpioides	Araliaceae	[79]
P-34	detetrahydroconidendrin	*Vitex negundo*	Verbenaceae	[38]
P-35	(*E*)-caffeic acid	*Origanum vulgare*	Lamiaceae	[61]
P-36	eicosanyl-(*E*)-*p*-coumarate	*Harpephyllum caffrum*	Anacardiaceae,	[93]
P-37	ethyl gallate	*Toona sinensis*	Meliaceae	[81]
P-38	ethyl protocatechuate	*Durio zibethinus*	Malvaceae	[36]
P-39	evofolin-B	*Durio zibethinus*	Malvaceae	[36]
P-40	ferulic acid	*Sideritis congesta*	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Pleioblastus kongosanensis f. *aureostriatus*	Poaceae	[74]

		Shibataea chinensis	Poaceae	[74]
		Sedum takesimense	Crassulaceae	[71]
P-41	furosin	*Phyllanthus debilis*	Phyllanthaceae	[88]
P-42	gallic acid	*Nasturtium officinale*	Brassicaceae	[77]
		Phyllanthus debilis	Phyllanthaceae	[88]
		Rhodiola sachalinensis	Crassulaceae	[44]
		Sedum takesimense	Crassulaceae	[71]
		Lagenaria siceraria	Cucurbitaceae	[63]
		Momordica charantia	Cucurbitaceae	[63]
P-43	gentisic acid	*Momordica charantia*	Cucurbitaceae	[63]
P-44	geraniin	*Phyllanthus debilis*	Phyllanthaceae	[88]
P-45	guangsangon J	*Morus macroura*	Moraceae	[72]
P-46	hirsutanonol	*Alnus japonica*	Betulaceae	[58]
P-47	kuwanon J	*Morus macroura*	Moraceae	[72]
P-48	laevifonol	*Dipterocarpus dryobalanops*	Dipterocarpus	[103]
		Dipterocarpus elongates	Dipterocarpus	[103]
		Dipterocarpus hasseltii	Dipterocarpus	[103]
		Dipterocarpus verrucosus	Dipterocarpus	[103]
P-49	lariciresinol	*Araucaria araucana*	Araucariaceae	[35]
P-50	methyl gallate	*Sedum takesimense*	Crassulaceae	[71]
		Toona sinensis	Meliaceae	[81]
		Phyllanthus urinaria	Phyllanthaceae	[40]
		Pyrus calleryana	Rosaceae	[104]
P-51	myricadenin A	*Myrica adenophora*	Myricaceae	[56]
P-52	myricadenin B	*Myrica adenophora*	Myricaceae	[56]
P-53	myricananin C	*Myrica adenophora*	Myricaceae	[56]
P-54	myricanone	*Alnus japonica Steud*	Betulaceae	[96]
		Myrica adenophora	Myricaceae	[56]
P-55	negundin B	*Vitex negundo*	Verbenaceae	[38]
P-56	oresbiusin A	*Origanum vulgare*	Lamiaceae	[61]
P-57	*p*-coumaric acid	*Sideritis congesta*	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Pleioblastus kongosanensis	Poaceae	[74]
		Shibataea chinensis	Poaceae	[74]

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P-58	phyltetralin	*Phyllanthus urinaria*	Phyllanthaceae	[40]
P-59	pinoresinol	*Araucaria araucana*	Araucariaceae	[35]
P-60	protocatechuic acid	*Lagenaria siceraria*	Cucurbitaceae	[63]
		Fagopyrum esculentum	Polygonaceae	[75]
P-61	punicalagin	*Punica granatum*	Lythraceae	[105]
P-62	rosmarinic acid	*Hypericum perforatum*	Hypericaceae	[106]
		Lavandula angustifolia	Lamiaceae	[106]
		Malva sylvetris	Malvaceae	[106]
		Melissa officinalis	Lamiaceae	[106]
		Rosmarinum officinalis	Lamiaceae	[106]
		Salvia officinalis	Lamiaceae	[106]
		Foeniculum vulgare	Apiaceae	[69]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
		Origanum vulgare	Lamiaceae	[61]
P-63	salvianolic acid A	*Salvia miltiorrhiza*	Labiatae	[107]
P-64	salvianolic acid B	*Salvia miltiorrhiza*	Labiatae	[107]
P-65	sargahydroquinoic acid	*Roldana barba-johannis*	Asteraceae	[35]
P-66	sargaquinoic acid	*Roldana barba-johannis*	Asteraceae	[35]
P-67	secoisolariciresinol	*Araucaria araucana*	Araucariaceae	[35]
P-68	syringic acid	*Cucurbita maxima*	Cucurbitaceae	[63]
P-69	thymol	*Thymus zygis*	Lamiaceae	[99]
P-70	*trans*-miyabenol	*Foeniculum vulgare*	Apiaceae	[101]
P-71	*trans*-miyabenol C	*Foeniculum vulgare*	Apiaceae	[102]
P-72	vitedoamine A	*Vitex negundo*	Verbenaceae	[38]
P-73	vitedoin A	*Vitex negundo*	Verbenaceae	[38]
P-74	vitrofolal E	*Vitex negundo*	Verbenaceae	[38]
P-75	α-conidendrin	*Durio zibethinus*	Malvaceae	[36]
P-76	(+)-(*R*)-butyl rosmarinate	*Origanum vulgare*	Lamiaceae	[61]
P-77	(+)-epimagnolin A	*Magnolia denudata*	Magnoliaceae	[108]
P-78	(+)-eudesmin	*Magnolia denudata*	Magnoliaceae	[108]
P-79	(+)-fargesin	*Magnolia denudata*	Magnoliaceae	[108]
P-80	(+)-magnolin	*Magnolia denudata*	Magnoliaceae	[108]

P-81	(6-ethoxy-3,5-dihydroxy-4-oxotetrahydro-2*H*-pyran-2-yl)methyl 4-hydroxybenzoate	*Protea magnifica* × *Protea susanne*	Proteaceae	[89]
P-82	1-(4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2- hydroxyethanone	*Sedum takesimense*	Crassulaceae	[71]
P-83	1,5-di-*O*-caffeoylquinic acid	*Centella asiatica*	Apiaceae	[79]
		Foeniculum vulgare	Apiaceae	[69]
P-84	3,5-di-*O*-caffeoyl-4-malonylquinic acid	*Centella asiatica*	Apiaceae	[79]
		Centella asiatica	Apiaceae	[79]
P-85	3,5-di-*O*-caffeoylquinic acid	*Centella asiatica*	Apiaceae	[79]
P-86	3-caffeoylquinic acid	*Foeniculum vulgare*	Apiaceae	[69]
		Hydrocotyle sibthorpioides	Apiaceae	[79]
		Centella asiatica	Apiaceae	[79]
P-87	4,5-di-*O*-caffeoylquinic acid	*Centella asiatica*	Apiaceae	[79]
P-88	4-caffeoylquinic acid	*Foeniculum vulgare*	Apiaceae	[69]
P-89	4-hydroxytremetone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
P-90	5′-methoxy-7′-*epi*-jatrorin A	*Durio zibethinus*	Malvaceae	[36]
P-91	5-caffeoylquinic acid	*Foeniculum vulgare*	Apiaceae	[69]
P-92	eudesmin	*Araucaria araucana*	Araucariaceae	[35]
P-93	methyl-pinoresinol	*Araucaria araucana*	Araucariaceae	[35]
P-94	sargachromenol	*Roldana barba-johannis*	Asteraceae	[35]
P-95	vitrofolal F	*Vitex negundo*	Verbenaceae	[38]
P-96	2,3,4-trihydroxy-5-methylacetophenone	*Borassus flabellifer*	Arecaceae	[109]
P-97	2,4-dihydroxycinnamic acid	*Aruncus dioicus*	Rosaceae	[31]
P-98	2,5-dihydroxybenzoic acid	*Origanum vulgare*	Lamiaceae	[61]
P-99	3,3′,5,5′-tetrahydroxy-4-methoxystilbene	*Yucca periculosa*	Asparagaceae	[35]
P-100	4- hydroxyacetophenone	*Baccharis linearis*	Asteraceae	[35]
		Baccharis magellanica	Asteraceae	[35]
		Baccharis umbelliformis	Asteraceae	[35]
P-101	4-ethoxy-2,3-dihydroxy-4-oxobutyl 4-hydroxybenzoate	*Protea magnifica* × *Protea susanne*	Proteaceae	[89]
P-102	6-hydroxy-4-(4-hydroxy- 3-methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde	*Vitex negundo*	Verbenaceae	[38]
		Vitex negundo	Verbenaceae	[38]
P-103	maltol	*Abies koreana*	Pinaceae	[67]

P-104	labd-3β,9β-diol-3α-D-glucopyranosyl-(2a→1b)-α-D-glucopyranosyl-(2b→1c)- α-D-glucopyranosyl-(2c→1d)-α-D-arabinofuranosyl-2d-p-hydroxybenzoate	*Lycium chinense*	Solanaceae	[110]
P-105	3,4-dihydroxybenzoic acid 3-octadecanoyl-4-*O*-L-α-arabinopyranosyl (2a→1b)-2a-*O*-L-α-arabinopyranosyl (2b→1c)-2b-*O*-L-α-arabinopyranoside	*Lycium chinense*	Solanaceae	[110]
P-106	specnuzhenise	*Ligustrum sinense*	Oleaceae	[48]
P-107	armandiside	*Syringa reticulata*	Oleaceae	[111]
P-108	(+)-*S*-myricanol 5-*O*-β-D-glucopyranoside	*Alnus japonica*	Betulaceae	[96]
P-109	2-(3,4-dihydroxy)-phenylethyl-β-D-glucopyranoside	*Syringa reticulata*	Oleaceae	[111]
P-110	3'-formyl-6',4-dihydroxy- 2'-methoxy-5'-methylchalcone 4'-O- β -D-glucopyranoside	*Cleistocalyx operculatus*	Myrtaceae	[46]
P-111	3'hydroxybenzyl-4-hydroxybenzoate-4'-*O*-β-glucopyranoside	*Pyrus calleryana*	Rosaceae	[104]
P-112	3-*O*-β-D-glucopyranoside of 3-hydroxy-1-(4'-hydroxy-3'-methoxyphenyl)-1-propanone	*Pyrus pyrifolia*	Rosaceae	[64]
P-113	alnuheptanoids B	*Alnus japonica*	Betulaceae	[96]
P-114	benzoyl-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
P-115	*cis*-miyabenol C 11a-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside,	*Foeniculum vulgare*	Apiaceae	[102]
P-116	hirsutanonol-5-*O*-β-D-glucopyranoside	*Alnus japonica*	Betulaceae	[58]
P-117	maltol 6'-*O*-(5-*O*-*p*-coumaroyl)-β-D-apiofuranosyl-β-D-glucopyranoside	*Origanum vulgare*	Lamiaceae	[61]
P-118	myricanol 11-*O*-β-D-glucopyranoside	*Myrica adenophora*	Myricaceae	[56]
P-119	myricanone 5-*O*-β-D-glucopyranoside	*Alnus japonica*	Betulaceae	[96]
P-120	*p*-hydroxyphenethyl-*O*-β-D-glucopyranoside	*Ligustrum sinense*	Oleaceae	[48]
P-121	protocatechuoylcalleryanin-3-*O*-β-glucopyranoside	*Pyrus calleryana*	Rosaceae	[104]
P-122	salidroside	*Smilacis Glabrae*	Smilacaceae	[65]
P-123	2,6-di-*O*-galloylarbutin	*Sedum takesimense*	Crassulaceae	[71]
P-124	3',5'-di-*C*-β-glucopyranosylphloretin	*Citrus japonica*	Rutaceae	[70]
P-125	arbutin	*Sedum takesimense*	Crassulaceae	[71]
P-126	eleocharin B	*Eleocharis tuberosa*	Cyperaceae	[41]
P-127	amburoside A	*Origanum vulgare*	Lamiaceae	[61]
P-128	protocatechuic acid 3-*O*-glucoside	*Pyrus calleryana*	Rosaceae	[104]
P-129	sinapyl glucoside	*Foeniculum vulgare*	Apiaceae	[102]
		Foeniculum vulgare	Apiaceae	[101]

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P-130	(*E*)-piceid	*Abies koreana*	Pinaceae	[67]
P-131	jaspolyoside	*Syringa reticulata*	Oleaceae	[111]
P-132	sinalbin	Cruciferae	Brassicaceae	[94]
P-133	3,4-dihydeoxyphenethyl alcohol	*Ligustrum sinense*	Oleaceae	[48]
P-134	10-hydroxyloleuropein	*Ligustrum sinense*	Oleaceae	[48]
P-135	oleuropein	*Syringa reticulata*	Oleaceae	[111]
P-136	1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose	*Toona sinensis*	Meliaceae	[81]
P-137	syringaresinol-4,4″-*O*-bis-β-D-glucoside	*Syringa reticulata*	Oleaceae	[111]
P-138	isosyringinoside	*Syringa reticulata*	Oleaceae	[111]
P-139	dillapiole	*Bunium Persicum*	Apiaceae	[91]
P-140	methyleugenol	*Rosmarinus officinalis*	Lamiaceae	[90]
P-141	myristicin	*Bunium Persicum*	Apiaceae	[91]
P-142	phyllanthin	*Phyllanthus urinaria*	Phyllanthaceae	[40]
P-143	(*E*)-anethole	*Nigella sativa*	Ranunculaceae	[100]
P-144	3,4,5-trimethoxyphenyl-β-D-glucopyranoside	*Prunus mume*	Rosaceae	[93]
P-145	syringin 4-*O*-β-glucoside	*Foeniculum vulgare*	Apiaceae	[101]
P-146	syringin	*Viscum album*	Loranthaceae	[93]
P-147	(+)-isolarisiresinol xylopyranoside	*Pinus densiflora*	Pinaceae	[82]
P-148	platyphyllonol-5- *O*-β-D-xylopyranoside	*Alnus japonica*	Betulaceae	[58]
P-149	alnuside A	*Alnus japonica*	Betulaceae	[58]
P-150	alnuside B	*Alnus japonica*	Betulaceae	[58]
P-151	alnuside C	*Alnus japonica*	Betulaceae	[58]
P-152	oregonin	*Alnus japonica*	Betulaceae	[58]
P-153	oregonin peracetate	*Alnus japonica*	Betulaceae	[58]
P-154	11-*O*-β-D-xylopyranosylmyricanol	*Myrica adenophora*	Myricaceae	[56]
P-155	verminoside	*Spathodea campanulata*	Bignoniaceae	[83]
P-156	(7S”,8S”,8′S*)-3,4,3′,4′-Tetramethoxy-9,7′-dihydroxy-8.8′,7.0.9′-lignan	*Magnolia denudata*	Magnoliaceae	[108]

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Table 8. Steroids and triterpenoids isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
S-1	2α-hydroxyursolic acid	*Pyrus pyrifolia*	Rosaceae	[64]
S-2	β-sitosterol	*Salvadora persica*	Salvadoraceae	[112]
		Aruncus dioicus	Rosaceae	[31]
S-3	betulinic acid	*Pyrus pyrifolia*	Rosaceae	[64]
S-4	campesterol	*Salvadora persica.*	Salvadoraceae	[112]
S-5	cryptotanshinone	*Salvia miltiorrhiza*	Labiatae	[107]
S-6	hindicusine	*Hemidesmus indicus*	Asclepiadaceae	[113]
S-7	limonexic acid	*Citrus aurantium*	Rutaceae	[31]
S-8	myricalactone	*Myrica adenophora*	Myricaceae	[56]
S-9	oleanolic acid	*Pyrus pyrifolia*	Rosaceae	[64]
S-10	stigmasterol	*Salvadora persica*	Salvadoraceae	[112]
S-11	tanshinone I	*Salvia miltiorrhiza*	Labiatae	[107]
S-12	tanshinone IIA	*Salvia miltiorrhiza*	Labiatae	[107]
S-13	ursolic acid	*Pyrus pyrifolia*	Rosaceae	[64]
S-14	Δ^5-avenasterol	*Salvadora persica*	Salvadoraceae	[112]
S-15	β-sitosterol-3-*O*-β-D-glucopyranoside	*Phyllanthus urinaria*	Phyllanthaceae	[40]
		Aruncus dioicus	Rosaceae	[31]
		Lycium chinense	Solanaceae	[110]

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Table 9. Terpenoids isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
T-1	(*Z*)-β-ocimene	*Bunium persicum*	Apiaceae	[91]
T-2	1,8-cineole	*Thymus zygis*	Lamiaceae	[99]
		Rosmarinus officinalis	Lamiaceae	[90]
T-3	1β-acetoxyfuranoeudesm-4(15)-ene	*Smyrnium olusatrum*	Apiaceae	[114]
T-4	2-hydroxy-8α-hydroxycalamenene	*Durio zibethinus*	Malvaceae	[36]
T-5	α-thujene	*Bunium Persicum*	Apiaceae	[91]
T-6	borneol	*Rosmarinus officinalis*	Lamiaceae	[90]
T-7	bornyl acetate	*Rosmarinus officinalis*	Lamiaceae	[90]
T-8	camphene	*Rosmarinus officinalis*	Lamiaceae	[90]
T-9	camphor	*Rosmarinus officinalis*	Lamiaceae	[90]
T-10	caryophyllene oxide	*Bunium Persicum*	Apiaceae	[91]
		Rosmarinus officinalis	Lamiaceae	[90]
T-11	chrysanthenone	*Rosmarinus officinalis*	Lamiaceae	[90]
T-12	clerodane	*Gutierrezia microcephala*	Asteraceae	[35]
T-13	copaene	*Cryptocarya latifolia*	Lauraceae	[87]
T-14	crocetin	*Crocus sativus*	Iridaceae	[115]
T-15	crocin 1	*Crocus sativus*	Iridaceae	[115]
T-16	crocin 2	*Crocus sativus*	Iridaceae	[115]
T-17	crocin 3	*Crocus sativus*	Iridaceae	[115]
T-18	crocin 4	*Crocus sativus*	Iridaceae	[115]
T-19	curzerene	*Smyrnium olusatrum*	Apiaceae	[114]
T-20	δ-3-carene	*Smyrnium olusatrum*	Apiaceae	[114]
T-21	furanoeremophil-1-one	*Smyrnium olusatrum*	Apiaceae	[114]
T-22	glechomafuran	*Smyrnium olusatrum*	Apiaceae	[114]
T-23	ɣ-terpinene	*Bunium Persicum*	Apiaceae	[91]
		Rosmarinus officinalis	Lamiaceae	[90]
		Thymus zygis	Lamiaceae	[99]
T-24	ɣ -tocopherol	*Salvadora persica*	Salvadoraceae	[112]
T-25	icetexane 1	*Premna tomentosa*	Verbenaceae	[116]
T-26	icetexane 2	*Premna tomentosa*	Verbenaceae	[116]
T-27	icetexane 3	*Premna tomentosa*	Verbenaceae	[116]
T-28	icetexane 4	*Premna tomentosa*	Verbenaceae	[116]

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T-29	iso-borneol	*Rosmarinus officinalis*	Lamiaceae	[90]
T-30	isofuranodiene	*Smyrnium olusatrum*	Apiaceae	[114]
T-31	limonene	*Bunium Persicum*	Apiaceae	[91]
		Thymus zygis	Lamiaceae	[99]
T-32	linalool	*Thymus zygis*	Lamiaceae	[99]
T-33	myrtenol	*Rosmarinus officinalis*	Lamiaceae	[90]
T-34	nerolidol	*Cryptocarya latifolia*	Lauraceae	[87]
T-35	neryl acetate	*Rosmarinus officinalis*	Lamiaceae	[90]
T-36	p-cymene	*Bunium Persicum*	Apiaceae	[91]
		Thymus zygis	Lamiaceae	[99]
T-37	p-cymene-7-ol	*Bunium Persicum*	Apiaceae	[91]
T-38	p-cymene-8-ol	*Bunium Persicum*	Apiaceae	[99]
T-39	phytol	*Aruncus dioicus*	Rosaceae	[31]
T-40	pinocarvone	*Rosmarinus officinalis*	Lamiaceae	[90]
T-41	safranal	*Crocus sativus*	Iridaceae	[115]
T-42	squalene	*Prunus mume*	Rosaceae	[93]
T-43	terpinene-4-ol	*Bunium Persicum*	Apiaceae	[91]
		Nigella sativa	Ranunculaceae	[100]
		Rosmarinus officinalis	Lamiaceae	[90]
T-44	thymoquinone	*Nigella sativa*	Ranunculaceae	[100]
T-45	*trans*-pinocamphone	*Rosmarinus officinalis*	Lamiaceae	[90]
T-46	*trans*-sabinene hydrate	*Rosmarinus officinalis*	Lamiaceae	[90]
T-47	*trans*-β-carotene	*Opuntia ficus-indica*	Cactaceae	[30]
T-48	tricyclene	*Rosmarinus officinalis*	Lamiaceae	[90]
T-49	verbenene	*Rosmarinus officinalis*	Lamiaceae	[90]
T-50	verbenone	*Rosmarinus officinalis*	Lamiaceae	[90]
T-51	widdrol	*Rosmarinus officinalis*	Lamiaceae	[90]
T-52	α-bisabolol	*Rosmarinus officinalis*	Lamiaceae	[90]
T-53	α-humulene	*Rosmarinus officinalis*	Lamiaceae	[90]
T-54	α-phellandrene	*Rosmarinus officinalis*	Lamiaceae	[90]
T-55	α-pinene	*Bunium persicum*	Apiaceae	[91]
		Rosmarinus officinalis	Lamiaceae	[90]
		Thymus zygis	Lamiaceae	[99]
T-56	α-terpinene	*Rosmarinus officinalis*	Lamiaceae	[90]

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		Rosmarinus officinalis	Lamiaceae	[90]
T-57	α-tocopherol	*Salvadora persica*	Salvadoraceae	[112]
		Sideritis congesta	Lamiaceae	[60]
		Sideritis arguta	Lamiaceae	[60]
T-58	α-tocopherol	*Opuntia ficus-indica*	Cactaceae	[30]
T-59	β-caryophyllene	*Aquilaria crassna*	Thymelaeaceae	[117]
		Rosmarinus officinalis	Lamiaceae	[90]
T-60	β-myrcene	*Bunium Persicum*	Apiaceae	[91]
		Rosmarinus officinalis	Lamiaceae	[90]
		Thymus zygis	Lamiaceae	[99]
T-61	β-pinene	*Bunium persicum*	Apiaceae	[91]
		Rosmarinus officinalis	Lamiaceae	[90]

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Table 10. Xanthenones isolated from plants exhibiting antioxidant effects.

Compound No	Name	Species	Family	Reference
X-1	1,3,5,6-tetrahydroxyxanthone	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-2	1,3,5,6-tetrahydroxyxanthone	*Hypericum perforatum*	Hypericaceae	[118]
X-3	1,5,6-trihydroxy-3-methoxyxanthone	*Hypericum perforatum*	Hypericaceae	[118]
X-4	10-*O*-methylmacluraxanthone	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-5	3-*O*-demethylswertipunicoside	*Swertia punicea*	Gentianaceae	[119]
X-6	5′-demethoxycadensin G	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-7	5-*O*-methyl-2-deprenylrheediaxanthone B	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-8	bellidifolin	*Swertia angustifolia*	Gentianaceae	[119]
		Swertia chirayita	Gentianaceae	[119]
		Swertia hookeri	Gentianaceae	[119]
		Swertia macrosperma	Gentianaceae	[119]
		Swertia mussotii	Gentianaceae	[119]
		Swertia paniculate	Gentianaceae	[119]
		Swertia perennis	Gentianaceae	[119]
		Swertia punctata	Gentianaceae	[119]
		Swertia punicea	Gentianaceae	[119]
		Swertia purpurascens	Gentianaceae	[119]
X-9	brasilixanthone B	*Hypericum perforatum*	Hypericaceae	[118]
X-10	cochinchinoxanthone	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-11	cratosumatranone C	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-12	cratosumatranone D	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-13	ferrxanthone	*Hypericum perforatum*	Hypericaceae	[118]
X-14	isocudraniaxanthone B	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-15	macluraxanthone	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-16	neolancerin	*Hypericum perforatum*	Hypericaceae	[118]
X-17	neriifolone B	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-18	pruniflorone M	*Cratoxylum sumatranum*	Hypericaceae	[43]
X-19	pruniflorone N	*Cratoxylum sumatranum*	Hypericaceae	[43]

(3) Case study: antioxidant activity of flavonoids

Flavonoids comprise a large group of phenolic compounds. Their basic chemical structure is the flavan nucleus, which consists of 15 carbon atoms arranged in three rings (C_6-C_3-C_6), as seen in **Figure 1**. The different classes of flavonoids differ in the oxidation level and substitution pattern of the C ring, while units within a class differ in the substitution pattern of the A and B rings [120].

Nowadays, flavonoids have gained huge interest due to their broad pharmacological activity. The interest in flavonoids' health benefits has increased due to their potent antioxidant and free radical scavenging activities observed *in vitro*. The antioxidant activity of flavonoids and their metabolites depends upon the arrangement of functional groups around the basic structure. Several *in vitro* investigations have been carried to elucidate the relationship between the flavonoid structure and their antioxidant effects [121–126]. Therefore, flavonoids' chemical structures are predictive of their antioxidant potential in terms of radical scavenging, hydrogen- or electron-donating and metal-chelating capacities.

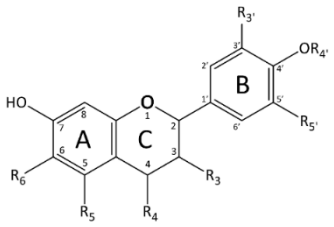


Figure 1. Basic structure of flavonoids

The following mechanisms have been cited in literature to explain the antioxidant activity of flavonoids: (1) Scavenging of free radicals or ROS, (2) metal chelating, (3) inhibition of enzymes associated with free-radicals generation (e.g., oxidases), (4) activation of antioxidant enzymes [120,127,128].

(a) Free-radical scavenging

The antioxidant capacities of flavonoids can occur from free radical scavenging or direct ROS scavenging. Flavonoids are able to donate a hydrogen atom to neutralize free radicals (**Figure 2**). Also, flavonoids may act by single-electron transfer. The products of these two mechanisms are harmless stable radicals.

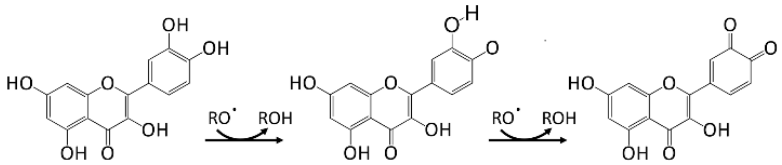
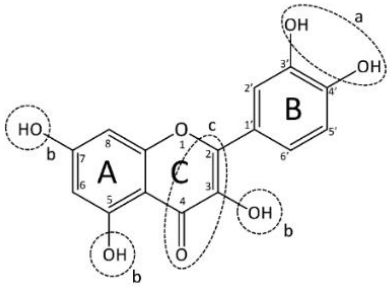


Figure 2. Mechanism of antioxidant by hydrogen atom donation of flavonoids.

In literature, it is well-known that some flavonoids present higher antioxidant activities than others, which is directly related to their chemical structures [127,129,130]. For efficient radical scavenging, the required structural features of flavonoids are summarized as follows: i) *o*-dihydroxy (catechol) structure in the B ring for electron delocalization (**Figure 3, ring a**); ii) hydroxyl groups at position 3 on C ring, 5 and 7 on A ring providing an increase in the antioxidant activity (**Figure 3, ring b**), and iii) C_2-C_3 double bond combined with the *oxo*-C_4 on C ring (**Figure 3, ring c**).

Figure 3. Antioxidant structural-activity relationships of flavonoids.



The most significant actor in scavenging free radicals is the B-ring hydroxyl structure. The hydroxyl groups on this ring stabilize hydroxyl, peroxyl and peroxynitrite radicals through donating hydrogen or electron. Quercetin has shown to be the flavonoid expressing the higher antioxidant activity due to the presence of hydroxyl groups and the twisting angle of the B-ring [131].

The total number of hydroxyl groups in the flavonoid structure influences the mechanism of antioxidant activity. To evaluate the antioxidant activity of flavonoids' hydroxyl groups, the bond dissociation enthalpy (BDE) is used where the lower the BDE value, the easier the dissociation of the hydroxyl bond and the reaction with free radicals [120,132].

(b) Metal-ion chelating

Metal ions, such as Fe^{2+} and Cu^{+}, are considered as a primary cause of ROS generation *in vivo*. These redox-active metal ions can react with H_2O_2, and the result is $OH^{\cdot}$, which damage DNA by strand breakage or base damage, leading to genetic mutations, cancer or even cell death [133,134].

Some flavonoids can chelate these metal ions decreasing one of the factors for the development of free radicals. The proposed binding sites for metal ions in flavonoid structure are the catechol moiety in the B-ring, the 3-hydroxyl, 4-oxo groups in the C-ring, and the 4-oxo, 5-hydroxyl groups between C and A-rings [135]. For iron-chelating mechanism by flavonoids, stability constants for flavonoid – iron interactions have been measured providing insight into their antioxidant behavior. The stability constant for Fe^{2+} monocatecholate is much lower than the Fe^{3+} monocatecholate complex. Due to this fact, through performing these measurements requires oxygen-free conditions to prevent oxidation of Fe^{2+} to Fe^{3+} [136].

(c) Inhibition of prooxidant enzymes

Enzymes, such as nitric oxide synthase (NOS), xanthine oxidoreductase (XOR), lipoxygenase (LOX), cyclooxygenase (COX), are responsible for ROS generation [23]. XOR is involved in the metabolism of xanthine to uric acid and is a source of oxygen free radicals [25]. XOR reacts with molecular oxygen and releases superoxide. Flavonoids have shown to inhibit XOR, amongst them quercetin and luteolin are the most widely cited [13,137]. Several reports investigated the structure-activity relationships of flavonoids as XOR inhibitors [137–139]. All these studies showed that the flavonoids' inhibitory activity is due to the planar flavone core (C_2-C_3 double bond), hydroxyl groups at C_5 and C_7 and the carbonyl group C_4 [137–

139]. COX and LOX are responsible for the inflammatory process of mediators' production. COX presents 2 isoforms, COX-1 and COX-2. During the inflammatory process, COX-1 mRNA and protein activity do not change, whereas a dramatic increase in COX-2 levels occurs leading to an increased proinflammatory prostanoids production [140].

Flavonoids have been investigated as selective COX-2 inhibitors. Selected flavonoids have shown to inhibit the COX pathway, like quercetin and quercetin 3'-sulfate [141]. Flavonoids with an ortho-dihydroxy (catechol moiety) in rings A or B were stronger inhibitors of COX-2 than those with a free 3-OH group. Planar flavonoid structure (C_2-C_3 double bond) seems to be a prerequisite for inhibitory activity [142]. The same observation about structure-activity relationships was made for LOX inhibition [143,144]. It has been shown that quercetin and quercetin monoglucosides exert the higher LOX inhibition potential [143]. Otherwise, it should be considered that the effect of plant antioxidants on several enzymes, such as XOR can have secondary effects on other drugs that are metabolized by XOR. In fact, as reported in a recent review [145], XOR activity is directly involved in the metabolism of several antiblastic and antimetabolic drugs used against neoplasia, autoimmune diseases, and viral infections. Sometimes, XOR activity has a degradative function toward a drug, while to other drugs, XOR has an activating role and is, thus, essential for their pharmacological action [145].

(d) Activation of antioxidant enzymes

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

Flavonoids have been shown to interact with cellular defense systems, through the antioxidant-responsive element/electrophile-responsive element (ARE/EpRE) [146]. Quercetin has been shown to stimulate both antioxidant response genes and proteins expression in various cell types, and these proteins may prevent

damage from subsequent oxidative insult, like heme oxygenase-1 (HO-1) in RAW264.7 macrophages [147]; and CAT, in trabecular meshwork cells of the eye [148] and (NQO-1) in HepG2 cells [146]. Kaempferol has also shown to be able to activate ARE more potently than quercetin, and lower concentrations of the combination of both compounds increased the mRNA expression of NADPH-quinone oxidoreductase and glutathione *S*-transferase to a higher extend compared with the individual treatments at higher concentrations [149]. Lee-Hilz et al. [150] showed that flavonoids were presenting a hydroxyl group at the 3-position of C-ring, like quercetin and myricetin, were the most effective inducers of firefly luciferase reporter gene in Hepa-1c1c7 mouse hepatoma cells.

(2) Phytochemicals as pro-oxidant agents: friend or foe?

Besides to the already stated phytochemicals with antioxidant effects, it has also been shown that some of these molecules may also play pro-oxidant effects. In particular, flavonoids have been found to be mutagenic *in vitro* [151,152]. In fact, as described above, the chemical structure of flavonoids exerts a key role in their antioxidant activities, as well as the copper-initiated pro-oxidant activities. As long as the OH substitution is necessary for the antioxidant activity, the subclasses of flavone and flavanone, which have no OH substitutions and provide the basic chemical structures for flavonoids, do not show antioxidant or copper-initiated pro-oxidant activities [151]. Higher OH substitutions are associated with stronger redox activity. *O*-Methylation, as well as probably other *O*-modifications of the flavonoid OH substituents, inactivate both antioxidant and pro-oxidant effects of flavonoids. In general, flavonoids occur in foods as *O*-glycosides with sugars bound at the C3 position. Methylation or glycosidic modification of the OH substitutions leads to inactivation of the transition metal-initiated pro-oxidant activity of a flavonoid [153]. On the other hand, flavonoids, such as quercetin and kaempferol, induce nuclear DNA damage and lipid peroxidation in the presence of transition metals. The *in vivo* copper-initiated pro-oxidant action of flavonoids is generally not considered significant, as a copper ion is largely sequestered in tissues, except in case of metal toxicity. In this context, flavonoids, such as catechins and quercetin, possess chelating

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properties, inhibiting their reactivity [154,155]. Besides, polyphenols are well-known scavenger/chain breaking phytochemicals (**Figure 4**). Although the well-known flavonoids' ability to prevent iron-induced lipid peroxidation in hepatocytes, including quercetin [156], it has been suggested that the pro-oxidant activity of some polyphenols is more prominent *in vitro* under particular conditions, such as high pH or in the presence of high concentrations of transition metal ions and oxygen molecules [2]. Specifically, the small phenolic molecules, which are easily oxidized, such as quercetin and gallic acid, have a known pro-oxidant activity. On the other hand, phenols with a high molecular weight (i.e., tannins), have little or no pro-oxidant activity [14]. Polyphenols' pro-oxidant properties may derive from different possible mechanisms, including metal-reducing activity, copper ions mobilization, chemical instability, cellular glutathione (GSH) depletion and sulfhydryl (SH) interactions [157].

Although reducing and antioxidant capacity are related, it must be considered that hydroxyl radical, the lipid peroxidation initiator, is produced from the reaction between reduced iron or copper and hydrogen peroxide (**Figure 4**). Moreover, some dietary polyphenols, such as resveratrol and caffeic acid, have been shown to trigger DNA damages through mobilization of endogenous copper ions, probably chromatin binding, leading to ROS production [158]. The preferential cytotoxicity towards tumor cells is probably due to the high levels of copper ions, and not of iron ions in cells and in tumor tissues. The mechanism through which copper concentration is increased in the tumor is not yet clear [158,159]. However, it has been shown that the copper transporter 1, with high affinity in humans, is over-expressed in malignant cells, resulting in increased absorption and accumulation of the metal. Also, it has been hypothesized that copper may be necessary for ceruloplasmin expression, which is the main protein that binds it and is over-expressed in cancer cells; thus, it has been proposed to be an endogenous stimulator of angiogenesis. Nonetheless, further *in vivo* studies are necessary to know these processes better.

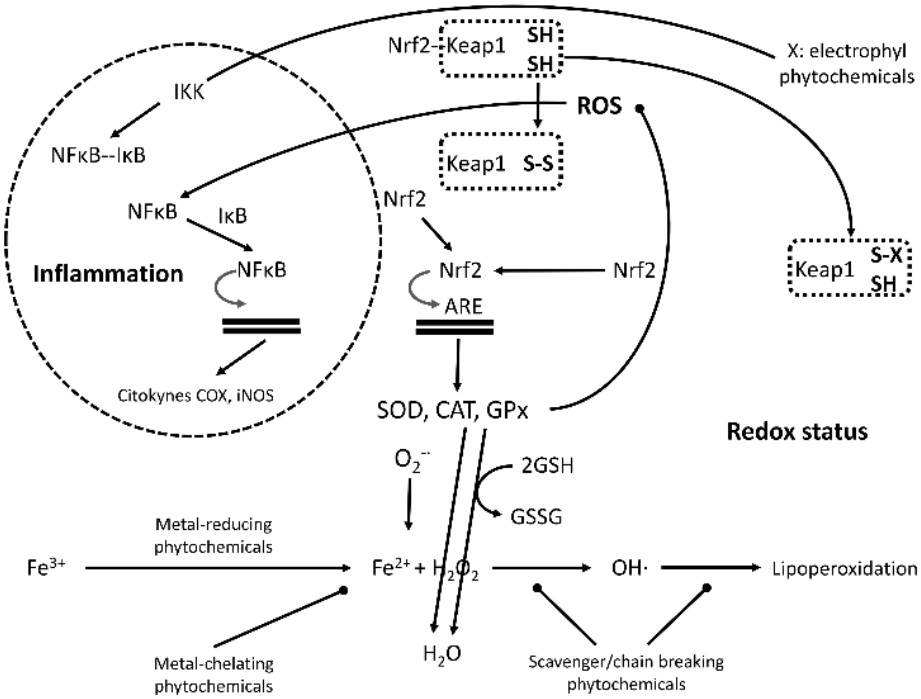

Figure 4. Glutathione (GSH); Glutathione *S*-transferases (GSTs); Glutathione peroxidase (GPX), Superoxide dismutase (SOD); Catalase (CAT); Nuclear factor-erythroid 2-related factor 2 (Nfr2); Antioxidant responsive elements (ARE); Kelch-like ECH-associated protein-1 (Keap1); Nuclear factor-kappa B (NF-κB); Iκ kinases (IKK); CREB-binding protein (CBP).

Regarding chemical instability, many polyphenols are structurally unstable and can undergo enzymatic or spontaneous oxidation in the presence of metal ions, particularly in cell culture, to form ROS [28,160,161]. For instance, it has been shown that EGCG produces significant amounts of H_2O_2 in cell cultures [162]. Likewise, green tea and red wine cytotoxicity in PC12 rat phaeochromocytoma cells, grown in DMEM medium, can be attributed to H_2O_2 produced from these drinks, at least partially [163]. The same hold for phytochemicals, including polyphenols that can become pro-oxidants, even if this has not yet been clearly elucidated. However, transition metal ions are known to be present in cell culture media. An example is Dulbecco's Modified Eagle's Medium (DMEM), which contains inorganic iron, usually $Fe(NO_3)_3$, which gives it greater pro-oxidant properties. Also, most of the cultured cells are kept in high O_2 conditions (95%

air/ 5% CO_2) and low ascorbate, vitamin E and selenium concentrations, which can lead to artefact results [28].

Through *in vitro* studies, several food polyphenols have been shown to determine cellular GSH depletion, which could contribute to apoptosis activation in tumor cells. For example, Kachadourian and Day [164] have shown that the flavones, cristine, and apigenin, deplete GSH in cell lines, while hydroxycarbonate and dihydroxycalcone perform this action more effectively in tumor prostate PC-3 cells. These authors found that the enhancement effects of these different flavones are related to mitochondrial dysfunction, through depletion of mitochondrial GSH levels, decrease in mitochondrial membrane potential and increase in cytochrome C release [164]. In this context, isothiocyanates are conjugated with GSH by glutathione *S*-transferases (GSTs) [165,166]. GPX, involved in hydrogen peroxide removal, consumes GSH (**Figure 4**). On the other hand, it has been suggested that some polyphenols have a pro-oxidant activity both *in vitro* and *in vivo*, which certainly contributes to their antioxidant and anti-cancer effects [28], through inducing antioxidant enzymes, such as SOD, catalyzing one-electron dismutation of superoxide into hydrogen peroxide and oxygen, and CAT, operating two electron dismutation into oxygen and water (**Figure 4**).

It is well-known that SH redox status has a primary role in nuclear factor-erythroid 2-related factor 2 (Nfr2)/ ARE pathway (**Figure 4**). Under physiological conditions, Nfr2 is bound to kelch-like ECH-associated protein-1 (Keap1) and, thereby, sequestered in the cytoplasm, whereas under conditions of oxidative stress, Nfr2 dissociates from Keap1, translocate to the nucleus and induces antioxidant enzymes transcription. The cysteine residues on Keap1, which are ultrasensitive to electrophiles, are critically important for Nrf2 binding. Antioxidants with catechol and electrophilic moieties induce Nrf2-mediated gene expression of antioxidant enzymes acting as pro-oxidants rather than antioxidants [167]. This effect is well-known for green tea catechins [168], but also to other bioactive phytochemicals, like triterpenoids, caffeic acid, and isothiocyanates (the breakdown products of glucosinolates), that can induce Nrf2 pathway, acting on cysteine residues of Keap1 [165,166,169–171].

As observed for Nrf2, ROS and some cysteine residues are involved in NF-κB translocation to the nucleus (**Figure 4**). In particular, cysteine 179 of I*κ* kinases (IKK) is a target of the *S*-glutathionylation-induced inactivation [172]. Electrophilic modifications of cysteine 179 of IKK inhibit NF-κB activation and have been suggested as one of the mechanisms involved in the anti-inflammatory and COX-inhibitory effects of phytochemicals [173,174]. On the other hand, it has been suggested that the crosstalk between Nrf2 and NF-κB can occur through other mechanisms, including common regulatory sequences in transactivation domains, co-activator CREB-binding protein (CBP) and up-regulation exerted by Nrf2 of antioxidant enzymes [165].

III. Therapeutic relevance of plant-derived antioxidants in disease prevention

Redox homeostasis plays a crucial role in health maintenance and disease prevention. Oxidative stress, generated by the unbalance between ROS and antioxidants leads to degradation of lipids, proteins, and nucleic acids, resulting in oxidative damage of cells. Such damages may result or contribute significantly to oncogenes over-expression, mutagen formation, atherogenic activity induction or inflammation. In fact, oxidative stress has been reported to play a major role in the development of chronic and degenerative diseases, such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative disorders, among others. As already stated, plants are rich sources of antioxidants that show health benefits through direct reduction of oxidative stress. Here we are focusing on some plants that involve the antioxidant-based mode of action in diseases management.

(1) Cardiovascular Diseases

Cardiovascular diseases are the leading cause of death globally. A plethora of herbal products are used to manage and/or treat chronic cardiovascular conditions and related problems. Evidence suggests that myocardial cell damage may be due to toxic ROS generation, such as superoxide radical, hydrogen peroxide and hydroxyl radical [175]. Several studies have demonstrated that polyphenols consumption limits the

incidence of coronary heart diseases [176]. Quercetin, an ample polyphenol in onion, has shown to decrease coronary heart disease-associated mortality through inhibiting metalloproteinase 1 (MMP1) expression and disrupting atherosclerotic plaques [142]. *Centella asiatica* from the Apiaceae family has been shown to prevent blood coagulation, to alleviate oxidative stress and can be used as a hypotensive [177]. Tea catechins have been shown to inhibit smooth muscle cells invasion and proliferation in the arterial wall, thereby slowing down atheromatous lesion formation. Tea polyphenols lower blood pressure due to antioxidant or estrogen-like activity [142]. *Convallaria majalis* from the Smilacaceae family has cardenolide glycosides. The other compounds in this plant are convallasaponin A, free flavonoids, heterosides, and mineral salts. Convallotoxin is used as cardiotonic [178]. Consumption of red wine or non-alcoholic wine reduces the bleeding time and platelet aggregation. Resveratrol, the wine polyphenol, prevents platelet aggregation via preferential inhibition of COX-1 activity, which synthesizes thromboxane A2, an inducer of the platelet aggregation and vasoconstrictor [179]. *Fraxinus excelsior,* a member of the Oleaceae family, has two phenolic classes of compounds, mainly iridoids and secoiridoid glucosides. It can be used as vasoprotective, venotonic and have anti-hypertensive effects too [180]. *Digitalis purpurea* and *Digitalis lanata,* from the Scrophulariaceae family, have cardiac glycosides. Being cardiotonic, it acts by increasing heterosides on cardiac contractility, decreasing excitability, conductivity, and rhythm, and decreasing the oxygen requirement for cardiac work [181]. *Hamamelis virginiana,* also called witch hazel, belongs to the Hamamelidaceae family. The leaves of this plant have phenolic compounds, such as flavonoids and hydroxycinnamic acids. This plant is used for varicose veins [182].

Beside these, *Allium cepa, Allium sativum, Veratrum album* and *Urginea maritima* (Smilacaceae), *Rauvolfia serpentina* and *Strophanthus gratus (*Apocynaceae), *Rhododendron molle* (Ericaceae), *Stephania tetrandra* (Menispermaceae), *Aesculus hippocastanum* (Hippocastanaceae), *Citrus limon* and *Citrus sinensis* (Rutaceae), *Coffea arabica* and *Coffea liberica* (Rubiaceae), *Corylus avellana* (Betulaceae), *Hordeum vulgare* (Poaceae), *Melissa officinalis* (Lamiaceae), *Ribes nigrum* (Grossulariaceae), *Vaccinium*

myrtillos (Ericaceae), *Valeriana officinalis* (Valerianaceae) are some of the plants having therapeutic effect in cardiovascular diseases, like hypertension, atherosclerosis and stroke [183].

(2) Cancer

Cancer development in humans is a complex process mediated by assorted endogenous and exogenous stimuli. It is reported that oxidative DNA damage is responsible for cancer development, involving free radicals-induced promotion and oncogene activation [184].

Polyphenols have been reported to decrease tumors growth in human cancer cell lines [185]. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol, and curcumin, have been reported to show protective effects in some models, despite their different mechanisms of action [186]. Apigenin, a flavone present in vegetables and in the Egyptian plant *Moringa peregrine*, demonstrates cytotoxic activities against breast cancer cell line (MCF 7) and colon cell line (HCT 116) comparable to that of doxorubicin [187]. Curcumin (diferuloylmethane) is the major component of the popular Indian spice turmeric, (*Curcuma longa* L.) a member of the ginger family. Its anti-cancer effects have been studied for colon and breast cancers, lung metastases, and brain tumor [188,189]. Cyanidin is a pigment extract from red berries, such as grapes, blackberry, cranberry, raspberry, or apples and plums, red cabbage and red onion. It possesses antioxidant and radical-scavenging effects, which may reduce the risk of cancer. It has been reported that cyanidin-3-glucoside (C3G) may prevent/reduce ethanol-induced breast cancer metastasis [190]. Indole-3-carbinol (I3C) is found in *Brassica* vegetables, such as broccoli, cauliflower, collard greens. Diindolylmethane (DIM) is a digestion derivative of I3C. I3C and DIM have demonstrated exceptional anti-cancer effects against hormone responsive cancers, like breast, prostate and ovarian cancers [191]. Epigallocatechin gallate (EGCG) is the most abundant catechin compounds in green tea. Increasing evidence have shown that EGCG can be beneficial in treating brain, prostate, cervical and bladder cancers [192–194]. Theaflavins and thearubigins, the abundant polyphenols in black tea have also been shown to possess strong anti-cancer properties. Fisetin,

a flavone found in various plants, such as *Acacia greggii*, *Acacia berlandieri*, Euroasian smoke tree, parrot tree, strawberries, apple, persimmon, grape, onion, and cucumber, is a potent antioxidant and modulates protein kinase and lipid kinase pathways [8]. Genistein, an isoflavone that originates from a number of plants, such as lupine, fava beans, soy beans, kudzu, and psoralea, *Flemingia vestita*, and coffee, acts as an antioxidant, and it is also useful in treating leukemia [195].

Beside this, gingerol (gingers), kaempferol (tea, broccoli and grapefruit), lycopene (tomato), phenethyl isothiocyanate (PEITC) and sulforaphane (cruciferous vegetable) and resveratrol (grapes), rosmarinic acid (rosemary), vitamin D from mushroom, and vitamin E from plant oil, *Aegle marmelos* (Bael), *Vernonia anthelmintica* (Kalijiri), *Tinospora cordifolia*, and *Phyllanthus acidus* (Amla), have also been reported to have potential anti-cancer properties due to the presence of antioxidants, like phenolic compounds [196].

The anti-cancer agents, vinblastine and vincristine, from *Catharanthus roseus* (Apocynaceae), revolutionized the use of plant material as a medication for treatment. These were the first agents into clinical use for cancer treatment. The isolation of paclitaxel (Taxol®) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (*Taxaceae*), was another milestone in the search for novel natural anti-cancer drugs [197].

(3) Diabetes

Diabetes is considered to be a metabolic disorder that principally occurs due to insulin secretion defects, insulin action, or both [198]. It has been postulated that the etiology of diabetes complications involves oxidative stress [198]. Most tests have demonstrated the benefits of medicinal plants containing hypoglycemic properties in diabetes management. The most common plant active ingredients used in treating diabetes are flavonoids, tannins, phenolics and alkaloids [199]. Tannins improve pancreatic beta-cells function and increase insulin secretion, whereas quercetin is an antioxidant that acts removing oxygen radicals, so as precluding lipid peroxidation [200]. The modes of action of hypoglycemic plants include: i)

increasing insulin secretion, ii) increasing glucose absorption by muscle and fat tissues, iii) preventing glucose absorption from the intestine, and iv) preventing glucose production from liver cells [201]. *Acacia arabica, Cassia auriculata, Glycine max, Tamarindus indica, Xanthocercis zambesiaca, Retama raetam* and *Butea monosperma* (Fabaceae), *Aegle marmelos, Citrus reticulata, Feronia elephantum, Murraya koenigii* and *Limonia acidissima* (Rutaceae), *Allium cepa* and *Allium sativum* (Amaryllidaceae), *Aloe barbadensis* (Asphodelaceae), *Azadirachta indica* and *Melia dubia* (Meliaceae), *Beta vulgaris* (Amaranthaceae), *Biophytum sensitivum* and *Averrhoa bilimbi* (Oxalidaceae), *Brassica juncea, Lepidium sativum* and *Raphanus sativus* (Brassicaceae), *Cajanus cajan, Withania somnifera* and *Lyceum barbarum* (Fabaceae), *Withania coagulans, Physalis alkekengi* and *Capsicum frutescens* (Solanaceae), *Catharanthus roseus* (Apocynaceae), *Curcuma longa* and *Zingiber officinale (Zingiberaceae), Eucalyptus globulus* (Myrtaceae), *Jatropha curcas* and *Emblica officinalis* (Euphorbiaceae) are some of the plants whose actions may be responsible for diabetic complications reduction or abolition [199].

(4) Neurodegenerative Disorders

Neurodegenerative disorders result from the progressive loss of neurons structure and/or function. Since oxidative stress has been reported to contribute in neurological diseases' etiology, like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, among others [202], compounds with antioxidant and anti-inflammatory activities have the potential to treat neurodegenerative diseases. A novel *C*-glucosylated xanthone, mangiferin, from mango extracts, shows medicinal effects related to redox potential [203]. The velvet bean extract effectively manages memory impairment in PD through reducing GSH, DPPH radicals and ROS content [204]. Quercetin, kaempferol, isorhamnetin, bilobalide, and ginkgolide from *Ginkgo biloba* possess antioxidant effects and are reported to improve the mini-mental state of AD [205]. Ginsenosides from *Panax ginseng* protect dopaminergic neurons from oxidative stress through promoting neurotrophic factors [206,207]. Furthermore, curcumin activates NRF2 antioxidant system in animals with AD [208]. Studies have reported that green tea consumption reduced the risk of developing PD. EGCG has

been shown to protect neurons by activating several signaling pathways, involving MAP kinases. The therapeutic role of catechins in PD is also due to their ability to chelate iron, a property that contributes to their antioxidant activity. Moreover, the antioxidant function is also related to the induction of the expression of antioxidant and detoxifying enzymes particularly in the brain [1]. *Dioscorea nipponica* and *Dioscorea japonica* (Dioscoreaceae), *Vitis vinifera* (Vitaceae), *Olea europaea* (Oleaceae), *Zingiber officinale* (Zingiberaceae), *Melia toosendan* (Meliaceae), *Abies holophylla* (Pinaceae), *Ptychopetalum olacoides* (Olacaceae), *Panax ginseng* (Araliaceae), *Schisandra chinensis* (Schisandraceae), and *Coptis chinensis* (Ranunculaceae) are some plants that provide potential therapeutic intervention against oxidative threats and neurodegenerative disorders [209].

(5) Antiaging

Aging is a predestined process for all living organisms. Oxygen-derived free radicals are responsible for the age-related damages at cellular and tissue levels. Many plants often contain considerable amounts of antioxidants (e.g., vitamins, carotenoids, terpenoids, polyphenols, alkaloids, tannins, saponins) that can be consumed to scavenge the excessive free radicals' production by the human body. It has been suggested that the amalgamation of antioxidant/anti-inflammatory phenolic compounds found in plants may show efficacy as anti-aging agents [210]. Interestingly, polyphenols are also useful in ameliorating the adverse effects of the aging process on the nervous system or brain due to the ability of these compounds to cross the blood-brain barrier [211].

Anthocyanins, highly abundant in brightly colored fruits, such as berries and grapes, have shown to have strong antioxidant/anti-inflammatory activities, besides being able to inhibit lipid peroxidation and the inflammatory mediators, COX-1 and -2 [212]. It has been reported that in aged rats the dietary supplementation with spinach, strawberry or blueberry extracts (high levels of flavonoids) reversed the age-related discrepancies in the brain and behavioral function [211]. A recent study demonstrates that tea catechins may delay the onset of aging [213]. Resveratrol has been found to consistently prolong the life

span; its action is linked to an event called caloric restriction or partial food deprivation [214]. The following plant species have demonstrated interesting anti-aging effects: *Dioscorea villosa, Ruscus aculeatus, Oenothera biennis, Borago officinalis* and *Trigonella foenum-graecum* as anti-inflammatory; *Luffa cylindrica* as photoprotective; *Persea gratissima* as skin repairing; *Hydrocotyle asiatica* as skin repair and strengthening skin, hair, nails and connective tissue*; Piper longum* in sunburn; *Glycine max* as cell regenerating agent; *Terminalia chebula* as free radical scavenger; *Aloe barbadensis* as skin radiation protector; *Calendula officinalis*, *Centella asiatica* and *Echinacea purpurea* as skin healer; and *Anthriscus sylvestris* and *Ginkgo biloba* as protectors of lipo-peroxidation in cells [215].

(6) Nephropathy

Oxidative stress associated with increased ROS/RNS production plays an imperative role in a wide variety of renal ailments, and it is reported to account for the nephrotoxicity of certain drugs, like cyclosporine and gentamycin [216]. It has been reported that medicinal plant-derived antioxidants can protect renal damage by reducing lipid peroxidation and increasing endogenous antioxidants levels. Quercetin, a tremendous antioxidant, has been shown to exert kidney protection against ROS-perpetrated injury [217]. The following plants, *Thunbergia laurifolia, Ocimum basilicum, Salvia miltiorrhiza, Ginseng* saponins, *Curcuma longa, Vitis vinifera,* and *Antidesma thwaitesianum* has been reported to protect against renal damage by suppressing free radicals [218].

(7) Others

In addition to the above described physiopathological events, plant-derived antioxidants have also shown several other health beneficial effects. *Aristolochia bractaeta, Boerhaavia diffusa, Alstonia scholaris, Cinnammomum zeylicanium, Curcuma longa,* and *Lantana camara* display significant anti-arthritic effects [219]. On the other hand, it has also been evidenced that polyphenols exert preventive effects in the treatment of asthma. In fact, it was shown that the increase in soy isoflavone consumption, genistein, is

associated with better lung function in asthmatic patients. However, polyphenols intake has also been reported to be beneficial in osteoporosis [1,93]. Furthermore, diets supplemented with genistein, daidzein or their glycosides for several weeks prevents the loss of bone mineral density. Indeed, among other polyphenols, black tea polyphenols are reported to be helpful in mineral absorption in the intestine as well as to possess antiviral activity [220].

IV. The evidence in humans

(1) Cardio-metabolic disorders

Oxidative stress is involved in most of the cardiometabolic risk factors, e.g., obesity, impaired lipid profiles, hypertension, atherogenesis. Several studies have investigated the use of plant extracts to control these factors and, indirectly, to prevent cardiovascular diseases, metabolic syndrome, and diabetes. Cigarette smoking induces oxidative stress and, thus, increases the risk of dyslipidemia and systemic inflammation, also predisposing to cardiometabolic disorders.

(2) Cardiovascular risk factors

Fruit juices have been investigated to control lipid profile, antioxidant and inflammatory status. In cigarette smokers, *Morinda citrifolia* (noni) fruit juice had a significant antioxidant activity, improving serum lipid profiles, like cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), and homocysteine [221]. F105, a phytochemical formulation resulting from the combination of bergamot fruit extract (*Citrus bergamia*) with nine 9 phytoextracts acting synergistically as antioxidant and anti-inflammatory agents, revealed, *in vitro*, a marked antioxidant activity and, in a clinical case report, a great ability to decrease the lipid profile[222]. In normal-weight and overweight volunteers, the intake of red-fleshed orange juice (red orange juice) [223] and polyphenol-rich chokeberry juice had similar effects, thanks to the antioxidant and reducing properties of citrus flavonoids, carotenoids and lycopene, and

improved the risk factors for metabolic syndrome, including insulin resistance and blood pressure [224]. Also, the combined supplementation of grape pomace and omija fruit extracts [225], as well as *Sambucus ebulus* L. fruit infusion [226] improved obesity-related dyslipidemia, inflammation, and serum oxidative stress, although without evident effects on patient body weight. Both body weight and lipid profile were, instead, improved by green tea (*Camellia sinensis* L.) intake [227], which also had a positive effect on DNA repair, via HO-1 expression, a cytoprotective enzyme against pro-oxidant changes [228].

Red grape seed extract, which contains antioxidant oligomeric proanthocyanidins, revealed to increase serum paraoxonase (PON) activity, an enzyme that protects against lipid oxidation, in patients with mild to moderate hyperlipidemia [229] and in hemodialysis patients [230]. Red wine extract of onion, in particular, suppressed both total cholesterol and LDL cholesterol levels, and also modulated inflammatory markers, such as factor VII [231]. A quercetin-rich onion skin extract was able to reduce day-time and night-time systolic blood pressure in overweight-to-obese patients with pre-hypertension and with stage I hypertension [232]. Red wine extract and red wine extract of onion did not produce significant changes in body weight and body mass index in hypercholesterolemic patients, but displayed remarkable antioxidant effects, delaying LDL oxidation [231].

Dietary wolfberry extract reduced oxidative stress in overweight and hypercholesterolemic patients, through decreasing erythrocyte SOD activity, increasing CAT activity, controlling inflammatory mRNAs expression. Likewise, the percentage of DNA damage in lymphocytes was significantly lower after 8-week wolfberry extract intake [233]. Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzymes activity, and LDL oxidation were demonstrated in healthy individuals, following a regulatory mechanism on plasma SOD, GSH, and CAT [234].

The Indian kudzu (*Pueraria tuberosa DC.*) showed a pronounced ability to decrease blood pressure, to enhance plasma fibrinolytic activity and serum total antioxidant status in patients with stage 1 hypertension [234]. The dietary supplementation with *Heracleum persicum* fruit, which is a well-known spice with beneficial effect against oxidative stress, was associated with reduced MDA production, increased GSH

and total antioxidant capacity (TAC) in subjects undergoing coronary angiography [235]. Also, MDA levels, resulting from postprandial oxidative stress, decreased after intake of an antioxidant-rich concentrate of berries, called BPC-350, as tested in healthy volunteers who ate a turkey burger [236].

On the other hand, some studies reported controversial results regarding the beneficial effect of certain plant products on cardiovascular risk factors. Indeed, the intake for 6 weeks of whole blueberry powder increased natural killer cell counts and reduced arterial stiffness in sedentary individuals, but without any effect on mass body composition, overall blood pressures and plasma redox potential [237]. The oral supplementation with pomegranate extract had beneficial effects in reducing systolic and diastolic blood pressure, but without impact on cardiovascular risk, physical function, oxidative stress, and inflammation in hemodialysis patients [238]. Moreover, a *Palmaria palmata*-enriched bread evidenced negative effects in preventing cardiovascular disorders; in a randomized placebo-controlled trial conducted in healthy adults, it stimulated inflammation, increasing serum triglycerides and altering thyroid function, although these changes appeared to have negligible influence since remaining within the normal clinical range [239].

(3) Diabetes Mellitus

Still, oxidative stress plays an important role in Diabetes Mellitus (DM) pathogenesis and its complications. A plethora of medicinal plants has been increasingly tested to achieve glycemic control, via antioxidant mechanisms of action.

Green tea has been extensively investigated at a pre-clinical level, but just one clinical trial focused on its anti-diabetic potential via a redox effect. Indeed, in type-2 DM patients, green tea reduced DNA damage and enhanced DNA repair through increasing plasma 8-oxoguanine glycosylase (hOGG1) activity and HO-1 protein levels, recognized protective factors against pro-oxidant changes [240].

Ginger (*Zingiber officinale*) is one of the functional foods which contains biological compounds, including gingerol, shogaol, paradol, and zingerone, and its effect, as 3-month supplementation, showed improved

glycemic indices, TAC and PON-1 activity in type-2 DM patients [241]. A similar finding was reported for *Nigella sativa* [242], and in healthy volunteers, for *Grewia asiatica* fruit [243].

Conversely, the antioxidant effect of Korean red ginseng in postmenopausal women was not associated with improved fasting glucose and insulin levels, and insulin resistance in a double-blind, randomized controlled trial [244].

(4) Sport performance

Several studies aimed to correlate redox effects of plant-derived products with ameliorated response to exercise and, thus, favoring sport performances. Dietary phytochemical supplementation may improve muscle recovery from exercise [245].

Tea and fruit juices represent interesting beverages for sport players to improve their performance. Green tea extract showed controversial evidence in reducing exercise-induced oxidative stress. The effect was, indeed, confirmed in soccer players, but not in male sprinters [246,247]. In fact, the ingestion of green tea extract, caffeinated or not, did not affect whole-body fat oxidation or fat metabolism blood biomarkers during exercise [248,249]. However, when green tea was combined with vitamin E intake, a significant reduction in body weight, waist circumferences and fasting insulin and glucose levels were found in elderly individuals, particularly in women [250]. Mate (*Ilex paraguariensis*) tea consumption did not influence muscle strength but favored serum antioxidant compounds concentration [245].

Similarly, tart cherry juice affected recovery and next day performance in well-trained water polo players [251]. Beetroot juice supplementation [252] and black currant nectar [253], instead, reduced muscle damage indices following eccentric exercise, attenuating muscle soreness, although the mechanisms remain largely unknown. Similarly, the antioxidant activity of lemon verbena (*Lippia citriodora*) extracts led to plasma protection from aerobic exercise oxidative damage, through modulating GSH-reductase activity in lymphocytes of university students [254].

Furthermore, plant extracts were also investigated as dietary supplements to improve the response to exercise oxidative stress. *Phlebodium decumanum* is a plant that showed, in adults, a pronounced ability to improve oxidative stress (decreasing the oxidative stress biomarkers, 8-hydroxy-2′-deoxyguanosine and isoprostanes, while increased total antioxidant status in plasma) and inflammatory responses (decreasing TNF-α, but keeping IL-6 levels and effects), both associated with muscle damage induced by extensive exercise [255]. On the other hand, a study conducted in members of the Polish rowing team reported the effect of *Aloe arborescens* extract in improving plasma TAC after strenuous exercise, but without affecting inflammatory markers [256]. Finally, and not least important, a mixture of green plant-derived antioxidants, called F42, which is a concentrate from the commercially available freeze-dried extracts of berries, root vegetables, and wheatgrass, was able to reduce stress-induced oxidative biomarkers and stress hormones, and to scavenge free radicals in healthy volunteers, within 30 min of ingestion [257].

(5) Miscellanea

Ocular stress

Blue light, mainly produced by digital display technologies in typical working environments, as tablets and laptops, has been increasingly correlated with oxidative stress in human corneal epithelial cells. Several studies investigated the role of herbal extracts (e.g., *Schizonepeta tenuifolia* var. *japonica* Kitagawa, *Angelica dahurica* Bentham et Hooker, *Rehmannia glutinosa* Liboschitz var. *purpurea* Makino and *Cassia tora* L.) in decreasing blue-light-induced oxidative ocular stress, due to their ability to increase the antioxidant activity of HO-1, CAT, and SOD-2 enzymes in corneal epithelial cells [258,259]. Also, herbal products have been linked to a reduction in both dry-eye disease and eye blinks, thus, enhancing attentive performance [260].

Liver disorders

In a clinical trial, Japanese male patients with hepatic abnormalities were enrolled to verify the efficacy of 2-month dietary supplementation of sulforaphane-rich broccoli sprout extract in improving liver conditions, namely the serum levels of liver function markers, ALT, γ-GTP, and the alkali phosphatase activity, as well as the urinary level of 8-hydroxy-2′-deoxyguanosine [261]. A prominent decrease in these markers was stated, which further confirm the evidence found in rats, preventing induced chronic liver failure through enzymatic pathways [261].

Anemia

Hemoglobin H disease is an intermediate form of α-thalassemia, an inherited blood disorder characterized by abnormal hemoglobin production and, thus, anemia. In patients suffering from this disease, the extract Yisui Shengxue Granule improved the level of red blood cell count and hemoglobin, thus ameliorating hemolysis and anemia. The mechanism involved a reduction in oxidative damage of erythrocytes, through increased SOD and decreased CAT activities, but without significant differences in GPX activity or MDA concentration, and efficient inhibition of the oxidative β-globin chains precipitation [262].

Chronic pulmonary lesions after exposition to sulfur mustard

Oxidative stress is also involved in the development of chronic pulmonary complications of sulfur mustard (SM). To further alleviate clinical symptoms in patients suffering from bronchiolitis obliterans due to SM exposure, already receiving standard treatments, the short-term co-administration of curcuminoids with piperine (to enhance curcuminoids bioavailability) led to an increase in serum GSH levels and reduction in serum MDA levels. The clinical counterpart of biomarker improvements was a better outcome in health-related quality of life questionnaires, providing support that phytochemicals could represent promising adjuvants to manage this painful condition [263].

V. Concluding remarks and upcoming perspectives

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In overall, and although antioxidants are not pharmaceuticals, they may markedly contribute to ameliorating a wide variety of chronic conditions and even to promote healthy longevity. Nonetheless, antioxidants may also act as pro-oxidant agents and, therefore, the intake of high doses of antioxidants should be carefully evaluated in both development and treatment of some diseases, because exist increasing evidence of some detrimental effects. However, when daily consumed as part of the daily diet and in balanced amounts, a wide range of phytochemicals may constitute a promising strategy in the treatment of several diseases, like cancer, diabetes, cardiovascular and neurodegenerative disorders.

Nevertheless, and although much has been discovered, some pathological mechanisms remain unclear, and even several detrimental effects of medicinal plants have to be further addressed. For example, it should be considered that the effect of plant antioxidants on several enzymes, such as XOR, can have secondary effects on other drugs that are metabolized by the same enzyme. Anyway, it is broadly recognized that plant-derived bioactive molecules possess an extraordinary therapeutic relevance both in disease prevention and treatment. So, further investigations are needed to deepen knowledge on many other macro and/or micromolecular aspects, still poorly explored, as also in other pharmacokinetic and pharmacodynamic aspects towards to provide, in the near future, and increasing variety of functional foods, nutraceuticals and even bioactive molecules for upcoming drug-derived formulation.

VI. Conflicts of interest

The authors declare no conflicts of interest.

VII. Acknowledgements

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