Food & Function

Linking the chemistry and physics of food with health and nutrition

Accepted Manuscript

View Article Online
DOI: 10.1039/D0FO00216J

Insights on potential application of polyphenol-rich dietary intervention on degenerative diseases management

Javier Quero[1], Inés Mármol[1], Elena Cerrada[2,*] and María Jesús Rodríguez-Yoldi[1,*]

[1] Departamento de Farmacología y Fisiología. Unidad de Fisiología, Facultad de Veterinaria, Universidad de Zaragoza, 50013, Zaragoza, CIBERobn (Carlos III), IIS Aragón, IA2, Spain, [2]Departamento de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogénea-ISQCH, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain.

Abstract

In recent times, a great number of plants have been studied in order to identify new components with nutraceutical properties, among which are polyphenols. Dietary polyphenols represent a large group of bioactive molecules widely found in food of plant origin and they have been found able to prevent onset and progression of degenerative diseases, as well as reducing and controlling their symptoms. These health protective effects have been mainly related to their antioxidant and anti-inflammatory properties. However, it must be considered that application of isolated polyphenols as nutraceuticals is quite limited due to their poor systemic distribution and relative bioavailability. The present review highlights the potential effect of dietary intervention with polyphenol-rich food and plant extracts in patients with cancer, diabetes and neurodegenerative, autoimmune, cardiovascular and ophthalmic diseases, as well as the possible molecular mechanisms of action suggested in numerous studies with animal models.

1.Introduction

Polyphenols are secondary metabolites from plants which represent the largest group of non-energetic compounds in food of vegetable origin. Plants are expose to multiple stress factors and polyphenols display protective roles against photosynthetic and oxidative stresses, herbivores, wounds and UV radiation, as well as being involved in other relevant physiological functions, including pigmentation, pollination and inhibition of pathogen development.[1, 2] Biosynthesis of polyphenols is indeed increased in plants exposed to previously mentioned stresses and polyphenol profile of plants has been reported to change depending on the environmental situation.[3, 4]

Different epidemiological studies have correlated high consumption of grain, fruits and vegetables that characterize Mediterranean and Nordic diet among others, with a lower risk of developing certain diseases.[5-8] In this context, the intake of polyphenols has

DOI: 10.1039/D0FO00216J

shown being beneficial towards health, lowering risk of cancer, cardiovascular, neurodegenerative and other degenerative diseases.[9-20] These protective effects might be linked to the antioxidant and anti-inflammatory properties of polyphenols, since_they are able to reduce the activity of multiple targets through direct interaction or modulation of gene expression.[14, 21-24].

The antioxidant effect of polyphenols may be exerted whether directly, as free radical scavengers, or indirectly, via modulation of genes expression and enzymes activity involved in redox homeostasis.[25] Therefore, polyphenols might help the endogenous antioxidant systems to control oxidative homeostasis by reducing the excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Regarding the direct antioxidant effect of polyphenols, *in vitro* studies have shown that polyphenols are able to donate an electron or hydrogen atom, thus neutralizing free radicals. In the reactions within the lipid peroxidation chain, polyphenols can turn free radicals into stable radicals by donating an electron, acting as chain breakers.[26] Polyphenols can also reduce the rate of oxidation by inhibition or deactivation of the precursors of free radicals and as a consequence suppress their generation.[9] Among the different interactions with enzymes, polyphenols have been found to induce antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase, thus decreasing levels of hydrogen peroxide, superoxide and hydroperoxides anions, as well as to inhibit the expression of pro-oxidant enzymes such as xanthine oxidase.[9]

However, polyphenols have also displayed a well-documented pro-oxidant effect. These results have been mainly observed in tumor cells and have been related to pro-apoptotic action. The dual pro-oxidant and antioxidant behavior of phenolic compounds not only depends on cell type but also on their concentration, chemical structure and pH status.[27-30]

On the other hand, modulation of the inflammatory process by dietary polyphenols is mediated by regulation of different signaling pathways involved in inflammation. As a result, release of proinflammatory metabolites and cytokines such as TNF-α is suppressed, whereas expression of anti-inflammatory modulators is enhanced.[31, 32] Besides, ROS and RNS scavenging capacity along with iron and copper chelating activity of polyphenols contribute to reduce inflammation, since they are causal factors strictly correlated to inflammatory diseases.[33]

However, less than 25% of total polyphenol intake is absorbed in the intestine[34]. This is due to low solubility, instability in the gastrointestinal (GI) tract (pH, enzymes, presence of other nutrients), insufficient gastric residence time and difficulty in traversing the lipid bilayer of the membranes, which cause low bioavailability and poor systemic distribution of polyphenols[35-37]. In order to overcome this drawback and enhance the potential of polyphenols with pharmacological purposes, it has been proposed the use of food macromolecules based on nanoparticles formed by reassembled proteins, cross-linked polysaccharides, protein-polysaccharide conjugates, as well as lipids emulsified

DOI: 10.1039/D0FO00216J

by a safe procedure that can be applied in food. Polymer-based delivery nanoparticle systems, which encapsulate biofunctional ingredients within networks, have been widely developed for the functional and biomedical food sectors enhancing their protection and transport by the blood [37, 38]. These biomacromolecular-based nanoparticles improve the absorption and bioavailability of the bioactive molecule mainly through different routes that includes: protection of the bioactive molecule from the hostile environment of the gastrointestinal tract, prolongation of the residence time in the intestine by muco-adhesion, endocytosis of the particles, and/or permeabilizing effect of the polymer. [35, 39, 40]On the other hand, there is evidence confirming that the intake of the hole plant-origin food might be more effective than its main isolated components,[41] since cooperation among the different phenolic compounds, as well as food matrix and other biologically-active components such as divalent metals or proteins influence polyphenols bioavailability [42]. Therefore, studies focusing on whole food or total plant extracts are more accurate than those using isolated phenolic compounds.

Polyphenols, which are mainly found as glycosylated derivatives in plants, must undergo various intestinal transformations by the digestive enzymes and the colonic microbiota, thus being hydrolyzed to aglycones and other bioactive metabolites which are absorbed by enterocytes [43]. Aglycones are again metabolized in the enterocytes before being led to the liver, where these products undergo final enzymatic transformations becoming conjugated metabolites, hydrophilic molecules that enter the blood stream and are distributed to the tissues and organs or eventually excreted [43] According to this metabolism routes for phenolic compounds, the beneficial effect of polyphenols towards human health is not caused by their direct antioxidant activity, but it is due to interaction of conjugated metabolites with genes and enzymes that modulate intracellular signaling cascades involved in cellular growth, proliferation and death, as well as in antioxidant and anti-inflammatory responses[44]. Therefore, studies which focus on the impact of polyphenols on human health should use animal models which consider the transformation processes that polyphenols undergo from food intake to final conjugated derivatives.

2. Classification of polyphenols

Polyphenols are characterized by the presence of one or more hydroxyl groups on an aromatic ring. These molecules are classified by their molecular weight, chemical structure and complexity in flavonoids (flavones, flavonols, flavanones, flavanonols, isoflavonoids, flavanols, anthocyanidins and chalcones) and non-flavonoids compounds (phenolic acids, stilbenes, curcuminoids, lignans and tannins).[45] Flavonoids are the most predominant polyphenols that comprises over 5000 molecules.[46]

Considering the location in the plant of the polyphenols, they can also be divided into soluble compounds, which refer to molecules with low and medium molecular weight not bound to components of cell wall and insoluble compounds, which include condensed tannins and other phenolic compounds linked to polysaccharides or proteins

View Article Online
DOI: 10.1039/D0FO00216J

of the cell wall. The later derivatives are not digested meanwhile the soluble compounds can cross the intestinal barrier more easily.[47]

All flavonoids are derived from L-phenylalanine, which is transformed into 4-coumaroylCoA through the phenylpropanoid pathway. The addition of three molecules of malonyl-CoA to 4-coumaroylCoA leads to the synthesis of a bicyclic chalcone, such as naringenin chalcone, which is the precursor of flavanones, which in turn, are the precursors for all the rest of flavonoids.[48-51] The presence of different enzymes in plants such as isomerases, reductases, hydrolases and dioxygenases introduces modifications in the basic flavonoid structure, leading to the diverse flavonoids subclasses,[52] including: antoxanthins (flavones and flavonols),[45, 53-57] flavanones,[45, 54, 58, 59] flavanonols,[60] isoflavonoides,[45, 61, 62] flavanols or catechins,[45, 63-66] anthocyanidins[67-70] and chalcones[59, 71, 72] (Figures 1-3). There are many examples of flavonoids found in plants with modifications in their structure, mainly as sugar O-conjugates in different positions.[73] The presence of sugars, namely glucose, rutinose, galactose, xylose, among others improve their stability during storage and their absorption and bioavailability and it is a prerequisite for their transport in the central vacuole of the plant cell.[71, 74]

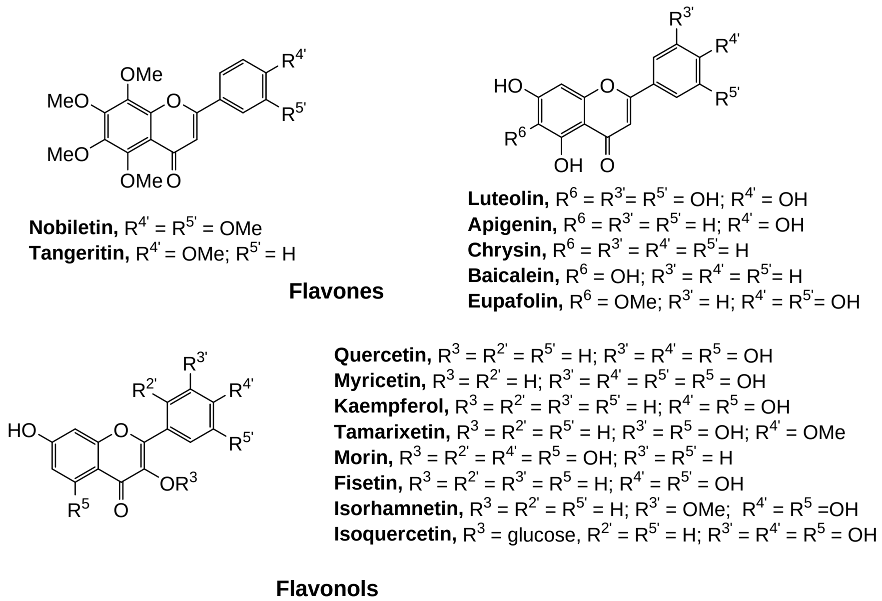
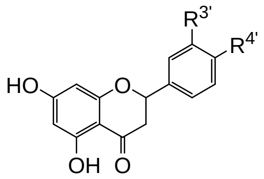
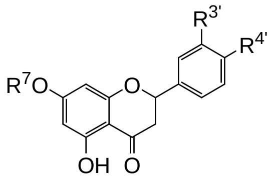


Figure 1. Chemical structures of flavonoids and some examples of representative antoxanthines (flavones and flavonols)

View Article Online
DOI: 10.1039/D0FO00216J

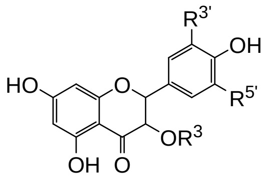


Naringenin, $R^{3'}$ = H;$R^{4'}$ = OH
Hesperitin, $R^{3'}$ = OH; $R^{4'}$ = OMe
Eriodictyol, $R^{3'}$ = $R^{4'}$ = OH
Pinocembrin, $R^{3'}$ = $R^{4'}$= H



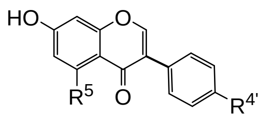
Naringin, $R^{3'}$ = H; $R^{4'}$ = OH; R^7 = Neohesperidose
Hesperidin, $R^{3'}$ = OH; $R^{4'}$ = OMe; R^7 = Rutinose
Neohesperidin, $R^{3'}$ = OH; $R^{4'}$ = OMe; R^7 = Neohesperidose
Narirutin, $R^{3'}$ = H; $R^{4'}$ = OH; R^7 = Rutinose

Flavanones



Taxifolin or dihydroquercetin, $R^{3'}$ = OH; $R^{5'}$ = H
Aromadedrin or dihydrokaempferol, $R^{3'}$ = $R^{5'}$ = H
Dihydroquercetin glucoside, $R^{3'}$ = OH; $R^{5'}$ = H; R^3 = glucoside
Dihydrokaempferol glucoside, $R^{3'}$ = $R^{5'}$ = H; R^3 = glucoside

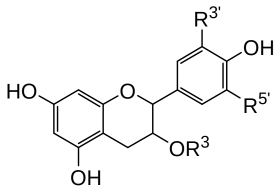
Flavanonols



Genistein, R^5 = $R^{4'}$ = OH
Daidzein, R^5 = H; $R^{4'}$ = OH
Formoninetin, R^5 = H;$R^{4'}$ = OMe
Biochanin A, R^5 = OH; $R^{4'}$ = OMe
Equol, R^5 = H; $R^{4'}$ = OH

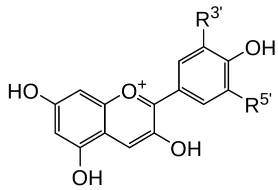
Isoflavonoids

Figure 2. Chemical structures of flavonoids and some examples of representative flavanones, flavononols and isoflavonoids



(+)-Catechin (C), R^3 = $R^{5'}$ = H; $R^{3'}$ = OH
(-)-Epicatechin (EC), R^3 = R^5 = H; $R^{3'}$ = OH
(+)-Gallocatechin (GC), R^3 = H; $R^{3'}$ = $R^{5'}$ = OH
(-)-Epigallocatechin (EGC), R^3 = H; $R^{3'}$ = $R^{5'}$ = OH
(-)-Epicatechin gallate (ECG), R^3 = GA; $R^{5'}$ = H; $R^{3'}$= OH
(-)-Epigallocatechin gallate (EGCG), R^3 = GA; $R^{3'}$ = $R^{5'}$= OH

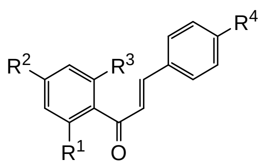
Flavanols



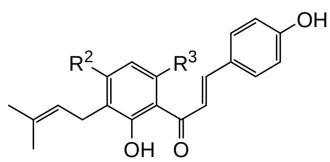
Cyanidin, $R^{3'}$ = OH; $R^{5'}$ = H
Delphinidin, $R^{3'}$ = $R^{5'}$ = OH
Pelargonidin, $R^{3'}$ = $R^{5'}$ = H
Peonidin, $R^{3'}$ = OMe; $R^{5'}$ = H
Malvidin, $R^{3'}$ = $R^{5'}$ = OMe

Anthocyanidins

Glc: glucose
GA: Galic acid



Naringenin-chalcone, R^1 = R^2 = R^3 = R^4 = OH
Isosalipurposide, R^1 = OGlc; R^2 = R^3 = R^4 = OH
Flavokawin A, R^1 = OH; R^2 = R^3 = R^4 = OMe
Flavokawin B, R^1 = R^2 = OH; R^3 = OMe; R^4 = OH
Cardamonin, R^1 = R^2 = R^4 = OH; R^3 = OMe



Xanthohumol, R^2 = OH; R^3 = OMe
Desxanthohumol, R^2 = R^3 = OH
4'-Methylxanthohumol, R^2 = R^3 = OMe
Isobavachalcone, R^1 = R^2 = OH; R^3 = H

Chalcones

Figure 3. Chemical structures of flavonoids and some examples of flavanols, anthocyanidins and chalcones.

View Article Online
DOI: 10.1039/D0FO00216J

Non-flavonoids compounds include phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids),[45, 75] stilbenes, tannins,[76-78] lignans[62, 79] and curcuminoids[80]. Some examples of these derivatives are included in Figures 4-6.

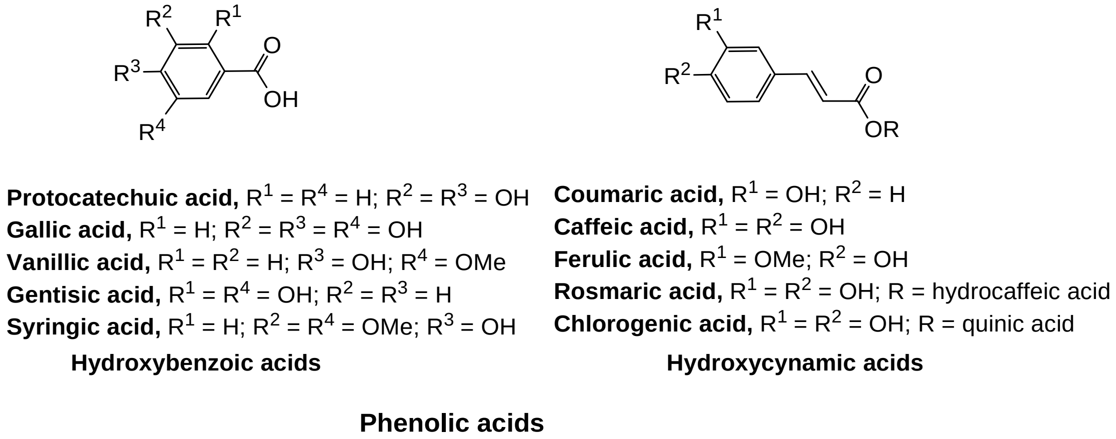


Figure 4. Chemical structures of phenolic acids

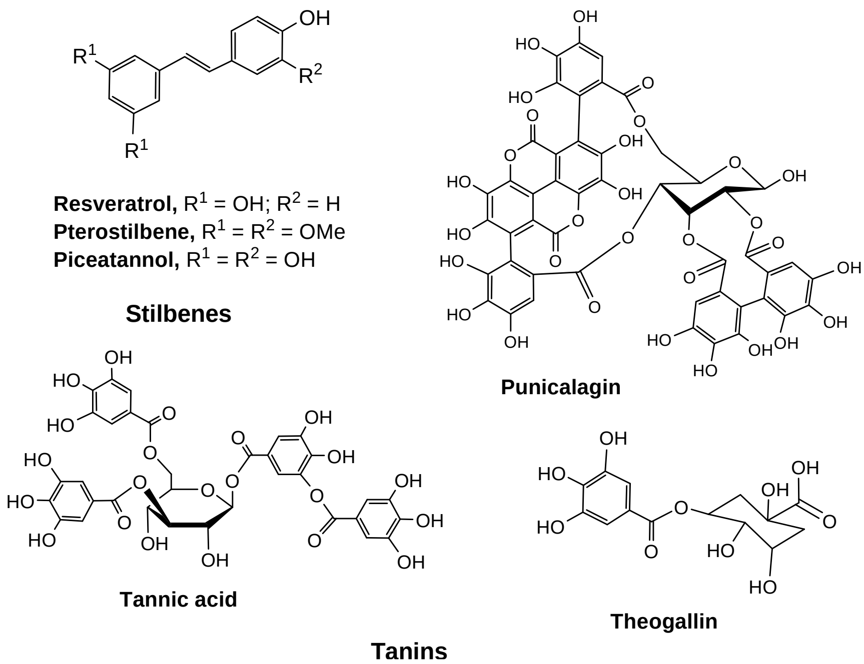


Figure 5. Chemical structures of stilbenes and tannins.

View Article Online
DOI: 10.1039/D0FO00216J

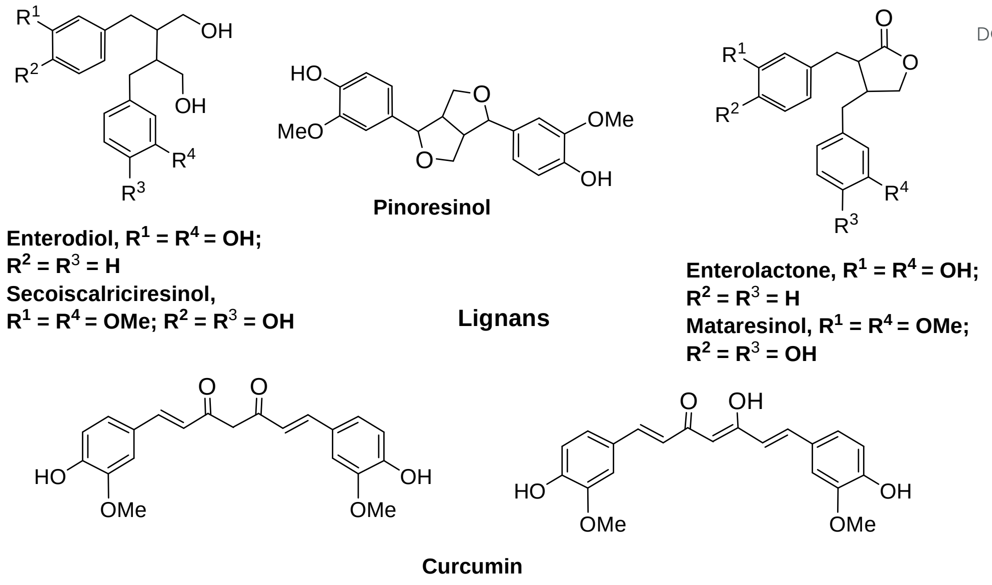


Figure 6. Chemical structures of lignans and curcuminoids

3. Therapeutic properties

The previously discussed properties of dietary polyphenols related to the improvement of human health have purposed them as novel tools for the management of chronic and/or degenerative diseases. Herein we have analyzed the most recent advances regarding to the use of dietary polyphenols with therapeutic purposes on several disorders that pose a serious global health situation due to their high incidence and mortality rate, from cancer to cardiovascular disease. The therapeutic potential of dietary polyphenols has been considered both as single agents as well as administered concomitant to other drugs as coadyuvants. The present review has mainly included preclinical studies on animal models and clinical trials with human volunteers.

3.1. Anticarcinogenic effect

Dietary polyphenols might exhibit a dual role in cancer approach, since they have been proved to be beneficial in chemoprevention as well as in cancer treatment.[81,82] Regarding to the chemopreventive effect, different epidemiological studies suggest that intake of polyphenol-rich foods and supplements would decrease the risk of developing colorectal[83, 84], gastric[83, 85], lung,[86] breast[87] or prostate cancer.[88] Antioxidant and anti-inflammatory properties of polyphenols play important roles as anticancer, since tumoral environment is associated to inflammation and oxidative stress.[89]

Numerous preclinical trials have demonstrated the positive effect of polyphenol-rich dietary interventions on cancer appearance and progression (Table 1), but only a few clinical trials have been conducted. These studies with human patients are limited by the great inter-individual variation in response to polyphenols intake due to differences in

View Article Online
DOI: 10.1039/D0FO00216J

the absorption and metabolization of polyphenols.[90] However, some clinical trials have produced promising results, suggesting the capacity of polyphenols to prevent onset of cancer and enhance clinical improvement on cancer patients.[91-93]

Table 1. Effect of polyphenol-rich dietary intervention on tumor prevention and progression studied on animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Tea	Oral carcinogenesis-induced golden Syrian hamsters	Topical application of 50 µl of 1.5% green tea, 0.1% tea pigments or 0.5% mixed tea in acetone 3 times per week	↓ Expression of EGFR	94
Green Tea	Wistar strain male rats	Oral administration of 200 mg/kg b.w. from 0 to 22 weeks daily	↓ Phase I and ↑ Phase II enzymes activity	95
		200 mg/kg b.w. oral intubations for 30 days.	Modulate expression of glycoconjugates	96
		Oral administration of 200 mg/kg b.w. for 30 days	Inhibit lipid peroxidation	97
Red Wine	Colon carcinogenesis-induced F344 rats	50 mg/kg b.w. administered with diet	Downregulation of over 350 genes	98
	BALB/c mice with C26 cells	100 mg/kg b.w. daily in the drinking water	↓ vascularization, upregulation of tumor suppressor genes	99
Red wine plus pomegranate	Carcinogen-induced rats	Administered with diet at concentration recommended by the supplier	↓ fecal nitrosyl iron	100

A growing body of evidence supports that polyphenol-rich supplements display multiple anticarcinogenic mechanisms and intracellular targets *in vivo*, as they are able to regulate different enzymes and signaling pathways involved in cellular growth, oxidative stress and inflammation[95, 97] through modulation of gene expression.[94, 96, 98] Moreover, polyphenols can induce nutritional privation through modulation of the vascular network formation.[99]

Bastide *et al.* [100] observed that polyphenol-rich red wine and pomegranate extracts were able to reduce the number of premalignant lesions (mucin-depleted foci, MDF) and prevent promotion of colorectal tumorigenesis. In contrast with cured meat-fed rats, feeding rats with red wine and pomegranate extracts resulted in a significant decrease in the number of azoxymethane-induced MDF per colon, together with the absence of fecal excretion of nitrosyl iron -a promoter of carcinogenesis-[100]. Li *et al.*[94] found that, in 7,12-dimethyl-benzanthacene (DMBA)-induced oral carcinogenesis hamsters, overexpression of epidermal growth factor receptor (EGFR) was reduced after oral administration of tea extracts. They also found that tea extracts reduced DNA damage and cell proliferation, altogether resulting in inhibition of DMBA-induced oral tumor formation.

Srinivasan *et al.* [95] induced oral carcinoma in Wistar strain male rats with 4-Nitroquinoline 1-oxide (4-NQO), which led to an increased activity of cytochrome *b*5, cytochrome P450, cytochrome *b*5 reductase (cyt *b*5 R), cytochrome P450 reductase, arryl hydrocarbon hydroxylase and DT-diaphorase (Phase I enzymes which bioactivate 4-NQO) and a decreased activity of glutathione-*S*-transferase and UDP-glucuronyl transferase (Phase II enzymes which enhances excretion of the carcinogen). However, they observed that upon treatment with green tea polyphenols these results were reversed, decreasing the activity of Phase I enzymes and activating Phase II enzymes, thus protecting the cells from the carcinogenic effect of 4-NQO, and reducing number and volume of the tumor. Therefore, these results suggested that green tea polyphenols could be used as both, chemopreventive and therapeutic agent. Previous studies had demonstrated that green tea polyphenols could inhibit lipid peroxidation[97] and modulate the expression of glycoconjugates and immunological markers in 4-NQO-induced oral carcinogenesis as well.[96]

Dolara *et al.* [98] showed the capacity of polyphenols from red wine to modulate the mutagenesis and reduce tumor yield in colon carcinogenesis-induced F344 rats. Upon diet supplementation with ethanol-free polyphenolic extracts from red wine, dimethylhydrazine-induced colorectal carcinoma rats reduced the numbers of adenomas and azoxymethane-induced rats diminished the number of total tumors. The proposed mechanism of action responsible for preventing tumor initiation and promotion was the downregulation of over 350 different genes involved in a wide range of physiological functions, including metabolism, transport, signal transduction and intercellular signaling. Besides, polyphenols were able to mimic the effect of fiber and prebiotics on gut microbiota, both of them well-known compounds for optimal intestinal function.[98] Further studies with red wine polyphenolic extracts evidenced that these polyphenols reduced tumor vascularization and inhibit proliferation in BALB/c mice with C26 colon carcinoma cells, while enhancing apoptosis, by modulating the expression of genes

View Article Online
DOI: 10.1039/D0FO00216J

involved in these processes, such as vascular endothelial growth factor, matrix metalloproteinase 2, cyclooxygenase 2, cyclin D1 or p53, among others.[99]

Therefore, results obtained on animal models of carcinogenesis have suggested induction of genetic and epigenetic changes as the major mechanism of action of polyphenols upon dietary supplementation.[101] Metabolic studies in cancer patients search to confirm these results, and Nuñez-Sánchez et *al.* [102] proved that, in patients with colorectal carcinoma, the expression of various genes in the colorectal tissue would be modulated upon pomegranate extracts intake (900 mg of pomegranate extracts capsules daily). However, significant data has not been produced in most of these studies with human subjects.

3.2. Type 2 diabetes mellitus management

Dietary intervention might display a key role in both prevention and treatment as coadjuvants in type 2 diabetes mellitus (T2D). Clinical studies performed with healthy volunteers[103-108] as well as with pre-diabetic individuals[105, 106, 109, 110] have shown that supplementation with food and beverages rich in polyphenols significantly decrease post-prandial blood glucose levels. This effect is mediated by a decrease in insulin resistance.[104, 105, 108] Moreover, Hoggard *et al.* [111] evaluated the potential role of *Vaccinium myrtillus* bilberry extract consumption (0.47 g of Mirtoselect®, equivalent to 50g of fresh bilberries) on T2D male patients and found a similar decrease in post-prandial glycaemia and insulinemia, thus proposing polyphenol supplementation as anti-diabetic coadyuvant agent. In a further study, Burton *et al.* [112] observed that food supplementation with a combination of inulin from agave (3.79 g), beta-glucan from oat (2.03 g) and polyphenols from blueberry pomace (723.99 mg) improved tolerance to metformin in male T2D patients with intolerance to this drug.

Studies on animal models have been performed in order to elucidate the mechanism of action by which the intake of polyphenol-rich supplements improve glucose control and thus ameliorate T2D symptoms and complications, as summarized in Table 2. Moreover, cell culture assays have provided additional information to further understand the beneficial role displayed by food supplements on the management of T2D.

Table 2. Effect polyphenol-rich dietary intervention on T2D analyzed on animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Cluster bean	High-fat diet-fed streptozocin-induced diabetic rat	Oral administration of 200 or 400 mg/kg b.w. for 30 days (once daily)	Protection of β-cell mass	113
Cocoa	Zucker diabetic	AIN-93G diet	Protection of β-	114

View Article Online
DOI: 10.1039/D0FO00216J

	rat	formulation supplemented with 100 g/kg b.w. of Natural Forastero cocoa powder for 15 weeks	cell mass; reversion of pancreatic oxidative damage	
Coffee	C57BL/6J mice	Gastric administration of coffee polyphenol extract 0.6 g/kg b.w., 0.28 g/kg b.w.	Secretion of GLP-1	115
Raspberry	High-fat diet-fed mice	High-fat diet supplemented with freeze-dried red raspberry powder (5% of dry feed weight) for 10 weeks	Increased expression of AMPKα-1	116
Concord grape	High-fat diet-fed mice	High-fat diet containing 1% of Concord grape polyphenols for 13 weeks	Restored dysbiosis, reduction in inflammation	117
Arctic berries	High-fat diet-fed mice	Daily oral doses of 200 mg powdered extract/kg b.w. for 8 weeks	Restored dysbiosis, improvement of hepatic function	118
Cinnamon	High-fat diet fed C57Bl/6J mice	Daily oral administration of 500, 300 or 100 mg/kg b.w. of cinnamon extract; or 600 mg/kg b.w. of cinnamon polyphenol-enriched defatted soy	Reduction of hyperglycemia	119

	flour

View Article Online
DOI: 10.1039/D0FO00216J

Loss of functional pancreatic β-cells is the critical stage of T2D development. Gandhi *et al.* [113] found that polyphenols of methanolic extracts of cluster bean (*Cyamopsis tetragonoloba*) successfully reversed β-cell damage on a diabetic rat model. The protective effect of *C. tetragonoloba* extracts resulted in a significant increase in sensitivity to insulin and consequently improved hyperglycemia. Further studies from Fernández-Millán *et al.* [114] observed that a cocoa-rich diet restored β-cell mass on diabetic rats and suggested that the protective effect of the mentioned supplement was mediated by its antioxidant effect. Authors observed that the administration of cocoa reduced oxidative stress in pancreatic tissue and as a result prevented apoptosis on β-cells.

The stimulation of the synthesis of glucagon-like peptide-1 (GLP-1) with dietary supplements has potential benefits in T2D management. In this line, Fujii *et al.* [115] found that coffee polyphenols administration increased the intestinal production of GLP-1 on a mice model. Authors suggested that daily coffee consumption might prevent the development of diabetes due to the increase in insulin tolerance mediated by GLP-1 production.

The potential benefits of dietary intervention with plant-derived food upon blood glucose control might be mediated, at least partially, by increasing the expression levels of AMP-activated kinase protein (AMPK). The isoform AMPKα1 is related to muscular glucose uptake and its activation is related to an improvement of tolerance to insulin. Intake of raspberry successfully activated AMPKα1 on an obese mice model, which contributed to an increase in the expression levels of the glucose transporter GLUT-4 on skeletal muscle[116]. An increased uptake of glucose by the skeletal muscle might contribute to a significant improvement of blood glucose control on diabetic patients.

The role of the interplay between diabetes onset and progression and gut microbiome is still poorly understood; however, a growing body of evidence support the potential benefits of the modulation of microbial population in order to ameliorate T2D symptoms. Firstly, Fernández-Millán *et al.* [120] observed that the previously mentioned protective effect of a cocoa-rich diet on β-cells might be mediated by the resulting products after gut bacteria processing. Microbial-derived flavonoid metabolites rescued β-cell from oxidative stress-induced cell death and promoted the secretion of insulin in response to glucose stimulation on INS-1E cell line. In this context, the intake of prebiotic compounds might ameliorate diabetes progression.

Regarding to gut microbiome composition and T2D, the total amount of *Akkermansia muciniphila* was shown to be inversely linked to inflammation, insulin resistance and hyperglycemia[121, 122] and its oral administration enhanced metformin anti-diabetic effect.[123] Dietary intervention with polyphenols-enriched food has been successfully used to restore microbial homeostasis. Roopchand *et al.* [117] administered polyphenols from Concord grape to an obese mice model and observed a significant increase in *A.*

View Article Online
DOI: 10.1039/D0FO00216J

muciniphila population along with a decrease in inflammation markers and an increase in insulin secretion. Authors proposed that the beneficial effects on dysbiosis of polyphenols are due to their ROS scavenger effect. In a further study, Anhê *et al.* [118] found that extracts from cloudberry, alpine bearberry and lingonberry were also capable of increasing *A. muciniphila* amount on an obese mice model. Moreover, authors noticed a significant decrease in hyperinsulinemia due to an increased hepatic sensitivity to insulin.

The hepatic effect of dietary intervention and its relationship with T2D management has been in-deeper investigated on cell models. Cinnamon polyphenols were found able to decrease the expression levels of two key genes involved in hepatic gluconeogenesis -phosphoenolpyruvate carboxykinase and glucose-6-phosphatase- on H4IIE rat hepatoma cells. The inhibition of hepatic glucose synthesis correlates with the decrease in hyperglycemia later found on a diabetic mouse model fed with cinnamon extract or cinnamon polyphenol-enriched defatted soy flour[119]. Extracts from various types of Nordic berries, namely black chokeberry, crowberry and elderberry, have also been found able to increase glucose uptake on HepG2 cell model (12.5, 25 and 50 µg/ml)[124].

3.3. Neuroprotective effect

A large number of studies in humans have suggested that intake of different dietary polyphenols from foods and preparations, such as those from cocoa, tea, grapes, blueberries or walnut among others, would have beneficial effects on central nervous system (CNS) function, improving cerebral blood flow (CBF) [125-127] and, thus, cognitive performance [128-130] in cognitive impairment patients,[131] as well as preventing or delaying the onset of neurodegenerative disorders.[132] While these benefits towards mental health used to be related to inherent antioxidant properties of polyphenols, recent data rejects this hypothesis considering the low concentration of polyphenols reached in CNS. This is a result of the action of blood-brain barrier (BBB), which complicates penetration of polyphenols preventing accumulation of these compounds in brain tissues and CNS.[133] Hence, despite innate antioxidant properties of polyphenols, alternative mechanisms of action have been proposed based on a wide variety of studies with animal model of neurological disorders.

Most of these studies support neuroprotective effects of dietary polyphenols through modulation of intracellular signaling cascades and transcription factors which regulate oxidative stress and neuroinflammation (Table 3). Wang *et al.* [134] observed that feeding stress-mediated depression C57BL/6 male mice with a bioactive dietary polyphenol preparation improved resilience. Two different actions regarding modulation of gene expression were found. On the one hand, compounds from the polyphenol preparation were able to reduce levels of IL-6 -inflammatory marker identified in patients with neurological disorders[135] by inhibiting methylation of genes encoding IL-6 protein[134]. On the other hand, different compounds would promote Rac1 expression by increasing histone acetylation along regulatory sequences of Rac1 gene[134]. Moreover, both Rac1

View Article Online
DOI: 10.1039/D0FO00216J

and IL-6 are involved in synaptic plasticity modulation, thus pointing these mechanisms as targets in stress-induced depression management.[134]

Loss of synaptic plasticity leads to erratic neuronal communication, which is a common feature of neurodegeneration, since it is basis for proper learning, memory and other brain functions. Accordingly, changes in hippocampal plasticity parameters were determined in aged male F344 rats fed with a blueberry-supplemented diet [136]. Results suggested that improvement of cognitive function upon blueberry intake might be mediated by their effects on neuronal plasticity. Zhao *et al.* [137] also observed that polyphenols were able to induce activation of the 'cAMP response element-binding (CREB) signaling pathway, related with synaptic plasticity, and promote resilience to sleep deprivation-induced cognitive dysfunctions in C57BL6/J mice. Wang *et al.* [138] studied the effect of a grape-derived polyphenolic preparation in a mouse model of Alzheimer disease (AD). They found that the preparation improved synaptic plasticity through activation of CREB signaling pathway, thus restoring brain function in AD.[138]

Different studies suggested that polyphenol-rich preparations were able to modulate cerebral blood flow (CBF) and spatial location of cerebrovascular network. Failure of the cerebrovascular system leads to a shortage of energy substrate and the consequent neuronal integrity disruption and cognitive malfunction.[133] Baron-Mengury *et al.* [139] observed that red wine polyphenols stimulated nitric oxide (NO) production and increased vascular endothelial growth factor (VEGF) expression, promoting angiogenesis and blood flow in a post-ischemic neovascularization rat model. This data suggested that polyphenols would have beneficial effects on cerebral ischemia and other neuronal diseases involving disruption of cerebrovascular coupling. Besides, supplementation with a cocktail of red wine polyphenols dissolved in water induced vasodilatation, which enhanced CBF, being restored in middle-cerebral occlusion-induced rats used as stroke model.[140]

Apart from the capability of polyphenols to regulate different pathways involved in redox homeostasis and inflammation, they can modify specific features of neurodegenerative diseases including abnormal aggregation and fibrillation of the neurotoxic beta-amyloid peptides and hyperphosphorylated tau protein in the brain of AD and mild cognitive impairment patients. Wang *et al.* [141] found that daily oral administration of grape-derived polyphenols significantly reduced the accumulation of abnormally hyperphosphorylated tau protein in the brain of TMHT mouse model of AD. In addition, the capacity of polyphenols to enhance CBF might help to reduce beta-amyloid peptides from brain.

Table 3. Neuroprotective effect of polyphenol-rich dietary intervention studied on animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Bioactive dietary	C57BL/6 male mice	5 mg/kg b.w. of	Reduction of IL-6 levels and promotion	134

View Article Online
DOI: 10.1039/D0FO00216J

polyphenol preparation		dihydrocaffeic acid and 0.5 µg/kg b.w. of malvidin-3'-O-glucoside delivered daily through drinking water	of Rac1 expression	
Blueberry	Aged male F344 rats	400 mg of blueberry extract/day combined with control diet	Improvement of neuronal plasticity	136
Grape	C57BL6/J mice	200 mg of grape seed polyphenols/kg b.w.; 400 mg resveratrol/kg b.w.; and 183 mg concord grape juice/kg b.w. delivered through drinking water	Activation of CREB signaling pathway and synaptic plasticity improvement	137
	Mouse model of AD	80 mg/kg b.w. of monomeric-enriched grape-derived polyphenolic preparation delivered through drinking water	Activation of CREB signaling pathway and synaptic plasticity improvement	138
	TMHT mouse model	Daily oral administration of 200 mg/kg b.w.	Reduction of hyperphosphorylated tau protein accumulation in brain	141
Red wine	Post-ischemic neovascularization rat model	Daily administration of 20 mg/kg b.w. or 0.2 mg/kg b.w. by gavage in a solution of 5% glucose	Angiogenesis and blood flow promotion through NO production and VEGF expression	139
	Middle-cerebral occlusion-induced rats	Administration of 30 mg/kg b.w. dissolved in water	Vasodilatation induction and CBF enhancement	140

View Article Online
DOI: 10.1039/D0FO00216J

3.4. Cardiovascular-protective effect

Under the term 'cardiovascular disease' are included a group of disorders that affect heart and blood vessels, some of which are coronary heart disease or congestive heart failure. Among the risk factors of cardiovascular disease highlight high blood pressure and atherosclerosis, which can be controlled by dietary intervention as discussed below.

3.4.1. Blood pressure regulator effect

Regular consumption of plant-derived food such as chokeberries has been related to a decrease of both diastolic and systolic blood pressure on hypertensive patients,[142] and the protective effect of polyphenol-rich foods might be correlated to gender, since Grosso *et al.* [143] observed a decreased risk of hypertension on female patients with the greatest intake of dietary polyphenols, whereas no significant anti-hypertensive effects were found on males. From a molecular point-of-view, dietary intervention based on plant-derived foods and/or polyphenol-enrichment contributes to the management of hypertension at various stages. Noad *et al.* [144] noticed an improvement of endothelium function on hypertensive patients with a polyphenol-rich diet (constituted by a daily intake of six portions of fruit and vegetables) that, in accordance with data collected by Grassi *et al.* [145] from hypertensive patients supplemented with black tea (150 mg of polyphenols) for eight days, might be mediated by an increase in the amount of active circulating endothelium progenitor cells, which are responsible for maintaining and repairing of the endothelium. Furthermore, Medina-Remón *et al.* [146] reported an increase in plasmatic levels of the vasodilator NO after supplementation with extra virgin olive oil (1 L/week) or 30 g of mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts), both rich in polyphenol content. Taken together, these results suggest that dietary polyphenols promote vasodilatation as well as an improvement of endothelium function, which leads to hypertension management.

Further research performed on animal models has pointed to the antioxidant properties of polyphenols as partly responsible of the amelioration of endothelial cells dysfunction (Table 4). Furuuchi *et al*. [147] observed a decrease on aortic ROS levels on a high-fat diet mice model after consumption of boysenberry polyphenols that might be mediated by an increase on the dimerization of endothelial NO synthase (eNOS). Dimeric eNOS produces NO instead of ROS, thus contributing to vasodilatation. Similarly, Mukai *et al.* [148] reported an increase in eNOS and inducible NO synthase (iNOS) expression levels in both aorta and kidney on a hypertensive rat model supplemented with azuki beans extract.

Independently from the NO-mediated vasodilator effect, the role of dietary supplements on hypertension management might be related to the activation of endothelium K^+ channels due to an increase in H_2S production, as shown by Horrigan *et al*. [149] on rat aortic rings exposed to blueberry juice.

Table 4. Effect polyphenol-rich dietary intervention on blood pressure regulation on animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Boysenberry	High-fat diet mice	0.1% boysenberry polyphenol extract in drinking water for 12 weeks	Decrease on aortic ROS levels	147
Azuki bean	Hypertensive rat model	0.9% azuki vean extract-containing diet for 8 weeks	Increase in eNOS and iNOS expression	148

3.4.2. Anti-atherosclerotic effect

An adequate dietary pattern characterized by an abundance of plant-derived fruits might be related to a decreased risk of cardiovascular disease due to their dual role on both prevention and treatment of hypercholesterolemia and atherosclerosis. Studies on healthy volunteers showed that dietary intervention enhanced overall high-density lipoprotein (HDL) function [150-152], thus contributing to a higher clearance of plasma cholesterol. Moreover, the antioxidant properties of polyphenols might contribute to a reduced risk of atherosclerotic lesion by avoiding the oxidation of low-density lipoprotein (LDL), according to data obtained from healthy women after daily intake of 200 g of açai pulp for 4 weeks.[150] This evidence was further validated on patients at high cardiovascular risk. The intake of olive oil enriched with its own polyphenols (500 ppm of phenolic compounds in comparison with 80 ppm of phenolic compounds found in regular olive oil) successfully reduced the total LDL particle/total HDL particle atherogenic ratio on hypercholesterolemic patients (daily dose of 25 ml for 3 weeks followed by a washout period of 2 weeks.[153] Furthermore, studies on early atherosclerosis patients showed that olive oil intake (daily doses of 30 ml for 4 months; polyphenol content: 340 mg/ kg) improved endothelial function by reducing vascular inflammation.[154] Taken together, these findings suggest that dietary polyphenols might be closely related to a more efficient management of atherosclerotic lesion onset and progression.

Dietary intervention might reduce the progression of atherosclerosis at different stages of the disease, according to *in vitro* experiments. Firstly, as above discussed, supplementation of different animal models with plant-based food resulted in a decrease in LDL particles concomitant to an increase in HDL levels, [155-157] as summarized in Table 5. Since the oxidation of LDL is the main responsible of the onset of atherosclerosis, the antioxidant effect of polyphenols might lead to an efficient prevention of foam cells formation and subsequent accumulation. Furthermore, polyphenols might be directly involved in the prevention of LDL oxidation, since

View Article Online
DOI: 10.1039/D0FO00216J

golden needle mushroom polyphenols were found able to reduce LDL oxidation *in vitro*.[158] Finally, food supplements might display a significant role on preventing foam cells formation trough the reduction of lipid accumulation on macrophages, as found upon incubation of THP-1-derived macrophages with anthocyanins or phenolic acids extracted from blueberry (concentrations ranging from 0.05 to 10 μg/ml) and then exposed to fatty acids.[159]

Table 5. Effect on hyperlipidemia of polyphenol-rich dietary intervention evaluated on different animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Citrus sinensis juice and *Citrus paradisi* juice	Hyperlipidemic rats	Once daily, oral administration for 8 weeks of 2, 5 or 8 ml/kg b.w. of *C. sinensis* juic; 0.1, 0.3 or 0.5 ml/kg b.w. of *C. paradise* juice; combination of both (2 ml/kg+0.1 ml/kg or 5 ml/kg+0.3 ml/kg)	Reduction of plasmatic triglycerides, total cholesterol and LDL-cholesterol Increase of HDL-cholesterol	155
Apple	ApoE$^{-/-}$ mice	Western-type diet supplemented with oral administration of 100 mg/kg b.w. of apple polyphenols for 12 weeks	Reduction of plasmatic triglycerides and LDL-cholesterol Increase of HDL-cholesterol	156
Yellow rice wine	LDL receptor$^{-/-}$ mice	High-fat diet supplemented with oral administration of 10, 30 or 50 mg/kg b.w./day of yellow wine polyphenolic compounds for 14 days	Reduction of total circulating cholesterol and LDL-cholesterol	160

View Article Online
DOI: 10.1039/D0FO00216J

Kiwi	Cholesterol-supplemented rats	Chow supplemented with 1% cholesterol and 5% lyophilized kiwifruits for 33 days	Reduction of plasmatic triglycerides and LDL-cholesterol Decrease of the atherogenic index total cholesterol/HDL-cholesterol	157
Green tea	APOE-knockout C57BL/6J mice	Oral administration of 3.2 or 6.4 g/l through drinking water for 15 weeks	Induction of autophagy and removal of damaged endothelial cells	161

Apart from the above-mentioned effect on the early stages of the disease, the intake of polyphenol-enriched foods and other nutritional approaches have a potential application on the management of the mature atherosclerotic plaque.[156, 160, 162, 163] Supplementation with polyphenols is inversely correlated with the expression levels of endothelial adhesion proteins such as intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM1), [156, 163] both involved on the recruitment of immune cells and thus on the maintenance of a pro-inflammatory status. This indirect anti-inflammatory activity might therefore be related to an amelioration of the lesion area, according to experiments on animal models. On the other hand, these kind of food supplements might display a direct effect on atherosclerotic lesion through a reduction of the activity of matrix metalloproteinases (MMPs), due to their key role on the growth of the atherosclerotic plaque. Authors have reported that dietary supplementation with polyphenol extracts and/or polyphenol-enriched foods are able to reduce MMPs activity directly by reducing their expression levels as well as indirectly by up-regulating the expression of tissue inhibitors of matrix metalloproteinases (TIMPs).[160, 162] Lastly, Ding *et al.* [161] noticed a significant recovering of the autophagic flux on the vessel wall of an ApoE knockout mice model after supplementation with green tea polyphenols The induction of autophagy after green tea polyphenols consumption leaded to a removal of damaged endothelial cells and consequently to a reduction of the atherosclerotic lesion area.

3.5. Immunomodulatory effect

Dietary intervention with plant-derived food might display a dual immunoregulatory role, being able of both potentiate or attenuate the immune response depending on the circumstances (Table 6). On one hand, stimulation of the immune response has been reported on situations characterized by an insufficient or deficient one such as cancer or ageing. Yi *et al.* [164] observed an increased amount of functional immune cells on Sarcoma 180-bearing mice after diet supplementation with purified polyphenols from

View Article Online
DOI: 10.1039/D0FO00216J

the pinecone of *Pinus koraiensis*. Similarly, results from De la Fuente *et al.* [165] revealed that supplementation with polyphenols-enriched biscuits (20% wt/wt) ameliorated the age-related loss of functionality of the immune system in terms of an improvement of the activities of macrophages and lymphocytes on a 32 week old ICR mice model.

On the other hand, dietary polyphenols might modulate an exacerbated immune response in chronic inflammation-related disorders. In this line, the anti-inflammatory effect of polyphenols might be, at least partially, mediated by its immunomodulatory effect as it has been reported by in-deep studies of obese animal models. Supplementation with polyphenol-rich green tea preparations on obese rats resulted in a reduced production of pro-inflammatory cytokines by lymphocytes (after 90 days of gavage with 500 mg/b.w. of green tea extract)[166] and neutrophils (500 mg/b.w. of green tea extract administered by gavage).[167] This down-modulation of the immune response might also have a potential application on allergies management. Dietary supplementation with polyphenol-enriched extracts for 8 days resulted on a significant modulation of allergic symptomatology due to a reduction in mucosal pro-inflammatory interleukins production on a murine model of food allergy.[168] Moreover, Kim *et al.* [169] reported that intraperitoneal injection of 1 to 100 mg/kg b.w. of aqueous extracts from *Diospyros kaki* successfully inhibited histamine release from mast cells through increasing intracellular levels of cAMP, which avoids intracellular calcium release and thus blocks the following histamine liberation. As a consequence, a high intake of polyphenols might be beneficial to manage the symptoms of allergic inflammation.

Table 6. Immunomodulatory effect of polyphenol-rich dietary intervention studied on animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Pinecone from Pinus koraiensis	Sarcoma 180-bearing mice	30, 150 or 300 mg/kg b.w. oral administration of polyphenols from *P. koraiensis* pinecone for 11 days	Increase of functional immune cells	164
Green tea	Obese rat model	Gavage with 500 mg/kg b.w. for 90 days	Reduction of pro-inflammatory cytokines	166, 167
Apple/cocoa	Balb/c mice sensitised to ovalbumin	1% polyphenol-enriched apple extracto r 6% polyphenol-enriched cocoa extract mixed with powdered mouse chow	Reduction of pro-inflammatory interleukins production in mucosa	168

View Article Online
DOI: 10.1039/D0FO00216J

		pellet for 8 weeks		
Persimmon	ICR mice administered with mast cell degranulator	Intraperitoneal injection of 1-100 mg/kg b.w. of aqueous extract from *Diospyros kaki*	Inhibition of histamine release from mast cells	169

3.6. Ameliorative effect on ophthalmic diseases

The eyes, essential sensory organs for vision, are quite sensitive to oxidative stress caused by continuous exposure to ultraviolet and visible light and retinal predisposition to produce reactive oxygen species[170, 171] due to its high metabolic rate and high oxygen consumption. ROS can also be produced by *N*-retinylidene-*N*-retinylethanolamine(A2E) photo oxidation generating singlet oxygen[172] and releases toxic metabolites such as endoperoxides and epoxides. In addition, oxidative stress may be involved in the production of pre-inflammatory cytokines in retinal tissue.[173] Their defensive system against oxidative stress decreases with age causing various ophthalmic diseases such as cataracts, macular degeneration and retinopathy.[174, 175],[176] Moreover, onset of these disorders might be influenced by lifestyle factors such as tobacco smoking , alcohol abuse or unhealthy diet.

In line with this, diets rich in antioxidant compounds could be interesting in the prevention and treatment of these diseases. Experimental studies have found that fruit and vegetables consumption contributes to preserve the vision and even reverse the visual impairment,[174, 177] which might be related, at least partially, by polyphenols.[178, 179 180] Some of the beneficial effects of polyphenols include scavenging free radicals, ameliorating inflammation, and improving ocular blood flow and transduction of visual signals.[181 182]

Age-related macular degeneration (AMD) is a multifactorial pathology, characterized by irreversible central vision loss, whose progression is increased by oxidative stress.[183] In the search for limiting the oxidative stress involved in AMD and reduce the progression of this pathology, many antioxidants have been studied. Among them, natural plant polyphenols have been used in the treatment of AMD. [184-190] Oral administration of polyphenol-enriched *Vaccinium uliginosum L.* fractions to Balb/c male mice reduced retinal damaged induced by exposure to blue light (10000 lux for 1 h/d for 2 weeks). [191]

Glaucoma induces vision loss by degeneration of retinal ganglion cells and oxidative stress due to low antioxidant levels is considered one of initiator steps. [190, 192] Therefore, studies in humans with *Ginkgo biloba* (40 to 80 mg daily for 1 to 6 months, depending on the dose) have shown that improve glaucoma.[193, 194] Further studies on a rabbit model showed that topical administration of *Ginkgo biloba* extract improved intraocular pressure.[195]

View Article Online
DOI: 10.1039/D0FO00216J

Cataract is one of the most prevalent causes of visual impairment. It is mediated by loss of less transparency, which might be accelerated by high ROS levels.[190, 196, 197] Studies on a rat model showed that the intraperitoneal injection of green tea leaf extract (*Camellia sinensis*) in rat inhibited selenite-induced cataractogenesis.[198] Likewise, a recent study in rat pups showed that extracts of *Vaccinium uliginosum L.* given by gavage displayed a preventive effect against cataract formation by inhibiting m-calpain-mediated proteolysis and oxidative stress in the lens.[199] However, no official consent has been approved for the use of natural polyphenols for the treatment of ocular diseases due to their moderate bioavailability *in vivo*.[200]Some studies with polyphenols loaded in nanoparticles, instead of isolated polyphenols, have increased their anti-cataract activity by improving their antioxidant capacity.[197]

Besides from controlling the previously discussed T2D symptoms, dietary intervention has been reported to ameliorate complications derived from this disease such as diabetic retinopathy. In this way, a study in diabetic rats showed that Bilberry (*Vaccinium myrtillus*) extract, reduced retinal degeneration and prevented the diabetic retinopathy.[201] Duarte *et al.*[202] found that cocoa enriched with polyphenols protected the retina of streptozocin-induced diabetic rats by down-regulating the expression of silent information regulator 1 (SIRT-1) protein. Furthermore, Ma *et al.* [203] observed a correlation between weekly green tea consumption and a decreased risk of diabetic retinopathy on diabetic volunteers. Taken together, these evidences suggest that an adequate dietary intervention might ameliorate eye-related diabetes-derived complications and thus improve patient's quality-of-life.

Table 7. Effect on ophthalmic diseases of polyphenol-rich dietary intervention evaluated on different animal models.

Food supplement	*Animal model*	*Methodology*	*Effect*	*Reference*
Vaccinium uliginosum L	BALB/c mice male expose to blue light	Oral administration of 25 mg/kg b.w., 50 mg/kg b.w. and 100 mg/kg b.w.	Reduction of retinal damage	191
	Rat pups to selenite-induced cataract formation	40 mg/kg b.w., 80 mg/kg b.w. and 120 mg/kg b.w. administered by gavage	Protection of cataract formation	199
Ginkgo biloba	Rabbit	Oral administration of 5mg 4 times a day	Intraocular pressure improvement	195

View Article Online
DOI: 10.1039/D0FO00216J

		for 14 days		
Green Tea	Wistar rat pups to selenite-induced oxidative stress	Intraperitoneal administration of 68 mg/kg b.w.	Reduction of cataract formation	198
Vaccinium myrtillus	Diabetic rats	Oral administration of 100 mg/kg b.w. for 6 weeks	Reduction of retinal degeneration and prevention of diabetic retinopathy	201
Cocoa	Streptozocin-induced diabetic rats	Daily oral administration of 0.12, 2.90 or 22.8 mg/kg b.w. for 16 weeks	Down-regulation of SIRT-1	202

4. Conclusions

Multiple degenerative diseases are characterized by disruption of homeostasis at different levels, which promotes oxidative and inflammatory environments that lead to tissue damage and, eventually, systemic malfunction. Thus, capacity of dietary polyphenols to reduce oxidative stress, whether directly or indirectly, together with the modulation of inflammation give them the ability to prevent onset and stop progression of degenerative diseases. This has been widely studied in animal models, as it has been explained along this work, and results evidence that intake of polyphenol extracts from different foods are effective in preventing and/or ameliorating symptoms of cancer, diabetes, ocular and neurodegenerative and cardiovascular diseases. Moreover, different epidemiological studies have confirmed these results in human, although further research is needed due to inter-individual variability in most of these studies. In conclusion, herein we have reviewed the most recent advances regarding the potential application of the intervention with polyphenol-rich dietary supplementation on the management of degenerative diseases, both as single agents and as coadjuvants of well-established drugs.

Acknowledgment

Authors thank The Ministerio de Economia y Competitividad (CTQ2016-75816-C2-1-P and SAF2016-75441-R), DGA (B16-R17and E104), CIBERobn (CB06/03/1012, Carlos III) and European Grant Interreg/SUDOE (Redvalue, SOE/PI/E0123) for financial support.

Author Contributions

Javier Quero and Ines Marmol have contributed equally to this work. Both have participated in the literature research and prepared the draft related to the therapeutic

View Article Online
DOI: 10.1039/D0FO00216J

properties of polyphenols. Maria Jesus Rodriguez Yoldi has participated in the literature research and preparation of bioavailability subject of polyphenols and ophthalmic diseases. Elena Cerrada is responsible for the subject of chemical structure and classification of polyphenols presented in this work. Maria Jesús Rodriguez-Yoldi and Elena Cerrada prepared the final version.

Conflict of Interest

The authors declare no conflict of interest.

References

View Article Online
DOI: 10.1039/D0FO00216J

1. M. Cipolletti, V. Solar Fernandez, E. Montalesi, M. Marino and M. Fiocchetti, Beyond the Antioxidant Activity of Dietary Polyphenols in Cancer: the Modulation of Estrogen Receptors (ERs) Signaling, *International journal of molecular sciences*, 2018, **19**.
2. T. Magrone, M. Magrone, M. A. Russo and E. Jirillo, Recent Advances on the Anti-Inflammatory and Antioxidant Properties of Red Grape Polyphenols: In vitro and In Vivo Studies *Antioxidants* 2020, **9**, 35.
3. M. D. Fernando, C. Brunetti, G. Agati and M. Tattini, Multiple functions of polyphenols in plants inhabiting unfavorable Mediterranean áreas. , *Environ. Exp. Botany*, 2014, **103**, 107-116.
4. B.M. Popovic, C. Stajner, R. Zdero-Pavlovic, V. Tumbas-Saponjac, J. Canadovic-Brunet and S. Orlovic, Water stress induces changes in polyphenol profile and antioxidant capacity in polar plants (Populus spp.) *Plant Physiol. Biochem.*, 2016, **105**, 242-250.
5. W. E. Hardman, Diet components can suppress inflammation and reduce cancer risk, *Nutrition research and practice*, 2014, **8**, 233-240.
6. M. P. St-Onge and F. M. Zuraikat, Reciprocal Roles of Sleep and Diet in Cardiovascular Health: a Review of Recent Evidence and a Potential Mechanism, *Current atherosclerosis reports*, 2019, **21**, 11.
7. I. Mármol, J. Quero and M. J. Rodríguez-Yoldi, in *Advances in health and disease*, ed. L. T. Duncan, Nova Science Publishers, Inc., New York, 1 edn., 2018, vol. 7, ch. 2, pp. 67-117.
8. L. V. Herrera-Marcos, J. M. Lou-Bonafonte, C. Arnal, M. A. Navarro and J. Osada, Transcriptomics and the Mediterranean Diet: A Systematic Review, *Nutrients*, 2017, **9**.
9. R. Tsao, Chemistry and biochemistry of dietary polyphenols, *Nutrients*, 2010, **2**, 1231-1246.
10. R. Estruch, E. Ros, J. Salas-Salvado, M. I. Covas, D. Corella, F. Aros, E. Gomez-Gracia, V. Ruiz-Gutierrez, M. Fiol, J. Lapetra, R. M. Lamuela-Raventos, L. Serra-Majem, X. Pinto, J. Basora, M. A. Munoz, J. V. Sorli, J. A. Martinez and M. A. Martinez-Gonzalez, Primary prevention of cardiovascular disease with a Mediterranean diet, *N Engl J Med*, 2013, **368**, 1279-1290.
11. E. Toledo, J. Salas-Salvado, C. Donat-Vargas, P. Buil-Cosiales, R. Estruch, E. Ros, D. Corella, M. Fito, F. B. Hu, F. Aros, E. Gomez-Gracia, D. Romaguera, M. Ortega-Calvo, L. Serra-Majem, X. Pinto, H. Schroder, J. Basora, J. V. Sorli, M. Bullo, M. Serra-Mir and M. A. Martinez-Gonzalez, Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial: A Randomized Clinical Trial, *JAMA Intern Med*, 2015, **175**, 1752-1760.
12. M. Asensi, A. Ortega, S. Mena, F. Feddi and J. M. Estrela, Natural polyphenols in cancer therapy, *Crit. Rev. Clin. Lab. Sci.*, 2011, **48**, 197-216.
13. E. Miadoková, Isoflavonoids – an overview of their biological activities and potential health benefits, *Interdisc. Toxicol.*, 2009, **2**, 211-218.
14. N. Fischer, E.-J. Seo and T. Efferth, Prevention from radiation damage by natural products, *Phytomed.*, 2018, **47**, 192-200.
15. R. K. Lall, D. N. Syed, V. M. Adhami, M. I. Khan and H. Mukhtar, Dietary Polyphenols in Prevention and Treatment of Prostate Cancer, *Int. J. Mol. Sci.*, 2015, **16**, 3350.
16. T. Costea, A. Hudita, O. A. Ciolac, B. Galateanu, O. Ginghina, M. Costache, C. Ganea and M. M. Mocanu, Chemoprevention of Colorectal Cancer by Dietary Compounds, *Int. J. Mol. Sci.*, 2018, **19**.
17. P. M. Kris-Etherton, K. D. Hecker, A. Bonanome, S. M. Coval, A. E. Binkoski, K. F. Hilpert, A. E. Griel and T. D. Etherton, Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer, *Am. J. Med.*, 2002, **113**, 71-88.

DOI: 10.1039/D0FO00216J

18. J. L. Adolphe, S. J. Whiting, B. H. J. Juurlink, L. U. Thorpe and J. Alcorn, Health effects with consumption of the flax lignan secoisolariciresinol diglucoside, *British J. Nutr.*, 2010, **103**, 929-938.
19. P. Basu and C. Maier, Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives, *Biomed. Pharmacother.*, 2018, **107**, 1648-1666.
20. D. K. Agrawal and P. K. Mishra, Curcumin and Its Analogues: Potential Anticancer Agents, *Med. Res. Rev.*, 2010, **30**, 818-860.
21. M. Singh, M. Kaur and O. Silakari, Flavones: An important scaffold for medicinal chemistry, *Eur. J. Med. Chem.*, 2014, **84**, 206-239.
22. K. B. Pandey and S. I. Rizvi, Plant polyphenols as dietary antioxidants in human health and disease, *Oxid. Med. Cell. Longev.*, 2009, **2**, 270-278.
23. A. Garcia-Lafuente, E. Guillamon, A. Villares, M. A. Rostagno and J. A. Martinez, Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease, *Inflamm. Res.*, 2009, **58**, 537-552.
24. L. H. Yao, Y. M. Jiang, J. Shi, F. A. Tomás-Barberán, N. Datta, R. Singanusong and S. S. Chen, Flavonoids in food and their health benefits. , *Plant Foods Hum. Nutr.*, 2004, **59**, 113-122.
25. J. M. Arbonés-Mainar, M. A. Navarro, J. M. Jou-Bonafonte, M. V. Martínez-Gracia and J. Osada, in *Olive oil phenolics as potential therapeutical agents* eds. J. M. Arbonés-Mainar, M. A. Navarro, J. M. Jou-Bonafonte, M. V. Martínez-Gracia and J. Osada, Nova Science Publishers, Inc., New York 2008, ch. 5, pp. 23-26.
26. J. J. Guo, H. Y. Hsieh and C. H. Hu, Chain-breaking activity of carotenes in lipid peroxidation: a theoretical study, *The journal of physical chemistry. B*, 2009, **113**, 15699-15708.
27. C. Kim and B. Kim, Anti-Cancer Natural Products and Their Bioactive Compounds Inducing ER Stress-Mediated Apoptosis: A Review, *Nutrients*, 2018, **10**.
28. F. M. F. Roleira, E. J. Tavares-da-Silva, C. L. Varela, S. C. Costa, T. Silva, J. Garrido and F. Borges, Plant derived and dietary phenolic antioxidants: Anticancer properties, *Food Chem.*, 2015, **183**, 235-258.
29. A. J. Leon-Gonzalez, C. Auger and V. B. Schini-Kerth, Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotherapy, *Biochem. Pharmacol.*, 2015, **98**, 371-380.
30. S. Chikara, L. D. Nagaprashantha, J. Singhal, D. Horne, S. Awasthi and S. S. Singhal, Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment, *Cancer Lett.*, 2018, **413**, 122-134.
31. D. Vauzour, Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects, *Oxidative medicine and cellular longevity*, 2012, **2012**, 914273.
32. F. Yang, H. S. Oz, S. Barve, W. J. de Villiers, C. J. McClain and G. W. Varilek, The green tea polyphenol (-)-epigallocatechin-3-gallate blocks nuclear factor-kappa B activation by inhibiting I kappa B kinase activity in the intestinal epithelial cell line IEC-6, *Mol Pharmacol*, 2001, **60**, 528-533.
33. L. Crascì, M. R. Lauro, G. Puglisi and A. Panico, Natural antioxidant polyphenols on inflammation management: Anti-glycation activity vs metalloproteinases inhibition, *Crit. Rev. Food Sci. Nutr.*, 2018, **58**, 893-904.
34. G. Hithamani, D. Kizhakayil and K. Srinivasan, Uptake of phenolic compounds from plant foods in human intestinal Caco-2 cells, *J Biosci*, 2017, **42**, 603-611.
35. I. A. Siddiqui, V. M. Adhami, D. J. Bharali, B. B. Hafeez, M. Asim, S. I. Khwaja, N. Ahmad, H. Cui, S. A. Mousa and H. Mukhtar, Introducing nanochemoprevention as a novel approach for cancer control: proof of principle with green tea polyphenol epigallocatechin-3-gallate, *Cancer Res*, 2009, **69**, 1712-1716.

36. S. A. Heleno, A. Martins, M. J. Queiroz and I. C. Ferreira, Bioactivity of phenolic acids: metabolites versus parent compounds: a review, *Food Chem*, 2015, **173**, 501-513.
37. Z. Li, H. Jiang, C. Xu and L. Gu, A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals, *Food Hydrocolloids*, 2015, **43**.
38. E. Acosta, Bioavailability of nanoparticles in nutrients and nutraceutical delivery, *Current Opinion in Colloid & Interface Science*, 2009, **14**, 3-15.
39. A. des Rieux, V. Fievez, M. Garinot, Y. J. Schneider and V. Preat, Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach, *J Control Release*, 2006, **116**, 1-27.
40. B. Hu, X. X. Liu, C. L. Zhang and X. X. Zeng, Food macromolecule based nanodelivery systems for enhancing the bioavailability of polyphenols, *J. Food Drug Anal.*, 2017, **25**, 3-15.
41. L. A. Faine, H. G. Rodrigues, C. M. Galhardi, G. M. Ebaid, Y. S. Diniz, C. R. Padovani and E. L. Novelli, Effects of olive oil and its minor constituents on serum lipids, oxidative stress, and energy metabolism in cardiac muscle, *Canadian journal of physiology and pharmacology*, 2006, **84**, 239-245.
42. C. Santos-Buelga, A. M. González-Paramás, T. Oludemi, B. Ayuda-Durán and S. González-Manzano, Plant phenolics as functional food ingredients, *Adv Food Nutr Res.* , 2019, **90**, 183-257.
43. L. Marin, E. M. Miguelez, C. J. Villar and F. Lombo, Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties, *Biomed Res Int*, 2015, **2015**, 905215.
44. A. Crozier, I. B. Jaganath and M. N. Clifford, Dietary phenolics: chemistry, bioavailability and effects on health, *Nat Prod Rep*, 2009, **26**, 1001-1043.
45. C. Manach, A. Scalbert, C. Morand, C. Remesy and L. Jimenez, Polyphenols: food sources and bioavailability, *Am. J. Clin. Nutr.*, 2004, **79**, 727-747.
46. L. H. Yao, Y. M. Jiang, J. Shi, F. A. Tomas-Barberan, N. Datta, R. Singanusong and S. S. Chen, Flavonoids in food and their health benefits, *Plant Foods Hum. Nutr.*, 2004, **59**, 113-122.
47. M. D. L. Reis Giada, *Food Phenolic Compounds: Main Classes, Sources and Their Antioxidant Power. In Oxidative Stress and Chronic Degenerative Diseases—A Role for Antioxidants*, Croatia InTech:, Rijeka, Croatia, 2013.
48. K. Saito, K. Yonekura-Sakakibara, R. Nakabayashi, Y. Higashi, M. Yamazaki, T. Tohge and A. R. Fernie, The flavonoid biosynthetic pathway in Arabidopsis: Structural and genetic diversity, *Plant Physiol. Biochem.*, 2013, **72**, 21-34.
49. I. B. Jaganath and A. Crozier, in *Plant Metabolism and Biotechnology*, ed. A. C. H. Ashhihara, A. Komamine John Wiley & Sons, 2011, pp. 299-313.
50. Y. Tanaka and A. Ohmiya, Seeing is believing: engineering anthocyanin and carotenoid biosynthetic pathways, *Curr. Opin. Biotechnol.*, 2008, **19**, 190-197.
51. M. L. F. Ferreyra, S. P. Rius and P. Casati, Flavonoids: biosynthesis, biological functions, and biotechnological applications, *Front. Plant Sci.*, 2012, **3**.
52. S. Martens, A. Preuss and U. Matern, Multifunctional flavonoid dioxygenases: Flavonol and anthocyanin biosynthesis in Arabidopsis thaliana L, *Phytochem.*, 2010, **71**, 1040-1049.
53. K. Herrmann, Flavonols and flavones in food plants: a review, *J. Food. Technol.*, 1976, **11**, 433-448.
54. E. B. Mojzer, M. K. Hrncic, M. Skerget, Z. Knez and U. Bren, Polyphenols: Extraction Methods, Antioxidative Action, Bioavailability and Anticarcinogenic Effects, *Molecules*, 2016, **21**.
55. A. F. Almeida, G. I. A. Borge, M. Piskula, A. Tudose, L. Tudoreanu, K. Valentova, G. Williamson and C. N. Santos, Bioavailability of Quercetin in Humans with a Focus on Interindividual Variation, *Compr. Rev. Food Sci. F.*, 2018, **17**, 714-731.

56. R. J. Nijveldt, E. van Nood, D. E. C. van Hoorn, P. G. Boelens, K. van Norren and P. A. M. van Leeuwen, Flavonoids: a review of probable mechanisms of action and potential applications, *Am. J. Clin. Nutr.*, 2001, **74**, 418-425.
57. R. V. Patel, B. M. Mistry, S. K. Shinde, R. Syed, V. Singh and H. S. Shin, Therapeutic potential of quercetin as a cardiovascular agent, *Eur. J. Med. Chem.*, 2018, **155**, 889-904.
58. K. Marinova, K. Kleinschmidt, G. Weissenböck and M. Klein, Flavonoid Biosynthesis in Barley Primary Leaves Requires the Presence of the Vacuole and Controls the Activity of Vacuolar Flavonoid Transport, *Plant Physiol.*, 2007, **144**, 432-444.
59. M. Ninomiya and M. Koketsu, in *Natural Products* eds. K. Ramawat and J. M. Mérillon, Springer, Berlin, Heidelberg, 2013.
60. M. Monagas, B. Bartolome and C. Gomez-Cordoves, Updated knowledge about the presence of phenolic compounds in wine, *Crit. Rev. Food Sci. Nutr.*, 2005, **45**, 85-118.
61. M. Bustamante-Rangel, M. M. Delgado-Zamarreño, L. Pérez-Martín, E. Rodríguez-Gonzalo and J. Domínguez-Álvarez, Analysis of Isoflavones in Foods, *Compr. Rev. Food Sci. F.*, 2018, **17**, 391-411.
62. R. A. Dixon, Phytoestrogens, *Annu. Rev. Plant Biol.*, 2004, **55**, 225-261.
63. F. Bonetti, G. Brombo and G. Zuliani, in *Nutrition and Functional Foods for Healthy Aging*, ed. R. R. Watson, Academic Press, 2017, DOI: https://doi.org/10.1016/B978-0-12-805376-8.00019-8, pp. 211-232.
64. P. Cos, T. D. Bruyne, N. Hermans, S. Apers, D. V. Berghe and A. J. Vlietinck, Proanthocyanidins in Health Care: Current and New Trends, *Curr. Med. Chem.*, 2004, **11**, 1345-1359.
65. V. Koleckar, K. Kubikova, Z. Rehakova, K. Kuca, D. Jun, L. Jahodar and L. Opletal, Condensed and hydrolysable tannins as antioxidants influencing the health, *Mini Rev. Med. Chem.* , 2008, **8**, 436-447.
66. J. Iglesias, I. Medina and M. Pazos, in *Polyphenols in Human Health and Disease*, eds. R. R. Watson, V. R. Preedy and S. Zibadi, Academic Press, 2014, vol. 1.
67. F. Pina, M. J. Melo, C. A. T. Laia, A. J. Parola and J. C. Lima, Chemistry and applications of flavylium compounds: a handful of colours, *Chem. Soc. Rev.*, 2012, **41**, 869-908.
68. H. E. Khoo, A. Azlan, S. T. Tang and S. M. Lim, Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits, *Food Nut. Res.*, 2017, **61**, 1-21.
69. M. A. Lila, Anthocyanins and Human Health: An In Vitro Investigative Approach, *J. Biomed. Biochnol.*, 2004, **2004**.
70. J. Fang, Classification of fruits based on anthocyanin types and relevance to their health effects, *Nutrition*, 2015, **31**, 1301-1306.
71. L. Marin, E. M. Miguelez, C. J. Villar and F. Lombo, Bioavailability of Dietary Polyphenols and Gut Microbiota Metabolism: Antimicrobial Properties, *Biomed. Res. Int.*, 2015, DOI: 10.1155/2015/905215.
72. B. Orlikova, D. Tasdemir, F. Golais, M. Dicato and M. Diederich, Dietary chalcones with chemopreventive and chemotherapeutic potential, *Genes Nutr.*, 2011, **6**, 125-147.
73. A. Crocier, I. B. Jaganath and M. N. Clifford, Dietary phenolics: chemistry, bioavailability and effects on health, *Nat. Prod. Rep.*, 2009, **26**, 1001-1043.
74. R. Tsao and J. McCallum, in *Chemistry of flavonoids*, eds. L. A. d. l. Rosa, E. Alvarez-Parrilla and G. Gonzalez-Aguilar, I.A. Ames. Blackwell Publishing, 2009, ch. 5, pp. 131-153.
75. J. Xu, W. Wang and Y. Li, Dough properties, bread quality, and associated interactions with added phenolic compounds: A review, *J. Funct. Foods*, 2019, **52**, 629-639.
76. T. Okuda and H. Ito, Tannins of Constant Structure in Medicinal and Food Plants-Hydrolyzable Tannins and Polyphenols Related to Tannins, *Molecules*, 2011, **16**, 2191-2217.

View Article Online
DOI: 10.1039/D0FO00216J

77. V. Cheynier, M. Duenas-Paton, E. Salas, C. Maury, J. M. Souquet, P. Sarni-Manchado and H. Fulcrand, Structure and properties of wine pigments and tannins, *Am. J. Enol. Vitic.*, 2006, **57**, 298-305.
78. F. Sato and K. Matsui, in *Plant Biotechnology and Agriculture*, eds. A. Altman and P. M. Hasegawa, Academic Press, San Diego, 2012, DOI: https://doi.org/10.1016/B978-0-12-381466-1.00028-6, pp. 443-461.
79. I. E. Milder, I. C. Arts, B. v. d. Putte, D. P. Venema and P. C. Hollman, Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol, *Br. J. Nutr.*, 2005, **93**, 393-402.
80. Y. Manolova, V. Deneva, L. Antonov, E. Drakalska, D. Momekova and N. Lambov, The effect of the water on the curcumin tautomerism: A quantitative approach, *Spectrochim. Acta A-M*, 2014, **132**, 815-820.
81. S. Eghbaliferiz and M. Iranshahi, Prooxidant Activity of Polyphenols, Flavonoids, Anthocyanins and Carotenoids: Updated Review of Mechanisms and Catalyzing Metals, *Phytother. Res.*, 2016, **30**, 1379-1391.
82. S. Perveen and A. Al-Taweel, in *Phenolic Compounds-Natural Sources, Importance and Applications*, ed. IntechOpen., 2017.
83. G. Tse and G. D. Eslick, Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis, *Eur J Nutr*, 2016, **55**, 63-73.
84. R. Zamora-Ros, C. Not, E. Guino, L. Lujan-Barroso, R. M. Garcia, S. Biondo, R. Salazar and V. Moreno, Association between habitual dietary flavonoid and lignan intake and colorectal cancer in a Spanish case-control study (the Bellvitge Colorectal Cancer Study), *Cancer Causes Control*, 2013, **24**, 549-557.
85. H. D. Woo, J. Lee, I. J. Choi, C. G. Kim, J. Y. Lee, O. Kwon and J. Kim, Dietary flavonoids and gastric cancer risk in a Korean population, *Nutrients*, 2014, **6**, 4961-4973.
86. K. Y. Christensen, A. Naidu, M. E. Parent, J. Pintos, M. Abrahamowicz, J. Siemiatycki and A. Koushik, The risk of lung cancer related to dietary intake of flavonoids, *Nutr Cancer*, 2012, **64**, 964-974.
87. Q. Xie, M. L. Chen, Y. Qin, Q. Y. Zhang, H. X. Xu, Y. Zhou, M. T. Mi and J. D. Zhu, Isoflavone consumption and risk of breast cancer: a dose-response meta-analysis of observational studies, *Asia Pac J Clin Nutr*, 2013, **22**, 118-127.
88. M. S. Geybels, B. A. Verhage, I. C. Arts, F. J. van Schooten, R. A. Goldbohm and P. A. van den Brandt, Dietary flavonoid intake, black tea consumption, and risk of overall and advanced stage prostate cancer, *Am J Epidemiol*, 2013, **177**, 1388-1398.
89. A. Salazar-Ramiro, D. Ramirez-Ortega, V. Perez de la Cruz, N. Y. Hernandez-Pedro, D. F. Gonzalez-Esquivel, J. Sotelo and B. Pineda, Role of Redox Status in Development of Glioblastoma, *Front Immunol*, 2016, **7**, 156.
90. C. Manach, D. Milenkovic, T. Van de Wiele, A. Rodriguez-Mateos, B. de Roos, M. T. Garcia-Conesa, R. Landberg, E. R. Gibney, M. Heinonen, F. Tomas-Barberan and C. Morand, Addressing the inter-individual variation in response to consumption of plant food bioactives: Towards a better understanding of their role in healthy aging and cardiometabolic risk reduction, *Mol Nutr Food Res*, 2017, **61**.
91. R. Thomas, M. Williams, H. Sharma, A. Chaudry and P. Bellamy, A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer--the U.K. NCRN Pomi-T study, *Prostate Cancer Prostatic Dis*, 2014, **17**, 180-186.
92. A. S. Tsao, D. Liu, J. Martin, X. M. Tang, J. J. Lee, A. K. El-Naggar, I. Wistuba, K. S. Culotta, L. Mao, A. Gillenwater, Y. M. Sagesaka, W. K. Hong and V. Papadimitrakopoulou, Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions, *Cancer Prev Res (Phila)*, 2009, **2**, 931-941.

DOI: 10.1039/D0FO00216J

93. A. Halder, R. Raychowdhury, A. Ghosh and M. De, Black tea (Camellia sinensis) as a chemopreventive agent in oral precancerous lesions, *J Environ Pathol Toxicol Oncol*, 2005, **24**, 141-144.
94. N. Li, C. Han and J. Chen, Tea preparations protect against DMBA-induced oral carcinogenesis in hamsters, *Nutr Cancer*, 1999, **35**, 73-79.
95. P. Srinivasan, S. Suchalatha, P. V. Babu, R. S. Devi, S. Narayan, K. E. Sabitha and C. S. Shyamala Devi, Chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-Nitroquinoline 1-oxide induced oral cancer, *Chem Biol Interact*, 2008, **172**, 224-234.
96. P. Srinivasan, K. E. Sabitha and C. S. Shyamaladevi, Modulatory efficacy of green tea polyphenols on glycoconjugates and immunological markers in 4-Nitroquinoline 1-oxide-induced oral carcinogenesis-A therapeutic approach, *Chem Biol Interact*, 2006, **162**, 149-156.
97. P. Srinivasan, K. E. Sabitha and C. S. Shyamaladevi, Therapeutic efficacy of green tea polyphenols on cellular thiols in 4-Nitroquinoline 1-oxide-induced oral carcinogenesis, *Chem Biol Interact*, 2004, **149**, 81-87.
98. P. Dolara, C. Luceri, C. De Filippo, A. P. Femia, L. Giovannelli, G. Caderni, C. Cecchini, S. Silvi, C. Orpianesi and A. Cresci, Red wine polyphenols influence carcinogenesis, intestinal microflora, oxidative damage and gene expression profiles of colonic mucosa in F344 rats, *Mutat Res*, 2005, **591**, 237-246.
99. A. Walter, N. Etienne-Selloum, D. Brasse, H. Khallouf, C. Bronner, M. C. Rio, A. Beretz and V. B. Schini-Kerth, Intake of grape-derived polyphenols reduces C26 tumor growth by inhibiting angiogenesis and inducing apoptosis, *FASEB J*, 2010, **24**, 3360-3369.
100. N. M. Bastide, N. Naud, G. Nassy, J. L. Vendeuvre, S. Tache, F. Gueraud, D. A. Hobbs, G. G. Kuhnle, D. E. Corpet and F. H. Pierre, Red Wine and Pomegranate Extracts Suppress Cured Meat Promotion of Colonic Mucin-Depleted Foci in Carcinogen-Induced Rats, *Nutrition and cancer*, 2017, **69**, 289-298.
101. M. T. Garcia-Conesa, Dietary polyphenols against metabolic disorders: How far have we progressed in the understanding of the molecular mechanisms of action of these compounds?, *Crit Rev Food Sci Nutr*, 2017, **57**, 1769-1786.
102. M. A. Nunez-Sanchez, A. Gonzalez-Sarrias, R. Garcia-Villalba, T. Monedero-Saiz, N. V. Garcia-Talavera, M. B. Gomez-Sanchez, C. Sanchez-Alvarez, A. M. Garcia-Albert, F. J. Rodriguez-Gil, M. Ruiz-Marin, F. A. Pastor-Quirante, F. Martinez-Diaz, F. A. Tomas-Barberan, J. C. Espin and M. T. Garcia-Conesa, Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: a randomized clinical trial, *J Nutr Biochem*, 2017, **42**, 126-133.
103. B. Sarria, S. Martinez-Lopez, J. L. Sierra-Cinos, L. Garcia-Diz, R. Mateos and L. Bravo-Clemente, Regularly consuming a green/roasted coffee blend reduces the risk of metabolic syndrome, *Eur J Nutr*, 2018, **57**, 269-278.
104. M. L. Castro-Acosta, S. G. Stone, J. E. Mok, R. K. Mhajan, C. I. Fu, G. N. Lenihan-Geels, C. P. Corpe and W. L. Hall, Apple and blackcurrant polyphenol-rich drinks decrease postprandial glucose, insulin and incretin response to a high-carbohydrate meal in healthy men and women, *J Nutr Biochem*, 2017, **49**, 53-62.
105. M. Paquette, A. S. Medina Larque, S. J. Weisnagel, Y. Desjardins, J. Marois, G. Pilon, S. Dudonne, A. Marette and H. Jacques, Strawberry and cranberry polyphenols improve insulin sensitivity in insulin-resistant, non-diabetic adults: a parallel, double-blind, controlled and randomised clinical trial, *Br J Nutr*, 2017, **117**, 519-531.
106. A. Butacnum, R. Chongsuwat and A. Bumrungpert, Black tea consumption improves postprandial glycemic control in normal and pre-diabetic subjects: a randomized, double-blind, placebo-controlled crossover study, *Asia Pac J Clin Nutr*, 2017, **26**, 59-64.

107. M. L. Castro-Acosta, L. Smith, R. J. Miller, D. I. McCarthy, J. A. Farrimond and W. L. Hall, Drinks containing anthocyanin-rich blackcurrant extract decrease postprandial blood glucose, insulin and incretin concentrations, *J Nutr Biochem*, 2016, **38**, 154-161.

108. G. Chiva-Blanch, M. Urpi-Sarda, E. Ros, P. Valderas-Martinez, R. Casas, S. Arranz, M. Guillen, R. M. Lamuela-Raventos, R. Llorach, C. Andres-Lacueva and R. Estruch, Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: a randomized clinical trial, *Clin Nutr*, 2013, **32**, 200-206.

109. M. S. Calvo, A. Mehrotra, R. B. Beelman, G. Nadkarni, L. Wang, W. Cai, B. C. Goh, M. D. Kalaras and J. Uribarri, A Retrospective Study in Adults with Metabolic Syndrome: Diabetic Risk Factor Response to Daily Consumption of Agaricus bisporus (White Button Mushrooms), *Plant Foods Hum Nutr*, 2016, **71**, 245-251.

110. C. J. Rebello, J. Burton, M. Heiman and F. L. Greenway, Gastrointestinal microbiome modulator improves glucose tolerance in overweight and obese subjects: A randomized controlled pilot trial, *J Diabetes Complications*, 2015, **29**, 1272-1276.

111. N. Hoggard, M. Cruickshank, K. M. Moar, C. Bestwick, J. J. Holst, W. Russell and G. Horgan, A single supplement of a standardised bilberry (Vaccinium myrtillus L.) extract (36 % wet weight anthocyanins) modifies glycaemic response in individuals with type 2 diabetes controlled by diet and lifestyle, *J Nutr Sci*, 2013, **2**, e22.

112. J. H. Burton, M. Johnson, J. Johnson, D. S. Hsia, F. L. Greenway and M. L. Heiman, Addition of a Gastrointestinal Microbiome Modulator to Metformin Improves Metformin Tolerance and Fasting Glucose Levels, *J Diabetes Sci Technol*, 2015, **9**, 808-814.

113. G. R. Gandhi, P. Vanlalhruaia, A. Stalin, S. S. Irudayaraj, S. Ignacimuthu and M. G. Paulraj, Polyphenols-rich Cyamopsis tetragonoloba (L.) Taub. beans show hypoglycemic and beta-cells protective effects in type 2 diabetic rats, *Food Chem Toxicol*, 2014, **66**, 358-365.

114. E. Fernandez-Millan, I. Cordero-Herrera, S. Ramos, F. Escriva, C. Alvarez, L. Goya and M. A. Martin, Cocoa-rich diet attenuates beta cell mass loss and function in young Zucker diabetic fatty rats by preventing oxidative stress and beta cell apoptosis, *Mol Nutr Food Res*, 2015, **59**, 820-824.

115. Y. Fujii, N. Osaki, T. Hase and A. Shimotoyodome, Ingestion of coffee polyphenols increases postprandial release of the active glucagon-like peptide-1 (GLP-1(7-36)) amide in C57BL/6J mice, *J Nutr Sci*, 2015, **4**, e9.

116. L. Zhao, T. Zou, N. A. Gomez, B. Wang, M. J. Zhu and M. Du, Raspberry alleviates obesity-induced inflammation and insulin resistance in skeletal muscle through activation of AMP-activated protein kinase (AMPK) alpha1, *Nutr Diabetes*, 2018, **8**, 39.

117. D. E. Roopchand, R. N. Carmody, P. Kuhn, K. Moskal, P. Rojas-Silva, P. J. Turnbaugh and I. Raskin, Dietary Polyphenols Promote Growth of the Gut Bacterium Akkermansia muciniphila and Attenuate High-Fat Diet-Induced Metabolic Syndrome, *Diabetes*, 2015, **64**, 2847-2858.

118. F. F. Anhe, T. V. Varin, M. Le Barz, G. Pilon, S. Dudonne, J. Trottier, P. St-Pierre, C. S. Harris, M. Lucas, M. Lemire, E. Dewailly, O. Barbier, Y. Desjardins, D. Roy and A. Marette, Arctic berry extracts target the gut-liver axis to alleviate metabolic endotoxaemia, insulin resistance and hepatic steatosis in diet-induced obese mice, *Diabetologia*, 2018, **61**, 919-931.

119. D. M. Cheng, P. Kuhn, A. Poulev, L. E. Rojo, M. A. Lila and I. Raskin, In vivo and in vitro antidiabetic effects of aqueous cinnamon extract and cinnamon polyphenol-enhanced food matrix, *Food Chem*, 2012, **135**, 2994-3002.

120. E. Fernandez-Millan, S. Ramos, C. Alvarez, L. Bravo, L. Goya and M. A. Martin, Microbial phenolic metabolites improve glucose-stimulated insulin secretion and protect pancreatic beta cells against tert-butyl hydroperoxide-induced toxicity via ERKs and PKC pathways, *Food Chem Toxicol*, 2014, **66**, 245-253.

121. X. Zhang, D. Shen, Z. Fang, Z. Jie, X. Qiu, C. Zhang, Y. Chen and L. Ji, Human gut microbiota changes reveal the progression of glucose intolerance, *PLoS One*, 2013, **8**, e71108.
122. M. Schneeberger, A. Everard, A. G. Gomez-Valades, S. Matamoros, S. Ramirez, N. M. Delzenne, R. Gomis, M. Claret and P. D. Cani, Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice, *Sci Rep*, 2015, **5**, 16643.
123. N. R. Shin, J. C. Lee, H. Y. Lee, M. S. Kim, T. W. Whon, M. S. Lee and J. W. Bae, An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice, *Gut*, 2014, **63**, 727-735.
124. G. T. T. Ho, T. K. Y. Nguyen, E. T. Kase, M. Tadesse, H. Barsett and H. Wangensteen, Enhanced Glucose Uptake in Human Liver Cells and Inhibition of Carbohydrate Hydrolyzing Enzymes by Nordic Berry Extracts, *Molecules*, 2017, **22**.
125. F. A. Sorond, L. A. Lipsitz, N. K. Hollenberg and N. D. Fisher, Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans, *Neuropsychiatr Dis Treat*, 2008, **4**, 433-440.
126. S. T. Francis, K. Head, P. G. Morris and I. A. Macdonald, The effect of flavanol-rich cocoa on the fMRI response to a cognitive task in healthy young people, *J Cardiovasc Pharmacol*, 2006, **47 Suppl 2**, S215-220.
127. D. Mastroiacovo, C. Kwik-Uribe, D. Grassi, S. Necozione, A. Raffaele, L. Pistacchio, R. Righetti, R. Bocale, M. C. Lechiara, C. Marini, C. Ferri and G. Desideri, Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study--a randomized controlled trial, *Am J Clin Nutr*, 2015, **101**, 538-548.
128. A. B. Scholey, S. J. French, P. J. Morris, D. O. Kennedy, A. L. Milne and C. F. Haskell, Consumption of cocoa flavanols results in acute improvements in mood and cognitive performance during sustained mental effort, *J Psychopharmacol*, 2010, **24**, 1505-1514.
129. E. Nurk, H. Refsum, C. A. Drevon, G. S. Tell, H. A. Nygaard, K. Engedal and A. D. Smith, Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance, *J Nutr*, 2009, **139**, 120-127.
130. R. Krikorian, M. D. Shidler, T. A. Nash, W. Kalt, M. R. Vinqvist-Tymchuk, B. Shukitt-Hale and J. A. Joseph, Blueberry supplementation improves memory in older adults, *J Agric Food Chem*, 2010, **58**, 3996-4000.
131. R. Krikorian, T. A. Nash, M. D. Shidler, B. Shukitt-Hale and J. A. Joseph, Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment, *Br J Nutr*, 2010, **103**, 730-734.
132. R. Krikorian, E. L. Boespflug, D. E. Fleck, A. L. Stein, J. D. Wightman, M. D. Shidler and S. Sadat-Hossieny, Concord grape juice supplementation and neurocognitive function in human aging, *J Agric Food Chem*, 2012, **60**, 5736-5742.
133. D. Zhao, J. E. Simon and Q. Wu, A critical review on grape polyphenols for neuroprotection: Strategies to enhance bioefficacy, *Crit Rev Food Sci Nutr*, 2019, DOI: 10.1080/10408398.2018.1546668, 1-29.
134. J. Wang, G. E. Hodes, H. Zhang, S. Zhang, W. Zhao, S. A. Golden, W. Bi, C. Menard, V. Kana, M. Leboeuf, M. Xie, D. Bregman, M. L. Pfau, M. E. Flanigan, A. Esteban-Fernandez, S. Yemul, A. Sharma, L. Ho, R. Dixon, M. Merad, M. H. Han, S. J. Russo and G. M. Pasinetti, Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice, *Nat Commun*, 2018, **9**, 477.
135. Y. Dowlati, N. Herrmann, W. Swardfager, H. Liu, L. Sham, E. K. Reim and K. L. Lanctot, A meta-analysis of cytokines in major depression, *Biol Psychiatry*, 2010, **67**, 446-457.
136. G. Casadesus, B. Shukitt-Hale, H. M. Stellwagen, X. Zhu, H. G. Lee, M. A. Smith and J. A. Joseph, Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats, *Nutritional neuroscience*, 2004, **7**, 309-316.

137. W. Zhao, J. Wang, W. Bi, M. Ferruzzi, S. Yemul, D. Freire, P. Mazzola, L. Ho, L. Dubner and G. M. Pasinetti, Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction, *Neurochem Int*, 2015, **89**, 191-197.

138. J. Wang, M. G. Ferruzzi, L. Ho, J. Blount, E. M. Janle, B. Gong, Y. Pan, G. A. Gowda, D. Raftery, I. Arrieta-Cruz, V. Sharma, B. Cooper, J. Lobo, J. E. Simon, C. Zhang, A. Cheng, X. Qian, K. Ono, D. B. Teplow, C. Pavlides, R. A. Dixon and G. M. Pasinetti, Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment, *J Neurosci*, 2012, **32**, 5144-5150.

139. C. Baron-Menguy, A. Bocquet, A. L. Guihot, D. Chappard, M. J. Amiot, R. Andriantsitohaina, L. Loufrani and D. Henrion, Effects of red wine polyphenols on postischemic neovascularization model in rats: low doses are proangiogenic, high doses anti-angiogenic, *FASEB J*, 2007, **21**, 3511-3521.

140. M. F. Ritz, P. Ratajczak, Y. Curin, E. Cam, A. Mendelowitsch, F. Pinet and R. Andriantsitohaina, Chronic treatment with red wine polyphenol compounds mediates neuroprotection in a rat model of ischemic cerebral stroke, *J Nutr*, 2008, **138**, 519-525.

141. J. Wang, I. Santa-Maria, L. Ho, H. Ksiezak-Reding, K. Ono, D. B. Teplow and G. M. Pasinetti, Grape derived polyphenols attenuate tau neuropathology in a mouse model of Alzheimer's disease, *J Alzheimers Dis*, 2010, **22**, 653-661.

142. B. M. Loo, I. Erlund, R. Koli, P. Puukka, J. Hellstrom, K. Wahala, P. Mattila and A. Jula, Consumption of chokeberry (Aronia mitschurinii) products modestly lowered blood pressure and reduced low-grade inflammation in patients with mildly elevated blood pressure, *Nutr Res*, 2016, **36**, 1222-1230.

143. G. Grosso, U. Stepaniak, A. Micek, M. Kozela, D. Stefler, M. Bobak and A. Pajak, Dietary polyphenol intake and risk of hypertension in the Polish arm of the HAPIEE study, *Eur J Nutr*, 2018, **57**, 1535-1544.

144. R. L. Noad, C. Rooney, D. McCall, I. S. Young, D. McCance, M. C. McKinley, J. V. Woodside and P. P. McKeown, Beneficial effect of a polyphenol-rich diet on cardiovascular risk: a randomised control trial, *Heart*, 2016, **102**, 1371-1379.

145. D. Grassi, R. Draijer, C. Schalkwijk, G. Desideri, A. D'Angeli, S. Francavilla, T. Mulder and C. Ferri, Black Tea Increases Circulating Endothelial Progenitor Cells and Improves Flow Mediated Dilatation Counteracting Deleterious Effects from a Fat Load in Hypertensive Patients: A Randomized Controlled Study, *Nutrients*, 2016, **8**.

146. A. Medina-Remon, A. Tresserra-Rimbau, A. Pons, J. A. Tur, M. Martorell, E. Ros, P. Buil-Cosiales, E. Sacanella, M. I. Covas, D. Corella, J. Salas-Salvado, E. Gomez-Gracia, V. Ruiz-Gutierrez, M. Ortega-Calvo, M. Garcia-Valdueza, F. Aros, G. T. Saez, L. Serra-Majem, X. Pinto, E. Vinyoles, R. Estruch, R. M. Lamuela-Raventos and P. S. Investigators, Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort. The PREDIMED randomized trial, *Nutr Metab Cardiovasc Dis*, 2015, **25**, 60-67.

147. R. Furuuchi, I. Shimizu, Y. Yoshida, Y. Hayashi, R. Ikegami, M. Suda, G. Katsuumi, T. Wakasugi, M. Nakao and T. Minamino, Boysenberry polyphenol inhibits endothelial dysfunction and improves vascular health, *PLoS One*, 2018, **13**, e0202051.

148. Y. Mukai and S. Sato, Polyphenol-containing azuki bean (Vigna angularis) extract attenuates blood pressure elevation and modulates nitric oxide synthase and caveolin-1 expressions in rats with hypertension, *Nutr Metab Cardiovasc Dis*, 2009, **19**, 491-497.

149. L. A. Horrigan, C. A. Holohan, G. A. Lawless, M. A. Murtagh, C. T. Williams and C. M. Webster, Blueberry juice causes potent relaxation of rat aortic rings via the activation of potassium channels and the H(2)S pathway, *Food Funct*, 2013, **4**, 392-400.

150. D. Pala, P. O. Barbosa, C. T. Silva, M. O. de Souza, F. R. Freitas, A. C. P. Volp, R. C. Maranhao and R. N. Freitas, Acai (Euterpe oleracea Mart.) dietary intake affects plasma lipids, apolipoproteins, cholesteryl ester transfer to high-density lipoprotein and redox metabolism: A prospective study in women, *Clin Nutr*, 2018, **37**, 618-623.

DOI: 10.1039/D0FO00216J

151. A. Hernaez, S. Fernandez-Castillejo, M. Farras, U. Catalan, I. Subirana, R. Montes, R. Sola, D. Munoz-Aguayo, A. Gelabert-Gorgues, O. Diaz-Gil, K. Nyyssonen, H. J. Zunft, R. de la Torre, S. Martin-Pelaez, A. Pedret, A. T. Remaley, M. I. Covas and M. Fito, Olive oil polyphenols enhance high-density lipoprotein function in humans: a randomized controlled trial, *Arterioscler Thromb Vasc Biol*, 2014, **34**, 2115-2119.
152. F. Rizzi, C. Conti, E. Dogliotti, A. Terranegra, E. Salvi, D. Braga, F. Ricca, S. Lupoli, A. Mingione, F. Pivari, C. Brasacchio, M. Barcella, M. Chittani, F. D'Avila, M. Turiel, M. Lazzaroni, L. Soldati, D. Cusi and C. Barlassina, Interaction between polyphenols intake and PON1 gene variants on markers of cardiovascular disease: a nutrigenetic observational study, *J Transl Med*, 2016, **14**, 186.
153. S. Fernandez-Castillejo, R. M. Valls, O. Castaner, L. Rubio, U. Catalan, A. Pedret, A. Macia, M. L. Sampson, M. I. Covas, M. Fito, M. J. Motilva, A. T. Remaley and R. Sola, Polyphenol rich olive oils improve lipoprotein particle atherogenic ratios and subclasses profile: A randomized, crossover, controlled trial, *Mol Nutr Food Res*, 2016, **60**, 1544-1554.
154. R. J. Widmer, M. A. Freund, A. J. Flammer, J. Sexton, R. Lennon, A. Romani, N. Mulinacci, F. F. Vinceri, L. O. Lerman and A. Lerman, Beneficial effects of polyphenol-rich olive oil in patients with early atherosclerosis, *Eur J Nutr*, 2013, **52**, 1223-1231.
155. N. Mallick and R. A. Khan, Antihyperlipidemic effects of Citrus sinensis, Citrus paradisi, and their combinations, *J Pharm Bioallied Sci*, 2016, **8**, 112-118.
156. Z. R. Xu, J. Y. Li, X. W. Dong, Z. J. Tan, W. Z. Wu, Q. M. Xie and Y. M. Yang, Apple Polyphenols Decrease Atherosclerosis and Hepatic Steatosis in ApoE-/- Mice through the ROS/MAPK/NF-kappaB Pathway, *Nutrients*, 2015, **7**, 7085-7105.
157. M. Leontowicz, I. Jesion, H. Leontowicz, Y. S. Park, J. Namiesnik, A. D. Rombola, M. Weisz and S. Gorinstein, Health-promoting effects of ethylene-treated kiwifruit 'Hayward' from conventional and organic crops in rats fed an atherogenic diet, *J Agric Food Chem*, 2013, **61**, 3661-3668.
158. M. A. Rahman, N. Abdullah and N. Aminudin, Antioxidative Effects and Inhibition of Human Low Density Lipoprotein Oxidation In Vitro of Polyphenolic Compounds in Flammulina velutipes (Golden Needle Mushroom), *Oxid Med Cell Longev*, 2015, **2015**, 403023.
159. C. Del Bo, Y. Cao, M. Roursgaard, P. Riso, M. Porrini, S. Loft and P. Moller, Anthocyanins and phenolic acids from a wild blueberry (Vaccinium angustifolium) powder counteract lipid accumulation in THP-1-derived macrophages, *Eur J Nutr*, 2016, **55**, 171-182.
160. X. Zhai, J. Chi, W. Tang, Z. Ji, F. Zhao, C. Jiang, H. Lv and H. Guo, Yellow wine polyphenolic compounds inhibit matrix metalloproteinase-2, -9 expression and improve atherosclerotic plaque in LDL-receptor-knockout mice, *J Pharmacol Sci*, 2014, **125**, 132-141.
161. S. Ding, J. Jiang, P. Yu, G. Zhang, G. Zhang and X. Liu, Green tea polyphenol treatment attenuates atherosclerosis in high-fat diet-fed apolipoprotein E-knockout mice via alleviating dyslipidemia and up-regulating autophagy, *PLoS One*, 2017, **12**, e0181666.
162. J. B. Daleprane, S. Freitas Vda, A. Pacheco, M. Rudnicki, L. A. Faine, F. A. Dorr, M. Ikegaki, L. A. Salazar, T. P. Ong and D. S. Abdalla, Anti-atherogenic and anti-angiogenic activities of polyphenols from propolis, *J Nutr Biochem*, 2012, **23**, 557-566.
163. N. Martinez, M. Urpi-Sarda, M. A. Martinez-Gonzalez, C. Andres-Lacueva and M. T. Mitjavila, Dealcoholised beers reduce atherosclerosis and expression of adhesion molecules in apoE-deficient mice, *Br J Nutr*, 2011, **105**, 721-730.
164. J. Yi, H. Qu, Y. Wu, Z. Wang and L. Wang, Study on antitumor, antioxidant and immunoregulatory activities of the purified polyphenols from pinecone of Pinus koraiensis on tumor-bearing S180 mice in vivo, *Int J Biol Macromol*, 2017, **94**, 735-744.

View Article Online
DOI: 10.1039/D0FO00216J

165. M. De la Fuente, S. Medina, I. Baeza and L. Jimenez, Improvement of leucocyte functions in mature and old mice after 15 and 30 weeks of diet supplementation with polyphenol-rich biscuits, *Eur J Nutr*, 2011, **50**, 563-573.

166. N. Molina, A. P. Bolin and R. Otton, Green tea polyphenols change the profile of inflammatory cytokine release from lymphocytes of obese and lean rats and protect against oxidative damage, *Int Immunopharmacol*, 2015, **28**, 985-996.

167. K. F. Albuquerque, M. P. Marinovic, A. C. Morandi, A. P. Bolin and R. Otton, Green tea polyphenol extract in vivo attenuates inflammatory features of neutrophils from obese rats, *Eur J Nutr*, 2016, **55**, 1261-1274.

168. A. Singh, A. Demont, L. Actis-Goretta, S. Holvoet, A. Leveques, M. Lepage, S. Nutten and A. Mercenier, Identification of epicatechin as one of the key bioactive constituents of polyphenol-enriched extracts that demonstrate an anti-allergic effect in a murine model of food allergy, *Br J Nutr*, 2014, **112**, 358-368.

169. H. H. Kim, D. S. Kim, S. W. Kim, S. H. Lim, D. K. Kim, T. Y. Shin and S. H. Kim, Inhibitory effects of Diospyros kaki in a model of allergic inflammation: role of cAMP, calcium and nuclear factor-kappaB, *Int J Mol Med*, 2013, **32**, 945-951.

170. J. T. Handa, M. Cano, L. Wang, S. Datta and T. Y. Liu, Lipids, oxidized lipids, oxidation-specific epitopes, and Age-related Macular Degeneration, *Biochim. Biophys. Acta-Molecular Cell Biol. Lipids*, 2017, **1862**, 430-440.

171. Mitra R, Conleyand S and N. M., in *Retinal Degenerative Diseases*, ed. M. L. C. Bowes Rickman, R. Anderson, C. Grimm, J. Hollyfield and J. Ash. Eds, Springer, 2016, vol. 854, pp. 463-469.

172. S. R. Kim, S. Jockusch, Y. Itagaki, N. J. Turro and J. R. Sparrow, Mechanisms involved in A2E oxidation, *Expe. Eye Res.*, 2008, **86**, 975-982.

173. Y. H. Zou and G. C. Y. Chiou, Apigenin inhibits laser-induced choroidal neovascularization and regulates endothelial cell function, *J. Ocular Pharmacol. Ther.*, 2006, **22**, 425-430.

174. S. Beatty, H. H. Koh, D. Henson and M. Boulton, The role of oxidative stress in the pathogenesis of age-related macular degeneration, *Survey Ophthalmol.*, 2000, **45**, 115-134.

175. J. Cejkova, S. Stipek, J. Crkovska, T. Ardan, J. Platenik, C. Cejka and A. Midelfart, UV rays, the prooxidant/antioxidant imbalance in the cornea and oxidative eye damage, *Physiol. Res.*, 2004, **53**, 1-10.

176. N. A. Vallabh, V. Romano and C. E. Willoughby, Mitochondrial dysfunction and oxidative stress in corneal disease, *Mitochondrion*, 2017, **36**, 103-113.

177. L. Tang, Y. N. Zhang, Y. Jiang, L. Willard, E. Ortiz, L. Wark, D. Medeiros and D. B. Lin, Dietary wolfberry ameliorates retinal structure abnormalities in db/db mice at the early stage of diabetes, *Experiment. Biol. Med.*, 2011, **236**, 1051-1063.

178. A. L. West, G. A. Oren and S. E. Moroi, Evidence for the use of nutritional supplements and herbal medicines in common eye diseases, *Am. J. Ophthalmol.*, 2006, **141**, 157-166.

179. A. Milani, M. Basirnejad, S. Shahbazi and A. Bolhassani, Carotenoids: biochemistry, pharmacology and treatment, *British J. Pharmacol.*, 2017, **174**, 1290-1324.

180. Z. H. Xu, T. Sun, W. N. Li and X. J. Sun, Inhibiting effects of dietary polyphenols on chronic eye diseases, *J. Functional Foods*, 2017, **39**, 186-197.

181. K. Srinivasan, *Polyphenols in Vision and Eye Health*, Edited by Preedy, V. R. Elsevier, 2014.

182. W. Kalt, A. Hanneken, P. Milbury and F. Tremblay, Recent Research on Polyphenolics in Vision and Eye Health, *J. Agricultur. Food Chem.*, 2010, **58**, 4001-4007.

183. J. Z. Nowak, Oxidative stress, polyunsaturated fatty acids-derived oxidation products and bisretinoids as potential inducers of CNS diseases: focus on age-related macular degeneration, *Pharmacol. Rep.*, 2013, **65**, 288-304.

View Article Online
DOI: 10.1039/D0FO00216J

184. J. H. Kang and S. Y. Choung, Protective effects of resveratrol and its analogs on age-related macular degeneration in vitro, *Arch. Pharma. Res.*, 2016, **39**, 1703-1715.

185. A. Hanneken, F. F. Lin, J. Johnson and P. Maher, Flavonoids protect human retinal pigment epithelial cells from oxidative-stress-induced death, *Invest. Ophth. Visual* 2006, **47**, 3164-3177.

186. C. N. Nagineni, R. Raju, K. K. Nagineni, V. K. Kommineni, A. Cherukuri, R. K. Kutty, J. J. Hooks and B. Detrick, Resveratrol Suppresses Expression of VEGF by Human Retinal Pigment Epithelial Cells: Potential Nutraceutical for Age-related Macular Degeneration, *Aging Dis.*, 2014, **5**, 88-100.

187. D. Cia, A. Cubizolle, C. Crauste, N. Jacquemot, L. Guillou, C. Vigor, C. Angebault, C. P. Hamel, J. Vercauteren and P. Brabet, Phloroglucinol protects retinal pigment epithelium and photoreceptor against all-trans-retinal-induced toxicity and inhibits A2E formation, *J. Cel. Mol. Med.*, 2016, **20**, 1651-1663.

188. S. Y. Liu, J. Y. Song, B. Fan, Y. Wang, Y. R. Pan, L. Che, Y. J. Sun and G. Y. Li, Resveratrol protects photoreceptors by blocking caspase- and PARP-dependent cell death pathways, *Free Radical Bio. Med.*, 2018, **129**, 569-581.

189. Z. Zhao, T. Sun, Y. Jiang, L. J. Wu, X. Z. Cai, X. D. Sun and X. J. Sun, Photooxidative damage in retinal pigment epithelial cells via GRP78 and the protective role of grape skin polyphenols, *Food Chem. Toxicol.*, 2014, **74**, 216-224.

190. S. Bungan, M. M. Abdel-Daim, D. M. Tit, E. Ghanem, S. Sato, M. Maruyama-Inoue, S. Yamane and K. Kadonosono, Heealth benefits of polyphenols and carotenoids in age-related eye diseases. , *Oxid. Med. Cell. Longev.*, 2019, 1-22.

191. B. L. Lee, J. H. Kang, H. M. Kim, S. H. Jeong, D. S. Jang, Y. P. Jang and S. Y. Choung, Polyphenol-enriched Vaccinium uliginosum L. fractions reduce retinal damage induced by blue light in A2E-laden ARPE19 cell cultures and mice, *Nutr. Res.*, 2016, **36**, 1402-1414.

192. X. Zhang, Y. F. Feng, Y. P. Wang, J. Wang, D. N. Xiang, W. R. Niu and F. Yuan, Resveratrol ameliorates disorders of mitochondrial biogenesis and dynamics in a rat chronic ocular hypertension model, *Life Sci.*, 2018, **207**, 234-245.

193. X. Guo, X. Kong and R. Huang, Effect of Ginkgo biloba on vision field and contrast sensitivity in Chinese patients with normal tension glaucoma: a randomized, crossover clinical trial, *Invest. Ophth. Visual Science*, 2014, **55**, 110.

194. J. Lee, S. W. Sohn and C. Kee, Effect of Ginkgo biloba Extract on Visual Field Progression in Normal Tension Glaucoma, *J. Glaucoma*, 2013, **22**, 780-784.

195. L. Y. Jia, L. Sun, D. S. P. Fan, D. S. C. Lam, C. P. Pang and G. H. F. Yam, Effect of Topical Ginkgo biloba Extract on Steroid-Induced Changes in the Trabecular Meshwork and Intraocular Pressure, *Arch. Ophthalmol.*, 2008, **126**, 1700-1706.

196. G. Goutham, R. Manikandan, M. Beulaja, R. Thiagarajan, C. Arulvasu, M. Arumugam, W. N. Setzer, M. Daglia, S. F. Nabavi and S. M. Nabavi, A focus on resveratrol and ocular problems, especially cataract: From chemistry to medical uses and clinical relevance, *Biomed. Pharmacother.*, 2017, **86**, 232-241.

197. D. Vora, S. Heruye, D. Kumari, C. Opere and H. Chauhan, Preparation, Characterization and Antioxidant Evaluation of Poorly Soluble Polyphenol-Loaded Nanoparticles for Cataract Treatment, *AAPS Pharmscitech*, 2019, **20**.

198. S. K. Gupta, N. Halder, S. Srivastava, D. Trivedi, S. Joshi and S. D. Varma, Green tea (Camellia sinensis) protects against selenite-induced oxidative stress in experimental cataractogenesis, *Ophth. Res.*, 2002, **34**, 258-263.

199. J. I. Choi, J. Kim and S. Y. Choung, Polyphenol-enriched fraction of Vaccinium uliginosum L. protects selenite-induced cataract formation in the lens of Sprague-Dawley rat pups, *Mol. Vis.*, 2019, **25**, 118-128.

View Article Online
DOI: 10.1039/D0FO00216J

200. E. Moine, P. Brabet, L. Guillou, T. Durand, J. Vercauteren and C. Crauste, New Lipophenol Antioxidants Reduce Oxidative Damage in Retina Pigment Epithelial Cells, *Antioxidants*, 2018, **7**.

201. J. Kim, C. S. Kim, Y. M. Lee, E. Sohn, K. Jo and J. S. Kim, Vaccinium myrtillus extract prevents or delays the onset of diabetes-induced blood-retinal barrier breakdown, *Int. J. Food Sci. Nutr.*, 2015, **66**, 236-242.

202. D. A. Duarte, M. A. Rosales, A. Papadimitriou, K. C. Silva, V. H. Amancio, J. N. Mendonca, N. P. Lopes, J. B. d. Faria and J. M. d. Faria, Polyphenol-enriched cocoa protects the diabetic retina from glial reaction through the sirtuin pathway, *J. Nutr. Biochem.*, 2015, **26**, 64-74.

203. Q. Ma, D. Chen, H. P. Sun, N. Yan, Y. Xu and C. W. Pan, Regular Chinese Green Tea Consumption is Protective for Diabetic Retinopathy: A Clinic-Based Case-Control Study, *J Diabetes Res*, 2015, **2015**, 231570.