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Polyphenols and their applications: An approach in food chemistry and innovation potential

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ABSTRACT

Polyphenols are compounds naturally present in fruits and vegetables that are gaining more and more attention due to their therapeutic effects and their potential technological applications. In this review, we intend to demonstrate the importance of some phenolic compounds, addressing their biological effects and potential for applications in various industrial fields. The intake of these compounds in appropriate concentrations can present promising effects in the prevention of diseases such as diabetes, obesity, Parkinson's, Alzheimer's, and others. They can also be used to improve the physicochemical properties of starch, in the preservation of foods, as natural dyes, prebiotic ingredients, hydrogels and nanocomplexes. In addition, these compounds have potential for innovation in the most diverse technological fields, including organic fine chemistry, basic materials chemistry, pharmaceuticals, food chemistry, chemical engineering, etc.

1. Introduction

The association between diet, health and the presence of bioactive compounds in food has received great attention in recent years. Thus, consumers are increasingly interested in food products that, in addition to meeting nutritional requirements, improve physical performance, promote well-being and reduce the risk of developing diseases (Araújo et al., 2019).

Polyphenols are compounds naturally synthesized by the secondary metabolism of plants, which has attracted great attention from the scientific community due to their potential therapeutic effects on health (Farias, Neri-Numa, de Araújo, & Pastore, 2020). Their biological effects are mainly attributed to the ability to sequester or inhibit reactive oxygen and nitrogen species, transfer electrons to free radicals, in addition to activating antioxidant enzymes, improving oxidative stress and inflammation, demonstrating promising effects in the prevention of various diseases such as diabetes, obesity, cancer, cardiovascular diseases, osteoporosis, neurodegenerative diseases, among others (Addepalli & Suryavanshi, 2018; Agunloye et al., 2019; Ali et al., 2019; Chen, Zhu et al., 2018; Fan, Gao, Chen, & Li, 2018; Farias et al., 2020; Fei, Liang, Jiang, Ni, & Wang, 2019; Huang et al., 2018).

However, the biological properties of these compounds depend on several factors, including concentration in food, bioaccessibility after ingestion, their interaction with other molecules, degree of polymerization, among others (Iglesias-Carres et al., 2019; Landete, 2011). In addition to their biological properties, phenolic compounds also have great potential to be used in commercial applications related to food dyes, bioactive packaging, cosmetic products, production of paints,

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fertilizers, surfactants, textiles, rubber, plastics and curing agents (Farrag et al., 2018; Mendoza et al., 2018). Despite the great technological potential, few studies have addressed the development of new products using these compounds.

Thus, considering the therapeutic and technological relevance of phenolic compounds, the objective of this review was to demonstrate the importance of some of these compounds, addressing their metabolic effects, bioavailability, toxicity, in addition to emphasizing their innovation potential for applications in the most diverse industrial fields.

2. Phenolic compounds

Polyphenols are an heterogenous groups of secondary metabolites biosynthesized from the pentose phosphate, shikimate, and phenylpropanoid pathways (Fig. 1) (Farias et al., 2020). They are widely distributed into plant kingdom, mainly fruits and vegetables, and it is estimated that more than 8000 structures have already been identified (Lourenço Neto, Agra, Suassuna Filho, & Jorge, 2018). In general, phenolic compounds are involved in plant defense as signaling molecules to protect plants against oxidative stress and ultraviolet radiation, or attracting pollinators and animals to disperse seeds (Vuolo, Lima, & Maróstica Junior, 2019).

Polyphenols belong to a broad group of chemical substances having one or more aromatic rings with two or more hydroxyl groups. Phenolic compounds occur in free forms or conjugated with sugars, acids and other biomolecules soluble or insoluble in water (Skrovankova et al., 2015). They can be divided into flavonoids, allied phenolic and polyphenolic compounds (Vuolo et al., 2019). In the following topics, some classes of compounds belonging to phenolic compounds will be addressed.

2.1. Flavonoids

Flavonoids are among the most commonly found phenolic compounds in fruits and vegetables (Table 1) since they play important role on color and taste, synthesis of enzymes and vitamins and minimizing lipid peroxidation effects (Vuolo et al., 2019). However, their content in the plant matrix depends on several factors, including genetic variety of species, edaphoclimatic conditions, plant part, growing conditions and degree of maturation (Rosa, Moreno-Escamilla, Rodrigo-Garcia, & Alvarez-Parrilla, 2019).

Regarding chemical structure, flavonoids have a phenyl benzopyran skeleton composed of two aromatic rings (A and B) attached to a tetrahydropyran ring (C). The pyran ring may present differences, which allows to classify the flavonoids within six groups (flavonols, flavonones, flavanols, flavones, anthocyanins and isoflavons) and within each group, these compounds presents a different pattern of hydroxylation and methylation of rings A and B (Gómez-Caravaca, Verardo, Segura-Carreteno, Fernández-Gutiérrez, & Caboni, 2014; Rosa et al., 2019).

Recent studies demonstrating the beneficial effects of flavonoid consumption on health are presented in Table 2. The long term consumption of foods rich in flavonoids offer health benefits to individuals with early-death risk factors (Bondonno et al., 2019). In addition, some studies have been linked flavonoids intake with the improvement of behavior and cognition, neuroinflammation decrease and attenuation of oxidative stress, once their play a pivotal role on pathways that are responsible for neuronal proliferation and survival (ERK/CREB/BDNF and PI3K/Akt) and thus, attenuating the Alzheimer's associated symptoms (Bakoyiannis, Daskalopoulou, Pergialiotis, & Perrea, 2019). An assay using RAW 264.7 cell line demonstrated that the anti-inflammatory properties of flavonoids from *Lotus plumule* (L-50 = 12.5–50 μg/mL) are due to inhibition of the production of inflammatory mediators such as NO radicals, prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α) and proinflammatory cytokines such as IL-1β and IL-6 (G.-L. Chen, Fan, Wu, Li, & Guo, 2019). In addition, these authors also observed that 12 flavonoids identified in *L. plumule* showed specific binding against COX-2 inflammation, including luteolin 6-*C*-glucoside, apigenin 8-*C*-glucoside, quercetin 3-*O*-glucoside, kaempferol 3-*O*-robinobioside, and others.

Similarly, Park, Lim, Bazer, Whang, & Song (2019) using experimental models with human eutopic endometrial cells (K2/E6E7 and End1/E6E7) found that quercetin (3,3 ', 4′, 5,7-pentahydroxyfavone) reduced proliferation, increased apoptosis and induced the expression of miR-503-5p, miR-1283, miR-3714 and miR-6867-5p related to CCND1 (cyclin D1) in both cell lines. In addition, the authors also found that intraperitoneal injection of quercetin on autoimplanted endometriosis mouse (35 mg/kg/day every 3 days for a month) had antiproliferative and anti-inflammatory effects, reduced Ccnd1 mRNA expression and promoted the expression of miR-503-5p and miR-546 in the animal model. Thus, they concluded that quercetin has great therapeutic potential to be used in the reduction and treatment of human endometriosis.

In another preclinical trial, oral administration of catechin using Wistar rats (25, 50, and 100 mg/kg) was shown to improve the functioning of the immune system by increasing antibody production and restoring leukocyte function (Ganeshpurkar & Saluja, 2018). According to Fan, Gao, Chen, & Li (2018), the intraperitoneal injection of myricetin in male Sprague-Dawley rats (1 mg/kg or 2.5 mg / kg, once every two days, for five weeks) improved dexamethasone-induced osteoporosis by increasing body weight gain, preventing bone mineral density reduction, improving alkaline phosphatase activity, up-regulating proteins like osteocalcin, bone morphogenetic protein 2, and runt-related transcription factor 2, in addition to reducing the activity of tartrate-resistant acid phosphatase, levels of C-terminal telopeptide of type I collagen and improvement of histological changes in the femurs of animals treated with this flavonoid.

2.2. Phenolic acids

Phenolic acids also are a class of compounds belonging to phenolic compounds, which are found naturally in fruits and vegetables (Table 1) (Lourenço Neto et al., 2018). They can be divided into two groups, i.e. those derived from hydroxybenzoic and hydroxycinnamic acids. The compounds derived from hydroxybenzoic acid are characterized by one carboxylic group (COOH) and its most common derivatives are ρ-hydroxybenzoic, gallic, protocatechuic and vanillic acids (Gómez-Caravaca et al., 2014; Lourenço Neto et al., 2018). While compounds derived from hydroxycinnamic acid are characterized by two carbon skeleton ($C_6H_5CHCHCOOH$) with at least one hydrogen molecule which can be replaced by a hydroxyl group; and they are represented mainly by ρ-hydroxycinnamic, ρ-coumaric, caffeic and ferulic acids (Heleno, Martins, João, Queiroz, & Ferreira, 2015; Lourenço Neto et al., 2018).

The biological potential of phenolic acids is as wide as their structural diversity since may acts as antidepressant (Barauna et al., 2018), antihypertensive (Agunloye et al., 2019), anti-inflammatory, neuroprotective (Zaitone et al., 2019), antihyperglycemic (Sanchez et al., 2017), anticancer and anti-diarrheal (Frauches, Amaral, Largueza, & Teodoro, 2016).

For example, in an experimental study using male Wistar rats, Bhandarkar, Brown, & Panchal (2019) demonstrate that the intake of chlorogenic acid (about 100 mg/kg/day added to the diet for 8 weeks) is effective against metabolic syndrome through an increase of gut microbiota diversity and also, providing amelioration of the cardiovascular, liver and metabolic functions. Likewise, Zhu, Gu, & Shen (2019) observed the anti-inflammatory effects of gallic acid in TNBS-induced ulcerative colitis in Balb/c mice. In this study, it was observed that the administration of gallic acid (60 mg/kg daily for 7 days by intragastric injection) increased the expression of anti-inflammatory interleukins (IL-4, and IL-10) and reduced the expression of pro-inflammatory biomarkers (IL-1, IL-6, IL-12, IL-17, IL-23, TGF-β and TNF-

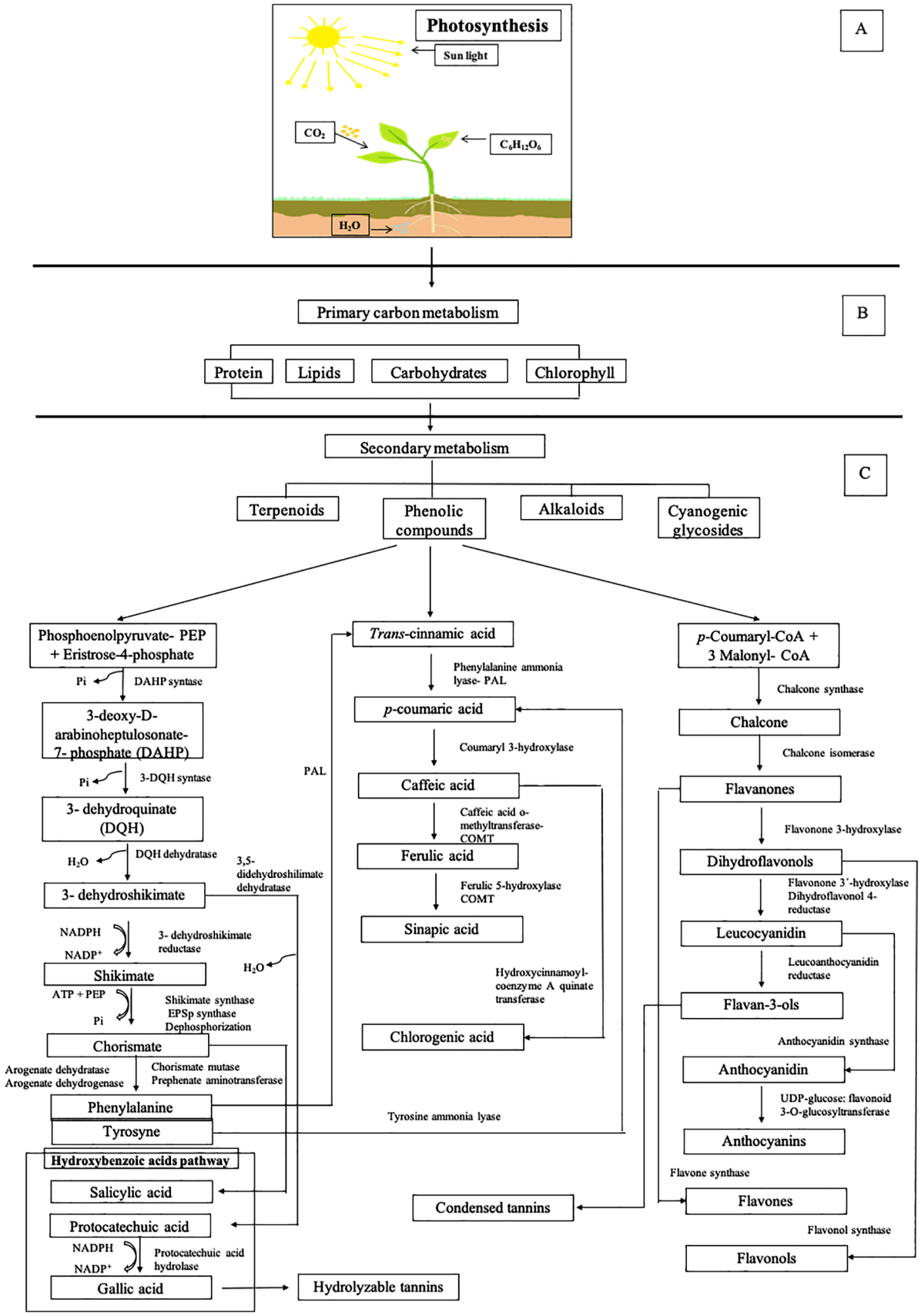

Fig. 1. Metabolism and phenolic compounds synthesis in plants. A: Schematic representation of photosynthesis; B: Primary metabolism of plants; C: Phenolic acids, flavonoids and tannins biosynthesis pathways (Adapted from Rosa et al., 2019; Vuolo et al., 2019).

Table 1
Some sources of phenolic compounds.

Source	Compounds (content)	Unit	Fraction/product	Reference
Blackcurrant	Myricetin (0.23), quercetin (0.12), delphinidin-3-*O*-glucoside (142), delphinidin-3-*O*-rutinoside (555), cyanidin (5.0), peonidin-3-*O*-glucoside (19.6), pelargonidin (16.8), malvidin (23.7), cyanidin-3-*O*-rutinoside (293), cyanidin-3-*O*-glucoside (38.0), malvidin-3-O-glucoside (5.6), gallic (32.3), and rosmarinic (11.2) acids	mg L^{-1}	Juice	Rashid et al. (2018)
Blueberry	Gallic (18.6), protocatechuic (8.82), caffeic (47.7), chlorogenic (1738), ferulic (43.7), and feruloylquinic (33.4) acids, catechin (39.9), epicatechin (11.3), epigallocatechin (20.9), myricetin (46.3), kaempferol (10.8), quercetin (242), rutin (74.6), cyanidins (219), delphinidins (1261), malvidins (1114), peonidins (532), and petunidins (2205)	mg 100 g^{-1} CE	Extract	Cladis et al. (2020)
Red wine Cabernet Sauvignon	Delphinidin-3-glucoside (10), cyanidin-3-glucoside (1.1), petunidin-3-glucoside (20.9), peonidin-3-glucoside (7.18), malvidin-3-glucoside (92.4), catechin (40.3), epicatechin (13.9), quercetin (0.48), myricetin (1.83) and rutin (0.04), gallic (28.8), vanillic (0.46), ellagic (4.20), and caffeic (1.58) acids	mg L^{-1}	Beverage	I. Lukić, Radeka, Budić-Leto, Bubola, & Vrhovsek (2019)
White wine Graševina	Gallic (6.62), vanillic (0.06), *trans*-caftaric (21.5), caffeic (0.43) and ferulic (0.07) acids, catechin (3.10), epicatechin (1.51), gallocatechin (0.24), and procyanidin B1 (2.11)	mg L^{-1}	Beverage	
White, green and black tea	Gallic acid (0.02; 0.01; 0.08), catechin (0.08; 0.28; 0.02), epigallocatechin (0.03; 1.21; 0.85), epigallocatechin gallate (0.21; 0.54; 0.46) and epicatechin gallate (0.12; 0.18; 0.23)	mg mL^{-1}	Beverage	Carloni et al. (2013)
Green Coffee and roasted Coffee	Tyrosol (15.6; 6.91), m-hydroxybenzoic (1.06; 1020), vanillic (0.37; 0.05), caffeic (28.1; 44.5), dimethyl caffeic (4.63; 5.84), p-cumaric (20.3; 25.2), ferulic (13.2; 422), chlorogenic (26.3; 9.5), and *p*-hydroxyphenylacetic (103; 6585) acids	mg L^{-1}	Powder	Muñoz, Hernández, Tolosa, Burillo, & Olalla-Herrera (2020)
Banana	Quercetin (0.29), protocatechuic (4.05), *p*-hydroxybenzoic (0.60), vanillic (5.41), caffeic (7.91), ferulic (7.71), and *p*-coumaric (1.73) acids	μg g^{-1} DM	Fruit	Park et al. (2015)
Persimmon	Quercetin (2.04), kaempferol (1.47), protocatechuic (6.75), *p*-hydroxybenzoic (2.16), vanillic (8.94), caffeic (2.04), syringic (1.82), ferulic (1.02), and *p*-coumaric (4.02) acids	μg g^{-1} DM	Fruit	
Strawberry	Quercetin (15.4), kaempferol (10.1), apigenin (5.14), gallic (82.4), protocatechuic (12.8), p-hydroxybenzoic (132), vanillic (11.2), caffeic (5.59), ferulic (32.3), cinnamic (92.6), and *p*-coumaric (92.6) acids	μg g^{-1} DM	Fruit	
Apple	Protocatechuic (24.7), *p*-hydroxybenzoic (5.05), vanillic (0.29), caffeic (106), ferulic (3.87), and *p*-coumaric (33.2) acids	μg g^{-1} DM	Pulp	
Kiwi	Protocatechuic (14.1), *p*-hydroxybenzoic (0.66), vanillic (5.41), caffeic (21.7), syringic (0.66), ferulic (1.50), and *p*-coumaric (4.05) acids	μg g^{-1} DM	Fruit	
Cocoa	Catechin (61.8), epicatechin (236), procyanidin B2 (25.4), gallic (11.8), protocatechuic (16.9), ellagic (4.54), *p*-coumaric (0.63), ferulic (0.24), and sinapic (0.78) acids	mg 100 g^{-1} DW	Beans	Oracz et al. (2019)

Concentrated extract (CE); lyophilized dry matter (DM); dry weight (DW).

Table 2
Metabolic effects of phenolic compounds.

Compound	Molecular Formula	Model	Effect	Reference
Rutin	$C_{27}H_{30}O_{16}$	*In vitro* model to study the hypoxia/reoxygenation-induced injury in myocardial cells (H9c2) (rutin: 50 μM)	↑ SIRT 1; ↑ cell viability; ↓ apoptosis rate; ↓ caspase-3 activity; ↓ LDH, AST, MDA and CK-MB levels; ↑ SOD, GSH-Px and CAT activities	Yang et al. (2019)
		In vivo model to investigate oxidative stress in Swiss albino rats induced by *t*-butyl hydroperoxide (16.3 μM for 7 days)	Modulated GSH, -SH, MDA and –CO levels; ↑ CAT, SOD, GPX, GR and GST activities; ↓ lipid peroxidation; ↑ Nrf2; ↓ iNOS	Singh et al. (2019)
Catechin	$C_{15}H_{14}O_6$	*In vivo* model to investigate the potential of catechin in the treatment of diabetic autonomic neuropathy in Sprague Dawley rats with streptozotocin-induced diabetes (25 and 50 mg/kg for 28 days)	↓ Plasma glucose levels; improvement of baseline hemodynamic parameters; ↓ MDA levels; ↑ GSH level; ↑ CAT and SOD activities; ↓ plasma MMP-9 levels; ↓ neuropathic lesions	Addepalli & Suryavanshi (2018)
		In vivo model to study the immunomodulatory effects of catechin in Wistar rats (25; 50; and 100 mg/kg for 15 days)	↑ Phagocytic index; ↑ number of white blood cells; ↑ neutrophil adhesion; ↑ hemagglutination titre; ↑ serum levels of immunoglobulins; modulation of the immune system.	Ganeshpurkar & Saluja (2018)
Epicatechin	$C_{15}H_{14}O_6$	*In vivo* model to evaluate the potential of epicatechin in the inhibition of the development of dilated cardiomyopathy in mice (1 mg/kg for 14 days)	↓ Number of vasoconstrictions; ↓ fibrosis; ↑ phosphorylation of eNOS; ↑ phosphorylation of PI3K , Akt, mTOR e p70S6K proteins; ↓ ANP and BNP levels; ↓ left ventricular loss; ↑ Cardiac growth (PI3K/Akt pathway)	Santos, Palma-Flores, Zentella-Dehesa, Canto, & Coral-Vázquez, 2018
		In vivo model to study the anti-inflammatory potential of epicatechin in acute lung injury induced by lipopolysaccharides in C57BL6/N mice (15 mg/kg)	↓ Lung damage; ↓ alveolocapillary membrane permeability; ↓ neutrophils; ↓ TNF-α mRNA level; ↓ IL-6 mRNA level; ↓ p38 MAPK phosphorylation; ↓ transcription factor AP-1	Xing et al. (2019)
Myricetin	$C_{15}H_{10}O_8$	*In vivo* model to evaluate the osteoporosis induced by glucocorticoids in Sprague Dawley rats (1 mg/kg and 2.5 mg/kg) and *in vitro* model to study the effect of myricetin on the reduction of osteoporosis in MC3T3-E1 cells	*In vivo* assay: ↑ body weight; ↑ ALT activity; ↓ TRAP activity; ↑ OCN and CTx levels; ↓ osteoporosis. *In vitro* assay: ↑ BMP2, Runx2, ALP, OCN, COL 1A1 and OPN levels	Fan et al. (2018)
		In vivo (2.5; 5 and 10 mg/kg for 25 days) and *in vitro* models to evaluate the potential of myricetin against lipopolysaccharide-induced Parkinson's disease in Wistar rats, in BV-2 murine microglia and SH-SY5Y neuroblastoma cell line	*In vivo* assay: Improvement of motor dysfunction; ↓ microglial activation; ↓ expression of Iba-1 protein; ↓ TNF-α mRNA; ↓ IL-1ß mRNA; ↓ IL-6 mRNA. *In vitro* assay: ↓ neuronal cell death; ↓ phosphorylation of ERK, JNK, p38 and p65-NF-κB	Huang et al. (2018)
Kaempferol	$C_{15}H_{10}O_6$	*In vitro* model to evaluate the potential of kaempferol in reducing diabetic nephropathy in NRK-52E and RPTEC cells (5; 10 and 50 μM)	↑ GSH level; ↓ MDA and nitrite levels; ↓ intracellular ROS production; ↓ fibronectin and CTGF mRNA expression; ↑ TGF-β1; ↓ TNF-α and IL-1β levels	Sharma, Gondaliya, Tiwari, & Kalia (2019)
		In vivo model to evaluate the vasorelaxation effect of kaempferol in the isolated pulmonary artery of Wistar rats (10^{-8} and $-10^{-4.5}$ M)	↑ Arterial relaxation; kaempferol induced relaxation independently of the endothelium through BKCa, L-type Ca^{2+} channels, sGC/cGMP and PKA signaling pathways	Mahobiya et al. (2018)
Luteolin	$C_{15}H_{10}O_6$	*In vitro* model to evaluate the anti-inflammatory potential of luteolin in chondrocytes of Wistar rats induced by IL-1β (0; 25; 50; and 100 μM for 12 h) and *In vivo* model to investigate the protective effect of luteolin in a MIA-induced model of OA (10 mg/kg/day for 45 days)	*In vitro* assay: ↓ nitric oxide; ↓ PGE2 level; ↓ TNF-α; ↓ MMP-2, MMP-8 and MMP-9 levels; ↓ protein expression of iNOS, COX-2, MMP-1, MMP-3 and MMP-13; ↓ degradation of collagen II; ↓ phosphorylation of NF-κB. *In vivo* assay: ↓ articular cartilage destruction	Fei, Liang, Jiang, Ni, & Wang (2019)
		In vivo model to study therapeutic effect of luteolin against Alzheimer on transgenic flies (5; 10; 15; and 20 μM for 30 days)	↓ LPO, PCC, GST, AChE, SOD, CAT, caspase 9 and caspase 3 activities; ↑ GSH content; ↓ AChE activity; ↓ Aβ42 peptides expression; ↓ oxidative stress; improved cognitive dysfunction	Ali et al. (2019)
Caffeic acid and chlorogenic acid	$C_9H_8O_4$ $C_{16}H_{18}O_9$	Cardio-protective and antioxidant properties of caffeic acid (10 and 15 mg/kg/day for 7 days) and chlorogenic acid (10 and 15 mg/kg/day for 7 days) in cyclosporine induced hypertensive rats	↓ SBP and HR, activity of ACE, AChE, BChE and arginase in the hypertensive rats, ↑ nitric oxide (NO) bioavailability, ↑ catalase activity, ↓ glutathione content and malondialdehyde	Agunloye et al. (2019)
Caffeic acid	$C_9H_8O_4$	*In vivo* model of rotenone-induced nigral neurodegeneration using albino mice (2.5; 5 and 10 mg/kg)	↓ Inflammatory markers, ↓ microglia expression and improved the nigral TH immunostaining and upregulation for genes encoding CD11b, COX-2, inducible nitric oxide synthase iNOS and nuclear factor-κB NFκB	Zaitone et al. (2019)
Chlorogenic acid	$C_{16}H_{18}O_9$	*In vitro* model using RINm5F cells to measure insulin secretion and sensitization (1; 10; 20; 50; 100; 200 and 500 μM)	↑ Insulin secretion, ↑ expression of PPARγ and GLUT4, as well PPARα and FATP	Sanchez et al. (2017)
Gallic acid	$C_7H_6O_5$	*In vivo* model using transgenic mouse to measure cognitive decline (3 and 30 mg/kg)	↓ Cognitive decline, ↑ the spatial reference memory and spatial working memory, ↓ severe deficits developed in the 9-month-old APP/PS1 mice in terms of spatial learning, reference memory, short-term recognition and spatial working memory, ↓ Aβ1–42-mediated intracellular calcium influx and neurotoxicity	Yu et al. (2019)
		In vitro model using THP-1 and MV411 cells to measure inhibition of mitochondrial respiration as a mechanism of gallic acids action in acute myeloid leukemia (AML) (10; 20 and 40 μM)	↑ Cellular apoptosis, enhances two standard AML chemotherapeutic agents' efficacy *in vitro* cell culture system and *in vivo* xenograft model, ↓ mitochondrial respiration, ATP production and oxidative stress	Gu et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Compound	Molecular Formula	Model	Effect	Reference
Ellagic acid	$C_{14}H_6O_8$	*In vitro* model using HepG2 cells to investigate the effect of ellagic acid on oxidative stress and insulin resistance in high glucose-induced T2DM (15 μM and 30 μM)	↑ Glucose consumption, IRS1, Akt and ERK phosphorylation under insulin stimulation, ↓ ROS and O^{2-} production and MDA level, ↑ SOD activity in high glucose-exposed HepG2 cells and activated keap1-Nrf2 system via elevating miR-223	Ding et al. (2019)
		In vivo model using mice and *in vitro* with NRK-52E cells to measure attenuation streptozotocin induced diabetic nephropathy (50; 100 and 150 mg kg^{-1} for 17 days)	Improve the daily state and body weight, ↓ blood glucose, levels of TNF-α and serum creatinine, ↑ activities of antioxidant enzymes, ameliorate the renal pathology, ↓ regulation of expression of proteins TLR4, IRAK4, TRAF6, IKK-β, NF-κBp65 and HMGB1	Zhou et al. (2019)
Delphinidin	$C_{15}H_{11}O_7^+$	*In vitro* model to evaluate the effect of delphinidin to induce protective autophagy in HER-2-positive breast cancer cells (0 – 280 μM)	Induction of autophagy; ↑ apoptosis; ↓ proliferation; ↑ LC3-II level; ↑ phosphorylation of LKB1 and AMPK; ↑ ULK1 and FOXO3 activities	Chen et al. (2018)
Cyanidin-3-rutinoside	$C_{27}H_{31}ClO_{15}$	*In vivo* model to investigate the effect of cyanidin-3-rutinoside on the reduction of cardiovascular abnormalities induced by methylglyoxal in Wistar-Kyoto rats (30 or 100 mg/kg/day)	↓ Plasma MG and AGEs accumulation in aortic tissue; restoration of vascular dysfunction; ↓ ALT and AST activities; ↑ eNOS mRNA and GLO1 mRNA expression; ↓ total number of ventricular extra beats; ↓ duration of ventricular tachycardia	Thilavech, Abeywardena, Dallimore, Adams, & Adisakwattana (2018)
Malvidin, cyanidin and delphinidin	$C_{17}H_{15}O_7^+$, $C_{15}H_{11}O_6^+$ $C_{15}H_{11}O_7^+$	*In vitro* model to evaluate the potential of anthocyanins in the differentiation of human adipose mesenchymal stem cells into adipocytes, chondrocytes and osteocytes (0–200 μM)	Delphinidin ↓ human mesenchymal stem cells adipogenesis (MSCs), downregulated FABP4, and adiponectin genes; malvidin ↑ calcium deposits in MSCs and the expression of BMP-2 and Runx-2 genes and promoted BMP-2 secretion; cyanidin and delfinidine induced chondrogenesis by positively modulating Col2a1 and aggrecan	Saulite et al. (2019)
Taninn	$(C_6C_3C_6)n$	*In vitro* model using tannins of caqui to assess hepatic steatosis in L02 cells (0–80 μg/mL)	↓ Lipid accumulation in L02 cells, ↓ expression miR-122, miR-33b and expression of CPT-1, thus improving liver steatosis	Zou et al. (2014)

miR: MicroRNAs; CPT-1: carnitine palmitoyltransferase-1; SIRT1: silent information regulator 1; LDH: lactate dehydrogenase; AST: aspartate transaminase; MDA: malondialdehyde; CK-MB: creatine kinase-MB; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; CAT: catalase; GPX: glutathione peroxidase; GR: glutathione reductase; GST: glutathione transferase; Nrf2: nuclear factor erythroid 2; iNOS: nitric oxide synthases; AMPK: AMP-activated protein kinase; ALT: serum alanine aminotransferase; AST: aspartate aminotransferase; MMP-9: matrix metalloproteinase-9; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; eNOS: endothelial nitric oxide synthase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; Tumor TNF-α: necrosis factor alpha; IL: interleucina ; MAPK: mitogen-activated protein kinase; AP-1: activator protein 1; ALT: alanine aminotransferase; TRAP: tartrate-resistant acid phosphatase; OCN: osteocalcin; BMP2: bone morphogenetic protein 2; ALP: alkaline phosphatase; JNK: jun *n*-terminal kinase; NF-κβ: nuclear factor kappa β; TGF-β: transforming growth factor beta; CTGF: connective tissue growth factor; MMP: matrix metalloproteinase; AChE: acetylcholinesterase activity; Aβ42: amyloid beta; BCHE: butyrylcholinesterase; ACE: angiotensin I-converting enzyme; COX-2: Cyclooxygenase-2; PPAR: peroxisome proliferator-activated receptor; GLUT4: glucose transporter; FATP: fatty acid transport protein; Keap1: kelch-like ECH-associated protein 1; TLR4: toll-like receptor 4; IRAK4: interleukin-1 receptor-associated kinase 4; TRAF6: TNF receptor associated factor 6; IKK β: inhibitor of nuclear factor kappa-B kinase β; HMGB1: high mobility group box-1 protein; AMP: activated protein kinase; ULK1: serine/threonine-protein kinase; FOXO3: forkhead box O3; SBP: systolic blood pressure; HR: heart rates.

α). In addition, the administration of gallic acid also increased the weight of the colon, reduced body weight gain, attenuated the histological changes resulting from ulcerative colitis, and suppressed the nuclear factor kappa B (NF-κB) signaling pathway in animals treated.

In the same line, Fikry, Gad, Eid, & Arab (2019) evaluated the effects of caffeic acid and ellagic acid on adjuvant-induced arthritis using adult male Sprague-Dawley rats. It was found that oral administration of caffeic acid or ellagic acid (50 mg/kg/day for 20 days) reduced the expression of NF-κB, the downstream effector chitinase-3-like protein-1, synthesis of IL-1β, levels of matrix mettaloproteinase-9, vascular endothelial growth factor and caspase-3 in paw of the evaluated animals. Thus, the authors concluded that both phenolic acids are as effective as the standard anti-inflammatory agent (celecoxib), and that these compounds are considered to be potential therapeutic agents for managing the disease and reducing joint damage. Other metabolic effects of phenolic acids can be seen in Table 2.

2.3. Anthocyanins

Anthocyanins are natural plant pigments from the flavonoid family, giving the colorful appearance (colors of red, blue, and purple) of fruits, vegetables and other foods (Table 1) (Khoo, Azlan, Tang, & Lim, 2017). In general, they are mainly found in the nature in the glycosylated form and less frequently as acyl glycosides of anthocyanidins, which are flavylium structures consisting of two aromatic rings attached by a three carbon heterocyclic ring containing oxygen once that conjugated double bonds of the anthocyanidin moiety constitute the chromophore (Rodriguez-Amaya, 2019).

According Khoo et al. (2017) the main anthocyanins found in plants, including fruits and vegetables are cyanidin, malvidin, delphinidin, pelargonidin, peonidin and petunidin. Pre-clinical trials have reported the action of anthocyanins against some pathologies such as cancer, inflammation, cardiovascular diseases and obesity (Chen, McClements et al., 2018; Saulite et al., 2019; Thilavech, Abeywardena, Dallimore, Adams, & Adisakwattana, 2018) (Table 2).

In a study carried out to assessed the effect of cyanidin on chondrogenic and hypertrophic differentiation of the mesenchymal stem cells (MSCs), Cao, Huang, Dou, Xiang, & Dong (2018) found that the treatment with this anthocyanin (10–20 μg/mL) inhibited the Sox9, Col2a1, Runx2 and Col10a1 genes, promoted expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and p62 protein and reduced the expression of microtubule-associated protein 1-light chain 3 (LC3B) during the chondrogenic stage of MSCs. Thus, this compound has great therapeutic potential in maintaining the function of the controcytes and to be used in the development of new drugs to treat defects in cartilaginous tissue (Cao et al., 2018).

Cyanidin and malvidin-3-glucoside (10 μg/mL) decrease TNF-α-mediated production of E-selectin and adhesion of monocytes to endothelial cells (Del Bo', Marino, Riso, Møller, & Porrini, 2019). Also, several recent data provide evidence that berry anthocyanin intake exerts benefits on cardiovascular health (Cassidy, 2018). For example, Edwards, Czank, Woodward, Cassidy, & Kay (2015) reported that cyanidin-3-O-glucoside is able to increase the expression of Hmox1 gene in human iliac artery endothelial cells.

Similarly, Rashid et al. (2018), reported that supplementation with blackcurrant juice (60 mg gallic acid equivalents/kg daily, for 3 weeks before surgery and 4 weeks thereafter) rich in anthocyanins (delphinidin-3-O-rutinoside, cyanidin-3-O-rutinoside, delphinidin-3-O-glucoside and cyanidin-3-O-glucoside) can stabilizes vascular oxidative stress and angiotensin system of cirrhotic Wistar rats induced by chronic bile duct ligation (CBDL), once both acetylcholine-induced nitric oxide and endothelium-dependent hyperpolarization (EDH)-mediated relaxations in mesenteric artery rings were significantly reduced in treated animals.

2.4. Tannins

Tannins are phenolic compounds that have the ability to form complexes with several other macromolecules. Depending on their structural characteristics and chemical properties, they can be divided into condensed and hydrolysable tannins. Hydrolysable tannins occur naturally in bark, trunks, leaves and fruits of various plant species, have carbohydrates as a central core and hydroxyls esterified with phenolic groups, while condensed tannins are formed by the polymerization of several monomeric flavon-3-ols (Santana & Macedo, 2018). Some sources of tannins can be seen in Table 1.

These compounds have several important functions in plants, acting as protectors against UV rays and free radicals, chemical signaling and as defense compounds against the attack of animals, insects, fungi and bacteria. They have as their main feature and advantage a phenolic structure quite similar to synthetic phenols, in addition to can be used in leather tanning, manufacture of adhesives, manufacture of drinks, animal feed, manufacture of biosustainable foams, wood preservatives, corrosion inhibitors, among others purposes (Shirmohammadli, Efhamisisi, & Pizzi, 2018).

Scientific evidence has shown that hydrolysable and condensed tannins are considered to be good natural antioxidants, but few studies have reported their benefits to health (Table 2). These compounds have the ability to modulate intracellular signalling through PI3K and p38 MAPK pathways, activity of target enzymes and gene expression. In addition, are considered as cardioprotective agents, antitumor, antibacterial, antiviral, anti-inflammatory and immunomodulator, besides enhance glucose uptake and inhibit adipogenesis (Kumari & Jain, 2012).

Links, Taylor, Kruger, & Taylor (2015) when evaluating the simulated gastrointestinal digestion of encapsulated sorghum tannins (312 mg/100 mg catechin equivalent), they found that these compounds had potential as a nutraceutical to soften hyperglycemia and control type 2 diabetes through inhibition of key enzymes such as α-glucosidase and α-amylase. A study performed by Shi, Wang, Wei, Hu, & Gao (2020) demonstrated that condensed tannins extracted from rice straw have good antimicrobial potential, being considered strong inhibitory agents in the growth of *Staphylococcus aureus*. Moreover, it was demonstrated that *in vitro* gastrointestinal digestion of quebracho (*Schinopsis lorentzii*) and chestnut (*Castanea sativa*) tannins showed good prebiotic potential, by stimulating the production of short chain fatty acids after microbial fermentation (Molino, Fernández-Miyakawa, Giovando, & Rufián-Henares, 2018).

3. Bioavailability of phenolic compounds

The beneficial health effects of phenolic compounds are mainly attributed to their metabolites. In this sense, phenolic compounds must be bioavailable to exercise their bioactivity, and bioavailability is influenced by processes such as digestion, absorption and metabolism, in addition to factors such as concentrations in the food, release in the food matrix, chemical structure, conjugation with other compounds, size molecular, degree of polymerization and solubility (Iglesias-Carres et al., 2019; Landete, 2011).

The absorption of phenolic compounds in the small intestine is low, where only about 5 to 10% of the total polyphenols ingested are absorbed (depending on their chemical complexity). Before being absorbed, the less complex phenolic compounds are deglycosylated and then undergo some transformations carried out by the liver, involving methylation, glucuronidation and sulfonation reactions so that they can enter the bloodstream and thus be distributed to other organs (Czubinski et al., 2019; Gowd et al., 2019). In turn, the most complex phenolics (e.g. tannins) that are not absorbed in the small intestine (about 90–95%), reach the colon, where they are biotransformed (by the microbiota present) in low molecular weight metabolites so that they can be absorbed. During this process, there is also the production

of short-chain fatty acids and significant changes in the gut microbiota. Therefore, the biotransformation of polyphenols by the gut microbiota, plays a fundamental role in bioavailability of these compounds (Farias et al., 2019; Gowd et al., 2019).

Mocciaro et al. (2019) when evaluating the bioavailability of phenolic compounds present in hazelnut skin drink, they verified bioavailability of approximately 27%, where 10 metabolites were identified in plasma and 24 in urine in healthy humans. Similarly, Castello et al. (2018) evaluating the acute administration of a drink made from red grape pomace in humans (250 mL of the drink, containing 625 mg/100 mL of total polyphenols) identified a total of 35 phenolic metabolites in the urine and 28 metabolites in the patients' blood, the main compounds included hydroxybenzoic acids, epicatechin derivatives, hydroxyphenylpropionic acids, simple phenols, among others. According Iglesias-Carres et al. (2019) the bioavailability of grape phenolic compounds in rats can be influenced by the phenolic composition and the amount and types of fibers present. In addition, these authors also reported higher metabolism of polyphenols in the small intestine, higher serum concentration of metabolites after two hours of ingestion and lower after 24 h.

Improving the bioavailability of phenolic compounds is essential to increase their therapeutic potential in preventing diseases. Some alternatives such as chemical and technological modification, use of prodrugs, polymers (for example chitosan, dendrimers and cyclodextrins) and nanotechnology can be used to increase the bioavailability of these compounds, and change parameters such as solubility, absorption and metabolism (L. Chen, Gnanaraj, Arulselvan, El-Seedi, & Teng, 2019).

4. Potential toxicological effects of phenolic compounds

Despite their beneficial properties for maintaining health, many studies have pointed out that phenolic compounds ingested in high concentrations can act as pro-oxidants and thus cause toxicological effects. These activities can be attributed to the production of reactive oxygen species as a consequence of the possible disturbance of these compounds to the cells, however their pro-oxidative nature cannot be simply defined as harmful, and the risks and benefits depend on the situation and concentration used (Murakami, 2014).

Cladis et al. (2020) when assessing the toxicity of oral intake of blueberry polyphenols (0–1000 mg total polyphenols/kg bw/day) in Sprague-Dawley rats for 90 days, found that there was no difference in behavior, body weight, consumption of food, development of tumors and histopathological changes at the maximum concentration administered. Thus, the authors concluded that a NOAEL (No Observed Adverse Effect Level) for blueberry polyphenols in the animals evaluated was ≥ 1000 mg of polyphenols kg bw/day. These results are important and can contribute to establish safe levels of daily intake of these compounds by humans.

In another study, Zheleva-Dimitrova et al. (2019) evaluated the acute and subacute toxicity of *Clinopodium vulgare* L. aqueous extract in mice and rats through intraperitoneal and oral administration. In this study, it was observed that the LD_{50} in acute intraperitoneal administration was 675 mg/kg for mice and 500 mg/kg for rats, resulting in toxic effects on the animals' central nervous system. On the other hand, the LD_{50} in oral administration was higher than 2000 mg/kg for both species and there was no toxic effect on hematological, biochemical blood/urine and histopathological parameters of the pancreas, liver, spleen and kidney. These results demonstrate that the toxicity of the phenolic compounds was dependent on the route of administration used, and suggest that the bioavailability of these compounds may be influenced by the transformations that occur throughout the digestive process.

Despite reducing the release of pro-inflammatory cytokines (IL-6 and IL-8), direct application of fisetin or luteolin standards (50 μM) stimulated apoptosis in human RPE cells, reduced cell viability and increased leakage of lactate dehydrogenase (Hytti et al., 2017). Urbatzka et al. (2018) also noted that at a concentration of 50 μM, some phenolic compounds and their derivatives induced cytotoxicity in 3T3-L1 cells after 24 h or 48 h of exposure. It is worth mentioning that high doses of polyphenols can aggravate diseases such as colitis and colon carcinogenesis, negatively regulate the expression of antioxidant enzymes and molecular chaperones, in addition to causing nephrotoxicity and hepatotoxicity (Murakami, 2014). A study demonstrated the potential of persimmon tannins to improve liver steatosis, however the authors reported that after 48 h of treatment, these compounds showed cytotoxicity in L02 cells at a concentration of 40 μg/mL, but in concentrations below 20 μg/mL none cytotoxic effect was observed (Zou et al., 2014).

These evidences suggest that the toxicological potential of phenolic compounds depends on the type of the compound and the concentration used. Therefore, their administration should be carried out with caution, in order to avoid possible harmful effects to health. Moreover, it is important to highlight that clinical studies must be carried out in order to establish safe concentration margins for the ingestion of these compounds.

5. Technological applications of phenolic compounds

With regard to the technological potential of phenolic compounds (Table 3), several applications have been proposed, not only in the food industry but also in other areas of commercial interest. However, it is important to note that food manufacturers must not only know the technology of combining ingredients to meet sensory and safety requirements, but also create a new framework for food recommendations based particularly on physics, storage and preservation techniques, nutrient restoration and food fortification, which enable the development of new products with functional claims and improved quality (Nehir El & Simsek, 2012). The following topics will discuss some applications of phenolic compounds in obtaining bioactive films, natural dyes, compounds with prebiotic properties, and others.

5.1. Bioactive films

Bioactive films can be used for making bioactive packaging and also for other technological purposes (Table 3). Active packaging has gained a lot of attention in recent years due to the possibility of incorporating preservatives or antioxidants that are intentionally released in packaged foods or in the atmosphere that surrounds the product (Kaewprachu et al., 2018). A great advantage of bioactive packaging is that it is eco-friendly and represents a major advance for the food sector, as it can replace plastic packaging derived from petroleum.

The elaboration of bioactive packaging based on starch, citrus pectin and functionalized with *Acca sellowiana* waste by-product (rich in phenolic compounds) showed antimicrobial activity against *Escherichia coli*, *Salmonella typhimurium*, and *Pseudomonas aeruginosa*. In addition, the packaging produced was also effective in maintaining the quality of apples, avoiding the loss of weight of the fruits until the fifth day of storage (Sganzerla et al., 2020).

The development of intelligent pH biofilm using biodegradable polymers and anthocyanins proved to be a promising approach for monitoring pork freshness (Zhang et al., 2019). Similarly, the combination of gallic acid and chitosan can be used to improve the food safety and quality on fresh pork (Fang, Lin, Warner, & Ha, 2018), while the production of films from chitosan/ellagic acid has a high antioxidant capacity and inhibit the growth of food-borne pathogens (Vilela et al., 2017).

Other applications of phenolic compounds involve the production of active fish gelatin films with addition of anthocyanins (Uranga, Etxabide, Guerrero, & de la Caba, 2018) and use of films composed of carboxymethylchitosan and quercetin that can be used as novel antioxidant and intelligent materials for detection of Al^{3+} in food

Table 3
Technological applications of phenolic compounds.

Compound	Technique (Description)	Purpose/application	Reference
Catechin	Gelatin films with nisin and catechin.	Minced pork preservation.	Kaewprachu et al. (2018)
Rutin	Synthesis and chemical modification of poly(butylene succinate) with rutin.	Reduction of silybin release.	Ferreira et al. (2017)
Luteolin	Production of palmitoylethanolamide (PEA) composite microparticles with polyvinylpyrrolidone and luteolin.	Reduction of crystallization of PEA.	Adami, Liparoti, Di Capua, Scognamiglio, & Reverchon (2019)
Quercetin	Protein-based excipient emulsions.	Enhancement of the solubility, stability and bioaccessibility of quercetin.	Chen et al. (2018)
	Starch films loaded with donut-shaped starch-quercetin microparticles.	Increased thermal stability and antioxidant activity of microparticles.	Farrag et al. (2018)
	Nanoformulations of quercetin and cellulose nanofibers.	Increased stability, water solubility and bioavailability of quercetin in nanoformulation.	Li et al. (2019)
Caffeic acid	Microencapsulation of caffeic acid by inclusion in hydroxypropyl-β-cyclodextrin.	Increased aqueous solubility, improved biological and chemical properties.	Garrido et al. (2018)
	Combination of cyclodextrin and ethanol (co-solvent) in the microencapsulation of caffeic acid.	Increased solubility and antioxidant activity.	Kfoury, Geagea, Ruellan, Greige-Gerges, & Fourmentin (2019)
Chlorogenic acid	Synthesis of chlorogenic acid-chitosan conjugates with different degrees of substitution by the EDC/HOBt method.	Increased solubility and antioxidant activity.	Rui et al. (2017)
	Addition of chlorogenic acid and effect on the structure and functionality of casein (CS) and whey protein (WPI).	Reduction of the hydrophobicity and increase of the foamy properties of the proteins.	Jiang, Zhang, Zhao, & Liu (2018)
Gallic acid	Modified atmosphere packaging combined with gallic acid/chitosan.	Maintenance of quality and conservation ofpork *in natura.*	Fang et al. (2018)
	Use of potato by-products and gallic acid for development of bioactive film packaging.	Improvement of the physical, chemical and functional parameters of bioactive packaging.	Zhao & Saldaña (2019)
Gallic acid and ellagic acid	Pre fermentative addition of gallic acid and ellagic acid on the red wine.	Improvement of color properties and phenolic profile increase during wine aging.	Zhang et al. (2018)
Ellagic acid	Production of bioactive chitosan/ellagic acid films.	Increase protection against ultraviolet light for active food packaging.	Vilela et al. (2017)
Cyanidin-3-*O*-glycoside	Addition of cyanidin-3-*O*-glycoside extract obtained from *Arbutus unedo* L. in wafers.	Addition of natural colorant with bioactive properties.	López et al. (2019)
Malvidin-3-glucoside	Lipophilization.	Increased color stability.	Mendoza et al. (2018)
Cyanidin and pelargonidin	Flavone-anthocyanin copigmentation for altered hues and improved shelf life of products.	Improves color stability, increases the shelf life of products, produces hyperchromic and bathochromic changes, in addition to presenting protective effect from flavone copigmentation was observed for glycosides.	Chatham, Howard, & Juvik (2020)
Tannins	Obtaining a bio-hybrid film with anti-oxidant and UV-absorbing properties from cellulose nanofibrils and tannin extract.	Increased mechanical resistance, thermal stability, anti-oxidant capacity and UV protection, in addition to improving the optical clarity of the film.	Li, Sirviö, Haapala, Khakalo, & Liimatainen (2019)
Tannins	Use of tannins to enhance the functional properties of protein based films.	The addition of tannins decreased the water barrier property and the solubility of the films. On the other hand, the addition of tannins caused an increase in antioxidant and microbial capacity of these active films.	Cano, Andres, Chiralt, & González-Martinez (2020)

packaging (Gunm, 2018).

5.2. Phenolic compounds as natural dyes

The growing awareness of the negative impacts of the use of synthetic dyes on human health has stimulated the search for new natural pigments (Lakshmi, 2014). Fruits, vegetables and their industrial residues are products rich in phenolic compounds, which have high added value, relatively low cost, in addition to having great potential to be used as natural dyes, providing shades of red, yellow-orange, blue and green (Phan et al., 2020; Vinha, Rodrigues, Nunes, & Oliveira, 2018). According Bener, Özyürek, Güçlü, & Apak (2010) flavonoids are compounds that in addition to gaining prominence due to their antioxidant potential, can also be used industrially as natural dyes to color fabrics. Moreover, due to their biocompatibility, biodegradability, non-toxicity, non-allergic responses and non-carcinogenic effects on human health, polyphenols can also be used in dyeing of nylon (Ebrahimi & Parvinzadeh Gashti, 2016).

Anthocyanins, despite their instability, are mainly applied as a food color, but they also have the potential to dye other products such as textile substrates, cotton, leather, silk and human hair (Phan et al., 2020). In the food industry, anthocyanins can be used as pigments in products such as curd, fermented milk, smoothies, low pH drinks, wines and solid matrices such as pancakes and omelets. These compounds can also be used to ensure food stability during storage and as copigments (Vinha et al., 2018). Some effects and applications of phenolic compounds as natural dyes can also be seen in Table 3.

Regarding the legislation that regulates the use of natural dyes as food additives, the European Union establishes the use of natural pigments such as anthocyanins, betalains, carotenoids, chlorophyll and chlorophyll derivatives, curcumines and carminic acid (European Commission and the Council, 2008; Vinha et al., 2018). On the other hand, the Food and Drug Administration (FDA) establishes the use of annatto extract, β-carotene, powdered beet, canthaxanthin, carrot oil, carmine, cottonseed meal, fruit juice, grape-colored extract, extract of grape skin, paprika and saffron (Code of Federal Regulations, 2016). However, more attention should be paid to other phenolic compounds that are not regulated by current legislation and that have the potential to be used as food additives, such as phenolic acids and other classes of flavonoids (in addition to anthocyanins).

5.3. Applications of polyphenols as prebiotics ingredients

Recently, polyphenols were encompassed in the prebiotics class due their ability to interact with gut microbes and host and/or modifying the set of microbial metabolites bioavailable to the host (Farias, de

Araújo, Neri-Numa, & Pastore, 2019; Gibson et al., 2017). For example, Jiao et al. (2019) reported that administration of blueberry polyphenol extract (PPE) for 12 weeks inhibited weight gain and normalized the lipid metabolism of C57BL/6J mice fed a high-fat diet. In addition, it was observed that the improvement of the lipid metabolism of the animals treated with the phenolic extract was correlated with the modulation of the composition of the intestinal microbiota, including *Proteobacteria*, *Deferribacteres*, *Actinobacteria*, *Bifidobacterium*, *Desulfovibrio*, *Adlercreutzia*, *Helicobacter*, *Flexispira*, and *Prevotella*.

Similarly, Chen et al. (2019) found that supplementation with green tea polyphenols in the diet of female db/db mice for 7 weeks significantly altered the composition of the microbiota in the cecon and colon, and this modification correlated with the reduction of blood glucose in the treated animals. In this study, the bacterial community belonged to the phyla *Firmicutes* and *Bacteroidetes*. In this line, Sabinsa Corporation/Sami Labs Limited (NJ, USA) registered the LactoCran™ as a symbiotic preparation combining LactoSpore with Fruit ́dOŕs Cran Naturelle cranberry seed powder which can be applied in the manufacture of nutrition bars, yogurts, smoothies, shakes, and other dairy products (Decker, 2018).

Similarly, Steed et al. (2017) found that deaminotyrosine (DAT), a metabolite derived from gut microbial metabolism of flavonoids, is able to increase interferon type I (IFN 1) signaling and decrease pulmonary immunopathology, thus increasing the survival of mice (Irgm1 $^{+/-}$ knockout) with influenza mortality. In this context, Iprona SpA (Lana, Italy) have produced the Cya-3-glu rich BerryPharma® black elderberry, an effective prebiotic/probiotic combination for immune support (BerryPharma® by Iprona).

The Diana Food Canada Inc. also have been investigating the positive impact of polyphenols (particularly, new raw materials from the Amazonian and Nordic regions of Canada) on the modulation of gut microbiota by creating a research chain to study the prebiotic role of polyphenols (Gunm, 2018).

5.4. Other applications of phenolic compounds

In addition to their applications as natural dyes, bioactive films and compounds with prebiotic properties, the use of phenolic compounds has been proposed in the most diverse technological fields (Table 3). Recently, a study verified the use of polyphenols of nuts in the manufacture of dielectric elastomers with improved electromechanical properties. Through the use of these compounds it was possible to obtain higher dielectric constants and less tangent dielectric loss, greater deformation of the driven area and greater electromechanical stability (Jiang et al., 2020).

According Liu, Wang, Yong, Kan, & Jin (2018) flavonoids conjugated to polysaccharides have strong antioxidant, antimicrobial and antitumor activities, and can be used in the development of hydrogels for controlled release of medications, micelles for oral administration of medications and emulsions for nutraceutical administration. The use of a novel triphenylamine-based flavonoid has also been proposed in the manufacture of organic fluorescent nanodots. The results demonstrated that the organic nanodots were easily manufactured without any additional modification on the surface, in addition to exhibiting low cytotoxicity, good resistance to photodegradation and good cell uptake (Liu et al., 2017). Another study demonstrated that anthocyanins can be used to obtain nanocomplexes with great potential for functional applications in food and nutraceuticals (Ge, Yue, Chi, Liang, & Gao, 2018).

In food technology, phenolic compounds are also of great importance. For example, the application of a laccase-chlorogenic acid recombinant system in the manufacture of curds, has resulted in an increase in the antioxidant potential and obtaining a final product with remarkable nutritional value. (Loi, Quintieri, Fanelli, Caputo, & Mulè, 2018). Moreover, the combination of quercetin and starch has been shown to be efficient in the production of a new resistant starch with potentiated antioxidant capacity, which can be used as packaging material and encapsulation agent (Liu, Wang, Yong, Kan, Zhang et al., 2018).

Recently studies on the interaction of carbohydrates and polyphenols have been gaining more and more prominence, since this type of interaction can improve the physicochemical properties of starch. For example, the use of phenolic acids, flavonoids and procyanidins can alter properties such as gelatinization, retrogradation, gelation and also the digestibility of starch. Ferulic acid, rutin and quercetin could reduce the gelatinization temperature, delay retrogradation and facilitate the formation of softer starch gel. In addition, compounds such as tannins can increase crystallinity, bonding temperature and maximum viscosity of starch (Du et al., 2019).

6. Innovation potential of phenolic compounds in the industrial field

Regarding the innovation potential of phenolic compounds, when searching in the Questel Intellectual Property Portal on the Internet: < URL: http://www.orbit.com > to check the number of patents granted for these compounds, it was possible to verify a total of 64871 alive orders using the following search terms: polyphenol, phenolic compounds, flavonoids, phenolic acids, anthocyanins and tannins, with 8685 orders between 2006 and 2010; 16641 for 2011–2015; and 20011 in the period after 2016. Among the Top 10 markets which are responsible for an expressive number of patent applications, China leads with a greater number of applications (3245), followed by Japan (2280), United States (1579), Korea (1292), Spain (1246), Taiwan (878), Germany (778), India (641), France (584) and the United Kingdom (544). The most representative players in the international patent market are companies of great commercial prominence such as Sumitomo Bakelite, Fujifilm, Sumitomo Chemical, Hitachi Chemical, Basf, DIC, Bayer, Shin Etsu Chemical, Xerox and Toray, and the technological domain is represented mainly by macro-molecular chemistry polymers, organic fine chemistry, basic materials chemistry, pharmaceuticals, food chemistry, chemical engineering, semi-conductors, textile and paper machines, etc.

Some of the patent applications involve the use of phenolic compounds for the elaboration of therapeutics drug for the treatment and prevention of disorders such as cancer, cardiac diseases, tumors, and obesity. They are also exploited in control of microorganisms and mycotoxins, besides use in the production of rigid foams, anti-adhesive coatings and metal nanoparticles (Table 4). An Australian invention has demonstrated that the combination of ascorbic acid, lysine, proline and at least one phenolic compound can be used as an agent for cancer prevention and treatment (AU2003235762B2, 2008). Similarly, the balanced combination containing super nutrients, phenolic compounds, anti-degenerative elements, and essencial micro-nutrients can be used in the prevention of cardiovascular disease, Alzheimer's disease, diabetes, regulation and reduction of blood sugar and insulin resistance (US8017147B2, 2009).

A stable, non-irritating topical composition formulated using vitamin C, vitamin E and a polyphenol can be used to prevent or treat skin damage caused by reactive oxygen species (KR20150143698A, 2014). The preparation of a cosmetic product using ellagic acid and some derivative compounds can prevent, mitigate or suppress the harmful effects to the skin caused by toxic gases and residues of organic compounds combustion (ES2225548T3, 2001).

A Chinese invention has shown that the combination of spirantol, quininic acid, vanilla polyphenol, green tea polyphenol and/or polyphenols of rosaceous plant results in a high intensity sweetening flavoring agent with the potential to be added to foods or drinks that contain high sweetness sweeteners (CN102481004B, 2014). In another invention, it was demonstrated that resveratrol and curcumin can be used after hydrogenation and in combination with other commercial monomers, to produce polymers such as polycarbonates (PC), polyurethanes (PU), co-polymers and biodegradable polymers

Table 4
Overview of patents for phenolic compounds to various purposes.

Title	Compound	Publication number	Publication date	Claim	Technological domain	Applicant/Assignee
Catechin multimers as therapeutic drug delivery agents	Catechin	US6562864	2002–05-03	Their use as carrier moieties for the delivery of nucleophilic and cationic bioactive therapeutic agents to target sites *in vivo*.	Analysis of biological materials and pharmaceuticals	Drake Larson and Mesquite Enterprises*
Composition comprising a complex of (+)-catechin and amino acid for the treatment and prevention of câncer	Catechin	CA2912128	2013–05-17	The invention relates to a gastro-enteric therapeutic composition for oral administration, comprising a compound of monomeric (+)-catechin and at least one basic amino acid for the curative and/or preventive treatment of câncer.	Basic materials chemistry and pharmaceuticals	Wa luolei
Composition for prevention and treating airway diseases by ros in beas-2b cells including kaempferol	Kaempferol	KR20150097275	2014–02-18	The present invention relates to a composition comprising kaempferol for preventing and treating bronchial diseases.	Pharmaceuticals	University Soonchunhyang Industry Acad Coop Found
Kaempferol for the treatment of cardiac diseases	Kaempferol	WO2017211780	2017–06-06	The present invention provides activators of the mitochondrial calcium uniporter (MCU), in particular kaempferol and its derivatives, for use in treatment of various cardiac diseases.	Pharmaceuticals	Ludwig Maximilians University Munich
Method for treating cancer with a combination of quercetin and a chemotherapy agent	Quercetin	CA2952953	2015–06-19	The use of an effective amount of a combination of a chemotherapy agent and a composition containing a quercetin for treating cancer.	Analysis of biological materials and pharmaceuticals	Quercegen Pharmaceuticals
Compositions comprising rutin useful for the treatment of tumors resistant to chemotherapy	Rutin	ITMI20131495	2013–09-10	The present invention relates to the use of rutin for increasing the effectiveness of chemotherapeutic treatments used in human and veterinary medicine for the treatment of tumors, in particular in case of resistance to chemotherapeutics currently in use.	Basic materials chemistry and pharmaceuticals	CERCAR Di Paolo Maestri Probiotical Probiotical Â· Societa Â· Pell Â· Ationi Probiotical SPA
A manufacturing method of functional powder comprising abundant rutin ingredient	Rutin	KR20180001850	2016–06-28	As the functional powder with an increased rutin content is applied to food, high value-added and functionally improved products are able to be developed and sold.	Food chemistry	Korea Rural Development Administration (RDA)
Caffeic acid and application of alkyl ester of caffeic acid in control of bacterial wilt	Caffeic acid	CN104365598	2014–10-30	The bacterial wilt can be inhibited by caffeic acid and one or more in alkyl ester.	Basic materials chemistry	Jiangsu University of Science & Technology
Caffeic acid tablets and preparation method thereof	Caffeic acid	CN105012261	2015–08-21	The caffeic acid tablets are easily absorbed by human bodies and have the very high stability.	Pharmaceuticals	Dezhou Deyao Pharmaceutical
Application of chlorogenic acid in activation of immune related signaling pathway of organism and research method of chlorogenic acid	Chlorogenic acid	CN105106187	2015–09-09	The chlorogenic acid can be used for treatment of tumors, and can also be used for building related research models for the specific action principle of the immune related signaling pathway or other related applications.	Pharmaceuticals	Sichuan Jiuzhang Biotechnology
Composition for preventing or treating auditory neuropathy comprising chlorogenic acid	Chlorogenic acid	KR20130023875	2011–08-30	A composition containing chlorogenic acid is provided to effectively prevent auditory neuropathy and to delay reaction reduction of auditory nerves.	Pharmaceuticals	Kyung Hee University
Cosmetic and pharmaceutical applications of gallic acid and gallic acid derivatives	Gallic acid	WO2015140470	2015–03-18	The use of gallic acid, and the cosmetic applications of same for stimulating or repairing the barrier function of the epidermis for treating damage caused by conditions such as Crohn's disease.	Organic fine chemistry and pharmaceuticals	Bioalternatives Greenpharma
Combination of compounds derived from gallic acid for the treatment of cancer	Gallic acid	CA2884784	2012–09-11	A combination with antitumoral, antimetastatic and immune response-inducing activity for the treatment of cancer.	Pharmaceuticals	Fundacion Universitaria Juan N Corpas Fundacion University
Conversion and synthesis method of ellagic acid from gallnut tannic acid production waste	Ellagic acid	CN103288843	2013–05-10	One or more gallic tannic acid production waste conversion of synthesis of ellagic acid method, characterized in: adjusting pH to 8–10 lye to NaOH, Na_2CO_3 or Na HCO_3	Organic fine chemistry	Hunan Agricultural University
	Ellagic acid	CN103622955	2013–12-09		Pharmaceuticals	

(*continued on next page*)

Table 4 (*continued*)

Title	Compound	Publication number	Publication date	Claim	Technological domain	Applicant/Assignee
Application of ellagic acid to preparation of drugs for treating and preventing fungal infection of human body				Ellagic acid in human therapy and prevention of a fungal infection of a medicament for application.		Uygur Medicine Research Institute Xinjiang Uygur Autonomous Region
Pharmaceutical composition for treatment of obesity comprising delphinidin or pharmaceutically acceptable salts thereof as an effective component	Delphinidin	KR20170054686	2015–11-10	The delphinidin have the effects of effectively suppressing accumulation of triglycerides in the cell with no side effects and promoting the breakdown of lipids in the cell.	Pharmaceuticals	University Soonchunhyang Industry Acad Coop Found
Delphinidin for combating melanoma cells	Delphinidin	CA2893883	2013–11-28	A composition comprising a complex of delphinidin and a sulfoalkyl ether β-cyclodextrin for use in the treatment of malignant melanoma.	Micro-structure and nano-technologyPharmaceuticals	SapiotecZipio Tec Gesellschaft Mitt Beshrenktel Huftung
Protection effect of cyanidin-3-glucoside for uvb (ultraviolet b)-induced hacat cell injury	Cyanidin 3-glucoside	CN105030560	2015–07-13	Preparation of sunscreening.	Organic fine chemistry	Jinan University
Cyanidin-3-glucoside and methods for using the same	Cyanidin 3-glucoside	US20130324487	2012–06-01	The present invention provides diet supplement compositions comprising cyanidin-3-glucoside (C3G) or C3G source or extracts and methods for using the same to aid in bodily fat loss.	Pharmaceuticals	Monsterops
Use of chestnut tannins extract as anti-oxidant, anti-microbial additive and to reduce nitrosamines and mycotoxins	Tannins	EP2904910	2015–02-05	Use of chestnut tannins extract and/or its fractions, alone or in mixtures with other polyphenols, as anti-oxidant, anti-microbial additive and to reduce nitrosamines and mycotoxins concentrations in food raw materials and in food for humans and for animals.	Basic materials chemistry, food chemistry and pharmaceuticals	Gruppo Mauro Saviola
Rigid foams made of formaldehyde-free prorobinetidin/profisetinidin tannins	Tannins	EP2757126	2013–01-16	Manufacture of foams using tannins.	Macromolecular chemistry, polymers, other special machines	Centre National de La Recherche Scientifique and Universite de Lorraine
Anti-adhesive coatings based on condensed tannins	Tannins	EP3344706	2015–09-02	Anti-adhesive coating composition comprising tannin type of composition for coatings.	Basic materials chemistry, macromolecular chemistry and polymersSurface technology	SEB
Green synthesis of metal nanoparticles using plant polyphenols present in the form of hydrolysable tannins	Hydrolysable tannins	IN2308/CHE/2011	2011–07-06	Providing seed extract containing hydrolysed tannins in the form of polyphenols and combining the metal ion solution and the seed extract to produce metal nanoparticles.	Chemical engineering	Mandal DR Badal Kumar

Source: Orbit (2020).

(US8513374B2, 2013).

These information demonstrates that the phenolic compounds have great potential to be applied in the most diverse technological domains. Approaches of this nature are essential to stimulate the development of new inventions and thus establish their possible applications, in order to increase the demand for these compounds and thus make them industrially exploited.

7. Conclusion

Polyphenols are compounds with bioactive potential that can be found naturally in some foods. These compounds are important for improving health, as they show promising effects in the prevention of various diseases. The beneficial effects of these compounds on health depend on factors such as quantity and bioavailability after ingestion. It is worth mentioning that clinical studies must be carried out to determine margins of safe concentrations for the ingestion of these compounds, since when consumed in high doses, they can present toxic effects.

Due to their antioxidant effects, phenolic compounds can be used for food preservation and making bioactive packaging, as natural dyes, elaboration of hydrogels and nanocomplexes, in addition to improving properties of starch such as gelatinization temperature, crystallization, viscosity and reduce retrogradation of this polysaccharide. Furthermore, these compounds have been applied in food chemistry, pharmacy, materials engineering, fine chemistry, as materials for the manufacture of semi-conductors, textile and special machines, demonstrating that these compounds are innovation hotspot in the most diverse technological domains.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Adami, R., Liparoti, S., Di Capua, A., Scognamiglio, M., & Reverchon, E. (2019). Production of PEA composite microparticles with polyvinylpyrrolidone and luteolin using Supercritical Assisted Atomization. *The Journal of Supercritical Fluids, 143*, 82–89. https://doi.org/10.1016/J.SUPFLU.2018.07.020.

Addepalli, V., & Suryavanshi, S. V. (2018). Catechin attenuates diabetic autonomic neuropathy in streptozotocin induced diabetic rats. *Biomedicine & Pharmacotherapy, 108*, 1517–1523. https://doi.org/10.1016/J.BIOPHA.2018.09.179.

Agunloye, O. M., Oboh, G., Ademiluyi, A. O., Ademosun, A. O., Akindahunsi, A. A., Oyagbemi, A. A., ... Adedapo, A. A. (2019). Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: Mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Biomedicine & Pharmacotherapy, 109*, 450–458. https://doi.org/10.1016/J.BIOPHA.2018.10.044.

Ali, F., Rahul, Jyoti, S., Naz, F., Ashafaq, M., Shahid, M., & Siddique, Y. H. (2019). Therapeutic potential of luteolin in transgenic Drosophila model of Alzheimer's disease. *Neuroscience Letters, 692*, 90–99. https://doi.org/10.1016/J.NEULET.2018.10.053.

Bakoyiannis, I., Daskalopoulou, A., Pergialiotis, V., & Perrea, D. (2019). Phytochemicals and cognitive health: Are flavonoids doing the trick? *Biomedicine & Pharmacotherapy, 109*, 1488–1497. https://doi.org/10.1016/J.BIOPHA.2018.10.086.

Barauna, S. C., Magro, D. D., Brueckheimer, M. B., Maia, T. P., Sala, A. G. B. N., Döhler, A. W., ... Lima, D. D. (2018). Antioxidant and antidepressant-like effects of Eugenia catharinensis D. Legrand in an animal model of depression induced by corticosterone. *Metabolic Brain Disease, 33*, 1985–1994. https://doi.org/10.1007/s11011-018-0306-3.

Bener, M., Özyürek, M., Güçlü, K., & Apak, R. (2010). Polyphenolic contents of natural dyes produced from industrial plants assayed by HPLC and novel spectrophotometric methods. *Industrial Crops and Products, 32*(3), 499–506. https://doi.org/10.1016/j.indcrop.2010.06.020.

Bhandarkar, N. S., Brown, L., & Panchal, S. K. (2019). Chlorogenic acid attenuates high-carbohydrate, high-fat diet–induced cardiovascular, liver, and metabolic changes in rats. *Nutrition Research, 62*, 78–88. https://doi.org/10.1016/J.NUTRES.2018.11.002.

Bondonno, N. P., Lewis, J. R., Blekkenhorst, L. C., Bondonno, C. P., Shin, J. H., Croft, K. D., ... Hodgson, J. M. (2019). Association of flavonoids and flavonoid-rich foods with all-cause mortality: The Blue Mountains Eye Study. *Clinical Nutrition*. https://doi.org/10.1016/J.CLNU.2019.01.004.

Cano, A., Andres, M., Chiralt, A., & González-Martinez, C. (2020). Use of tannins to enhance the functional properties of protein based films. *Food Hydrocolloids, 100*, Article 105443. https://doi.org/10.1016/j.foodhyd.2019.105443.

Cao, Z., Huang, S., Dou, C., Xiang, Q., & Dong, S. (2018). Cyanidin suppresses autophagic activity regulating chondrocyte hypertrophic differentiation. *Journal of Cellular Physiology, 233*(3), 2332–2342. https://doi.org/10.1002/jcp.26105.

Carloni, P., Tiano, L., Padella, L., Bacchetti, T., Customu, C., Kay, A., & Damiani, E. (2013). Antioxidant activity of white, green and black tea obtained from the same tea cultivar. *Food Research International, 53*(2), 900–908. https://doi.org/10.1016/j.foodres.2012.07.057.

Cassidy, A. (2018). Berry anthocyanin intake and cardiovascular health. *Molecular Aspects of Medicine, 61*, 76–82. https://doi.org/10.1016/J.MAM.2017.05.002.

Castello, F., Costabile, G., Bresciani, L., Tassotti, M., Naviglio, D., Luongo, D., ... Mena, P. (2018). Bioavailability and pharmacokinetic profile of grape pomace phenolic compounds in humans. *Archives of Biochemistry and Biophysics, 646*, 1–9. https://doi.org/10.1016/j.abb.2018.03.021.

Catroux, P., Cotovio, J., & Duche, D. (2001). ES2225548T3.

Chatham, L. A., Howard, J. E., & Juvik, J. A. (2020). A natural colorant system from corn: Flavone-anthocyanin copigmentation for altered hues and improved shelf life. *Food Chemistry, 310*, Article 125734. https://doi.org/10.1016/j.foodchem.2019.125734.

Chen, G.-L., Fan, M.-X., Wu, J.-L., Li, N., & Guo, M.-Q. (2019). Antioxidant and anti-inflammatory properties of flavonoids from *Lotus plumule*. *Food Chemistry, 277*, 706–712. https://doi.org/10.1016/J.FOODCHEM.2018.11.040.

Chen, J., Zhu, Y., Zhang, W., Peng, X., Zhou, J., Li, F., ... Yu, X. (2018). Delphinidin induced protective autophagy via mTOR pathway suppression and AMPK pathway activation in HER-2 positive breast cancer cells. *BMC Cancer, 18*(1), 342. https://doi.org/10.1186/s12885-018-4231-y.

Chen, L., Gnanaraj, C., Arulselvan, P., El-Seedi, H., & Teng, H. (2019). A review on advanced microencapsulation technology to enhance bioavailability of phenolic compounds: Based on its activity in the treatment of Type 2 Diabetes. *Trends in Food Science and Technology.*. https://doi.org/10.1016/j.tifs.2018.11.026 Elsevier Ltd.

Chen, T., Liu, A. B., Sun, S., Ajami, N. J., Ross, M. C., Wang, H., ... Yang, C. S. (2019). Green Tea Polyphenols Modify the Gut Microbiome in *db/db* Mice as Co-Abundance Groups Correlating with the Blood Glucose Lowering Effect. *Molecular Nutrition & Food Research, 63*(8), 1–10. https://doi.org/10.1002/mnfr.201801064.

Chen, X., McClements, D. J., Zhu, Y., Chen, Y., Zou, L., Liu, W., ... Liu, C. (2018). Enhancement of the solubility, stability and bioaccessibility of quercetin using protein-based excipient emulsions. *Food Research International, 114*, 30–37. https://doi.org/10.1016/J.FOODRES.2018.07.062.

Cladis, D. P., Li, S., Reddivari, L., Cox, A., Ferruzzi, M. G., & Weaver, C. M. (2020). A 90 day oral toxicity study of blueberry polyphenols in ovariectomized sprague-dawley rats. *Food and Chemical Toxicology, 139*, Article 111254. https://doi.org/10.1016/j.fct.2020.111254.

Code of Federal Regulations (2016). *Title 21, Part 73-Listing of Color Additives Exempt.* From Certification.

Czubinski, J., Wroblewska, K., Czyzniejewski, M., Górnaś, P., Kachlicki, P., & Siger, A. (2019). Bioaccessibility of defatted lupin seed phenolic compounds in a standardized static *in vitro* digestion system. *Food Research International, 116*, 1126–1134. https://doi.org/10.1016/j.foodres.2018.09.057.

Dasgupta, F. (2013). US8513374B2.

Decker, K. J. (2018). Can Polyphenols Serve as Prebiotics?

de Araújo, F. F. de, Neri-Numa, I. A., Farias, D. de P., Cunha, G. R. M. C. da, & Pastore, G. M. (2019). Wild Brazilian species of Eugenia genera (Myrtaceae) as an innovation hotspot for food and pharmacological purposes. *Food Research International*. https://doi.org/10.1016/j.foodres.2019.03.018 Elsevier Ltd.

Del Bo', C., Marino, M., Riso, P., Møller, P., & Porrini, M. (2019). Anthocyanins and metabolites resolve TNF-α-mediated production of E-selectin and adhesion of monocytes to endothelial cells. *Chemico-Biological Interactions, 300*, 49–55. https://doi.org/10.1016/J.CBI.2019.01.002.

Ding, X., Jian, T., Wu, Y., Zuo, Y., Li, J., Lv, H., ... Chen, J. (2019). Ellagic acid ameliorates oxidative stress and insulin resistance in high glucose-treated HepG2 cells via miR-223/keap1-Nrf2 pathway. *Biomedicine & Pharmacotherapy, 110*, 85–94. https://doi.org/10.1016/J.BIOPHA.2018.11.018.

Du, J., Yao, F., Zhang, M., Khalifa, I., Li, K., & Li, C. (2019). Effect of persimmon tannin on the physicochemical properties of maize starch with different amylose/amylopectin ratios. *International Journal of Biological Macromolecules, 132*, 1193–1199. https://doi.org/10.1016/j.ijbiomac.2019.04.046.

Ebrahimi, I., & Parvinzadeh Gashti, M. (2016). Extraction of polyphenolic dyes from henna, pomegranate rind, and *Pterocarya fraxinifolia* for nylon 6 dyeing. *Coloration Technology, 132*(2), 162–176. https://doi.org/10.1111/cote.12204.

Edwards, M., Czank, C., Woodward, G. M., Cassidy, A., & Kay, C. D. (2015). Phenolic metabolites of anthocyanins modulate mechanisms of endothelial function. *Journal of Agricultural and Food Chemistry, 63*(9), 2423–2431. https://doi.org/10.1021/jf5041993.

European Commission and the Council (2008). Regulation (EC) No. 1333/2008 – regulation on food additives, annex I, point 2. *Official Journal of the European Union, 16*.
Fan, S., Gao, X., Chen, P., & Li, X. (2018). Myricetin ameliorates glucocorticoid-induced osteoporosis through the ERK signaling pathway. *Life Sciences, 207*, 205–211. https://doi.org/10.1016/J.LFS.2018.06.006.
Fang, Z., Lin, D., Warner, R. D., & Ha, M. (2018). Effect of gallic acid/chitosan coating on fresh pork quality in modified atmosphere packaging. *Food Chemistry, 260*, 90–96. https://doi.org/10.1016/J.FOODCHEM.2018.04.005.
Farias, D. de P., de Araújo, F. F., Neri-Numa, I. A., & Pastore, G. M. (2019). Prebiotics: Trends in food, health and technological applications. *Trends in Food Science and Technology*. https://doi.org/10.1016/j.tifs.2019.09.004 Elsevier Ltd.
Farias, D. de P., Neri-Numa, I. A., de Araújo, F. F., & Pastore, G. M. (2020). A critical review of some fruit trees from the Myrtaceae family as promising sources for food applications with functional claims. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2019.125630 Elsevier Ltd.
Farrag, Y., Ide, W., Montero, B., Rico, M., Rodríguez-Llamazares, S., Barral, L., & Bouza, R. (2018). Starch films loaded with donut-shaped starch-quercetin microparticles: Characterization and release kinetics. *International Journal of Biological Macromolecules, 118*, 2201–2207. https://doi.org/10.1016/J.IJBIOMAC.2018.07.087.
Fei, J., Liang, B., Jiang, C., Ni, H., & Wang, L. (2019). Luteolin inhibits IL-1β-induced inflammation in rat chondrocytes and attenuates osteoarthritis progression in a rat model. *Biomedicine & Pharmacotherapy, 109*, 1586–1592. https://doi.org/10.1016/J.BIOPHA.2018.09.161.
Ferreira, L. P., da Cunha, B. P., Kuster, R. M., Pinto, J. C., Souza, M. N., & de Souza, F. G. (2017). Synthesis and chemical modification of poly (butylene succinate) with rutin useful to the release of silybin. *Industrial Crops and Products, 97*, 599–611. https://doi.org/10.1016/J.INDCROP.2016.12.064.
Fikry, E. M., Gad, A. M., Eid, A. H., & Arab, H. H. (2019). Caffeic acid and ellagic acid ameliorate adjuvant-induced arthritis in rats via targeting inflammatory signals, chitinase-3-like protein-1 and angiogenesis. *Biomedicine and Pharmacotherapy, 110*, 878–886. https://doi.org/10.1016/j.biopha.2018.12.041.
Frauches, N. S., Amaral, T. O. do, Largueza, C. B. D., & Teodoro, A. J. (2016). Brazilian Myrtaceae fruits: A review of anticancer proprieties. *British Journal of Pharmaceutical Research, 12*(1), 1–15. https://doi.org/10.9734/BJPR/2016/26782.
Ganeshpurkar, A., & Saluja, A. K. (2018). Protective effect of catechin on humoral and cell mediated immunity in rat model. *International Immunopharmacology, 54*, 261–266. https://doi.org/10.1016/J.INTIMP.2017.11.022.
Garrido, E. M. P. J., Cerqueira, A. S., Chavarria, D., Silva, T., Borges, F., & Garrido, J. M. P. J. (2018). Microencapsulation of caffeic acid phenethyl ester and caffeic acid phenethyl amide by inclusion in hydroxypropyl-β-cyclodextrin. *Food Chemistry, 254*, 260–265. https://doi.org/10.1016/J.FOODCHEM.2018.02.007.
Ge, J., Yue, P., Chi, J., Liang, J., & Gao, X. (2018). Formation and stability of anthocyanins-loaded nanocomplexes prepared with chitosan hydrochloride and carboxymethyl chitosan. *Food Hydrocolloids, 74*, 23–31. https://doi.org/10.1016/j.foodhyd.2017.07.029.
Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., … Reid, G. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology, 14*(8), 491. https://doi.org/10.1038/nrgastro.2017.75.
Gómez-Caravaca, A. M., Verardo, V., Segura-Carreteno, A., Fernández-Gutiérrez, A., & Caboni, M. F. (2014). Phenolic compounds and saponins in plants grown under different irrigation regimes. In R. R. Watson (Ed.), Polyphenols in Plants: Isolation, purification and extract preparation (1st ed., pp. 37–48). Tucson, AZ, USA: Elsevier.
Gowd, V., Karim, N., Shishir, M. R. I., Xie, L., & Chen, W. (2019). Dietary polyphenols to combat the metabolic diseases via altering gut microbiota. *Trends in Food Science and Technology, 93*, 81–93. https://doi.org/10.1016/j.tifs.2019.09.005 Elsevier Ltd.
Gu, R., Zhang, M., Meng, H., Xu, D., & Xie, Y. (2018). Gallic acid targets acute myeloid leukemia via Akt/mTOR-dependent mitochondrial respiration inhibition. *Biomedicine & Pharmacotherapy, 105*, 491–497. https://doi.org/10.1016/J.BIOPHA.2018.05.158.
Gunm, L. (2018). Gut-boosting potential: Diana Food explores prebiotic role of polyphenols. Retrieved May 20, 2020, from https://www.nutritioninsight.com/news/gut-boosting-potential-diana-food-explores-prebiotic-role-of-polyphenols.html.
Heleno, S. A., Martins, A., João, M., Queiroz, R. P., & Ferreira, I. C. F. R. (2015). Bioactivity of phenolic acids: Metabolites versus parent compounds: A review. *Food Chemistry, 173*, 501–513. https://doi.org/10.1016/j.foodchem.2014.10.057.
Huang, B., Liu, J., Ma, D., Chen, G., Wang, W., & Fu, S. (2018). Myricetin prevents dopaminergic neurons from undergoing neuroinflammation-mediated degeneration in a lipopolysaccharide-induced Parkinson's disease model. *Journal of Functional Foods, 45*, 452–461. https://doi.org/10.1016/J.JFF.2018.04.018.
Hytti, M., Szabó, D., Piippo, N., Korhonen, E., Honkakoski, P., Kaarniranta, K., … Kauppinen, A. (2017). Two dietary polyphenols, fisetin and luteolin, reduce inflammation but augment DNA damage-induced toxicity in human RPE cells. *Journal of Nutritional Biochemistry, 42*, 37–42. https://doi.org/10.1016/j.jnutbio.2016.12.014.
Iglesias-Carres, L., Mas-Capdevila, A., Bravo, F. I., Aragonès, G., Arola-Arnal, A., & Muguerza, B. (2019). A comparative study on the bioavailability of phenolic compounds from organic and nonorganic red grapes. *Food Chemistry, 299*, Article 125092. https://doi.org/10.1016/j.foodchem.2019.125092.
Jiang, J., Zhang, Z., Zhao, J., & Liu, Y. (2018). The effect of non-covalent interaction of chlorogenic acid with whey protein and casein on physicochemical and radical-scavenging activity of in vitro protein digests. *Food Chemistry, 268*, 334–341. https://doi.org/10.1016/J.FOODCHEM.2018.06.015.
Jiang, L., Wang, Y., Wen, S., Zhou, Y., Ma, J., Chen, S., & Jerrams, S. (2020). Fabrication of dielectric elastomers with improved electromechanical properties using silicone rubber and walnut polyphenols modified dielectric particles. *Materials and Design, 192*, Article 108674. https://doi.org/10.1016/j.matdes.2020.108674.
Jiao, X., Wang, Y., Lin, Y., Lang, Y., Li, E., Zhang, X., … Li, B. (2019). Blueberry polyphenols extract as a potential prebiotic with anti-obesity effects on C57BL/6 J mice by modulating the gut microbiota. *Journal of Nutritional Biochemistry, 64*, 88–100. https://doi.org/10.1016/j.jnutbio.2018.07.008.
Kaewprachu, P., Amara, C. Ben, Oulahal, N., Gharsallaoui, A., Joly, C., Tongdeesoontorn, W., … Degraeve, P. (2018). Gelatin films with nisin and catechin for minced pork preservation. *Food Packaging and Shelf Life, 18*, 173–183. https://doi.org/10.1016/J.FPSL.2018.10.011.
Kfoury, M., Geagea, C., Ruellan, S., Greige-Gerges, H., & Fourmentin, S. (2019). Effect of cyclodextrin and cosolvent on the solubility and antioxidant activity of caffeic acid. *Food Chemistry, 278*, 163–169. https://doi.org/10.1016/J.FOODCHEM.2018.11.055.
Khoo, H. E., Azlan, A., Tang, S. T., & Lim, S. M. (2017). Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food & Nutrition Research, 61*(1), 1361779. https://doi.org/10.1080/16546628.2017.1361779.
Kumari, M., & Jain, S. (2012). Tannin: An antinutrient with positive effect to manage diabetes. *Research Journal of Recent Sciences, 1*(12), 1–4.
Lakshmi, C. (2014). Food Coloring: The natural way. *Research*. Retrieved from www.isca.me. *Journal of Chemical Sciences, 4*(2), 87–96.
Landete, J. M. (2011). June 1). Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Research International. Elsevier.*. https://doi.org/10.1016/j.foodres.2011.04.027.
Li, P., Sirviö, J. A., Haapala, A., Khakalo, A., & Liimatainen, H. (2019). Anti-oxidative and UV-absorbing biohybrid film of cellulose nanofibrils and tannin extract. *Food Hydrocolloids, 92*, 208–217. https://doi.org/10.1016/j.foodhyd.2019.02.002.
Li, X., Liu, Y., Yu, Y., Chen, W., Liu, Y., & Yu, H. (2019). Nanoformulations of quercetin and cellulose nanofibers as healthcare supplements with sustained antioxidant activity. *Carbohydrate Polymers, 207*, 160–168. https://doi.org/10.1016/J.CARBPOL.2018.11.084.
Links, M. R., Taylor, J., Kruger, M. C., & Taylor, J. R. N. (2015). Sorghum condensed tannins encapsulated in kafirin microparticles as a nutraceutical for inhibition of amylases during digestion to attenuate hyperglycaemia. *Journal of Functional Foods, 12*, 55–63. https://doi.org/10.1016/j.jff.2014.11.003.
Liu, B., Luo, Z., Si, S., Zhou, X., Pan, C., & Wang, L. (2017). A photostable triphenylamine-based flavonoid dye: Solvatochromism, aggregation-induced emission enhancement, fabrication of organic nanodots, and cell imaging applications. *Dyes and Pigments, 142*, 32–38. https://doi.org/10.1016/J.DYEPIG.2017.03.023.
Liu, J., Wang, X., Yong, H., Kan, J., & Jin, C. (2018). Recent advances in flavonoid-grafted polysaccharides: Synthesis, structural characterization, bioactivities and potential applications. *International Journal of Biological Macromolecules, 116*, 1011–1025. https://doi.org/10.1016/J.IJBIOMAC.2018.05.149.
Liu, J., Wang, X., Yong, H., Kan, J., Zhang, N., & Jin, C. (2018). Preparation, characterization, digestibility and antioxidant activity of quercetin grafted *Cynanchum auriculatum* starch. *International Journal of Biological Macromolecules, 114*, 130–136. https://doi.org/10.1016/J.IJBIOMAC.2018.03.101.
Loi, M., Quintieri, L., Fanelli, F., Caputo, L., & Mulè, G. (2018). Application of a recombinant laccase-chlorogenic acid system in protein crosslink and antioxidant properties of the curd. *Food Research International, 106*, 763–770. https://doi.org/10.1016/j.foodres.2018.01.050.
López, C. J., Caleja, C., Prieto, M. A., Sokovic, M., Calhelha, R. C., Barros, L., & Ferreira, I. C. F. R. (2019). Stability of a cyanidin-3-*O*-glucoside extract obtained from *Arbutus unedo* L. and incorporation into wafers for colouring purposes. *Food Chemistry, 275*, 426–438. https://doi.org/10.1016/J.FOODCHEM.2018.09.099.
Lourenço Neto, M., Agra, K. L., Suassuna Filho, J., & Jorge, F. E. (2018). TDDFT calculations and photoacoustic spectroscopy experiments used to identify phenolic acid functional biomolecules in Brazilian tropical fruits *in natura*. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 193*, 249–257. https://doi.org/10.1016/J.SAA.2017.12.036.
Lukić, I., Radeka, S., Budić-Leto, I., Bubola, M., & Vrhovsek, U. (2019). Targeted UPLC-QqQ-MS/MS profiling of phenolic compounds for differentiation of monovarietal wines and corroboration of particular varietal typicity concepts. *Food Chemistry, 300*, Article 125251. https://doi.org/10.1016/j.foodchem.2019.125251.
Mahobiya, A., Singh, T. U., Rungsung, S., Kumar, T., Chandrasekaran, G., Parida, S., & Kumar, D. (2018). Kaempferol-induces vasorelaxation via endothelium-independent pathways in rat isolated pulmonary artery. *Pharmacological Reports, 70*(5), 863–874. https://doi.org/10.1016/J.PHAREP.2018.03.006.
Mazed, M. A., & Mazed, S. (2009). US8017147B2.
Mendoza, J., Pina, F., Basílio, N., Guimarães, M., de Freitas, V., & Cruz, L. (2018). Extending the stability of red and blue colors of malvidin-3-glucoside-lipophilic derivatives in the presence of SDS micelles. *Dyes and Pigments, 151*, 321–326. https://doi.org/10.1016/J.DYEPIG.2018.01.007.
Mocciaro, G., Bresciani, L., Tsiountsioura, M., Martini, D., Mena, P., Charron, M., … Ray, S. (2019). Dietary absorption profile, bioavailability of (poly)phenolic compounds, and acute modulation of vascular/endothelial function by hazelnut skin drink. *Journal of Functional Foods, 63*, Article 103576. https://doi.org/10.1016/j.jff.2019.103576.
Molino, S., Fernández-Miyakawa, M., Giovando, S., & Rufián-Henares, J.Á. (2018). Study of antioxidant capacity and metabolization of quebracho and chestnut tannins through *in vitro* gastrointestinal digestion-fermentation. *Journal of Functional Foods, 49*, 188–195. https://doi.org/10.1016/j.jff.2018.07.056.
Muñoz, A. E., Hernández, S. S., Tolosa, A. R., Burillo, S. P., & Olalla-Herrera, M. (2020). Evaluation of differences in the antioxidant capacity and phenolic compounds of green and roasted coffee and their relationship with sensory properties. *LWT, 128*, Article 109457. https://doi.org/10.1016/j.lwt.2020.109457.

Murakami, A. (2014). Dose-dependent functionality and toxicity of green tea polyphenols in experimental rodents. *Archives of Biochemistry and Biophysics, 557*, 3–10. https://doi.org/10.1016/j.abb.2014.04.018.

Nehir El, S., & Simsek, S. (2012). Food technological applications for optimal nutrition: An overview of opportunities for the food industry. *Comprehensive Reviews in Food Science and Food Safety, 11*(1), 2–12. https://doi.org/10.1111/j.1541-4337.2011.00167.x.

Netke, S., Niedzwiecki, A., & Rath, M. (2008). AU2003235762B2.

Oracz, J., Nebesny, E., & Żyżelewicz, D. (2019). Identification and quantification of free and bound phenolic compounds contained in the high-molecular weight melanoidin fractions derived from two different types of cocoa beans by UHPLC-DAD-ESI-HR-MSn. *Food Research International, 115*, 135–149. https://doi.org/10.1016/j.foodres.2018.08.028.

Orbit. (2020). Questel new portal for patent, design, and legal professionals looking for a comprehensive coverage and powerful tool. https://www.orbit.com.

Park, S., Lim, W., Bazer, F. W., Whang, K.-Y., & Song, G. (2019). Quercetin inhibits proliferation of endometriosis regulating cyclin D1 and its target microRNAs *in vitro* and *in vivo*. *The Journal of Nutritional Biochemistry, 63*, 87–100. https://doi.org/10.1016/J.JNUTBIO.2018.09.024.

Park, Y. S., Cvikrová, M., Martincová, O., Ham, K. S., Kang, S. G., Park, Y. K., Namiesnik, J., Rombolà, A. D., Jastrzebski, Z., & Gorinstein, S. (2015). *In vitro* antioxidative and binding properties of phenolics in traditional, citrus and exotic fruits. *Food Research International, 74*, 37–47. https://doi.org/10.1016/j.foodres.2015.04.021.

Phan, K., Van Den Broeck, E., Van Speybroeck, V., De Clerck, K., Raes, K., & De Meester, S. (2020). The potential of anthocyanins from blueberries as a natural dye for cotton: A combined experimental and theoretical study. *Dyes and Pigments, 176*, Article 108180. https://doi.org/10.1016/j.dyepig.2019.108180.

Rashid, S., Idris-Khodja, N., Auger, C., Kevers, C., Pincemail, J., Alhosin, M., ... Schini-Kerth, V. B. (2018). Polyphenol-rich blackcurrant juice prevents endothelial dysfunction in the mesenteric artery of cirrhotic rats with portal hypertension: Role of oxidative stress and the angiotensin system. *Journal of Medicinal Food, 21*(4), 390–399. https://doi.org/10.1089/jmf.2017.0078.

Rodriguez-Amaya, D. B. (2019). Update on natural food pigments - A mini-review on carotenoids, anthocyanins, and betalains. *Food Research International, 124*, 200–205. https://doi.org/10.1016/j.foodres.2018.05.028.

Rosa, L. A. de la, Moreno-Escamilla, J. O., Rodrigo-Garcia, J., & Alvarez-Parrilla, E. (2019). Phenolic compounds. In E. M. Yahia, & A. Carrilo-López (Eds.). *Postharvest Physiology and Biochemistry of Fruits and Vegetables* (pp. 253–271). Woodhead Publishing.

Rui, L., Xie, M., Hu, B., Zhou, L., Saeeduddin, M., & Zeng, X. (2017). Enhanced solubility and antioxidant activity of chlorogenic acid-chitosan conjugates due to the conjugation of chitosan with chlorogenic acid. *Carbohydrate Polymers, 170*, 206–216. https://doi.org/10.1016/J.CARBPOL.2017.04.076.

Sanchez, M. B., Miranda-Perez, E., Verjan, J. C. G., Barrera, M. de L. A. F., Perez-Ramos, J., & Alarcon-Aguilar, F. J. (2017). Potential of the chlorogenic acid as multitarget agent: Insulin-secretagogue and PPAR α/γ dual agonist. *Biomedicine & Pharmacotherapy, 94*, 169–175. https://doi.org/10.1016/J.BIOPHA.2017.07.086.

Santana, Á. L., & Macedo, G. A. (2018). August 1). Health and technological aspects of methylxanthines and polyphenols from guarana: A review. *Journal of Functional Foods*. https://doi.org/10.1016/j.jff.2018.05.048 Elsevier Ltd.

Santos, S. D. los, Palma-Flores, C., Zentella-Dehesa, A., Canto, P., & Coral-Vázquez, R. M. (2018). (−)-Epicatechin inhibits development of dilated cardiomyopathy in δ sarcoglycan null mouse. *Nutrition, Metabolism and Cardiovascular Diseases, 28*(11), 1188–1195. https://doi.org/10.1016/J.NUMECD.2018.06.019.

Saulite, L., Jekabsons, K., Klavins, M., Muceniece, R., & Riekstina, U. (2019). Effects of malvidin, cyanidin and delphinidin on human adipose mesenchymal stem cell differentiation into adipocytes, chondrocytes and osteocytes. *Phytomedicine, 53*, 86–95. https://doi.org/10.1016/J.PHYMED.2018.09.029.

Sganzerla, W. G., Rosa, G. B., Ferreira, A. L. A., da Rosa, C. G., Beling, P. C., Xavier, L. O., ... de Lima Veeck, A. P. (2020). Bioactive food packaging based on starch, citric pectin and functionalized with *Acca sellowiana* waste by-product: Characterization and application in the postharvest conservation of apple. *International Journal of Biological Macromolecules, 147*, 295–303. https://doi.org/10.1016/j.ijbiomac.2020.01.074.

Sharma, D., Gondaliya, P., Tiwari, V., & Kalia, K. (2019). Kaempferol attenuates diabetic nephropathy by inhibiting RhoA/Rho-kinase mediated inflammatory signalling. *Biomedicine & Pharmacotherapy, 109*, 1610–1619. https://doi.org/10.1016/J.BIOPHA.2018.10.195.

Shi, J., Wang, Y., Wei, H., Hu, J., & Gao, M. T. (2020). Structure analysis of condensed tannin from rice straw and its inhibitory effect on *Staphylococcus aureus*. *Industrial Crops and Products, 145*, Article 112130. https://doi.org/10.1016/j.indcrop.2020.112130.

Shirmohammadli, Y., Efhamisisi, D., & Pizzi, A. (2018). Tannins as a sustainable raw material for green chemistry: A review. *Industrial Crops and Products*. https://doi.org/10.1016/j.indcrop.2018.10.034 Elsevier B.V.

Singh, S., Singh, D. K., Meena, A., Dubey, V., Masood, N., & Luqman, S. (2019). Rutin protects t-butyl hydroperoxide-induced oxidative impairment via modulating the Nrf2 and iNOS activity. *Phytomedicine, 55*, 92–104. https://doi.org/10.1016/J.PHYMED.2018.07.009.

Skrovankova, S., Sumczynski, D., Mlcek, J., Jurikova, T., Sochor, J., Skrovankova, S., ... Sochor, J. (2015). Bioactive compounds and antioxidant activity in different types of berries. *International Journal of Molecular Sciences, 16*(10), 24673–24706. https://doi.org/10.3390/ijms161024673.

Steed, A. L., Christophi, G. P., Kaiko, G. E., Sun, L., Goodwin, V. M., Jain, U., ... Stappenbeck, T. S. (2017). The microbial metabolite desaminotyrosine protects from influenza through type I interferon. *Science (New York, N.Y.), 357*(6350), 498–502. https://doi.org/10.1126/science.aam5336.

Thilavech, T., Abeywardena, M. Y., Dallimore, J., Adams, M., & Adisakwattana, S. (2018). Cyanidin-3-rutinoside alleviates methylglyoxal-induced cardiovascular abnormalities in the rat. *Journal of Functional Foods, 49*, 258–266. https://doi.org/10.1016/J.JFF.2018.08.034.

Uranga, J., Etxabide, A., Guerrero, P., & de la Caba, K. (2018). Development of active fish gelatin films with anthocyanins by compression molding. *Food Hydrocolloids, 84*, 313–320. https://doi.org/10.1016/J.FOODHYD.2018.06.018.

Urbatzka, R., Freitas, S., Palmeira, A., Almeida, T., Moreira, J., Azevedo, C., ... Vasconcelos, V. (2018). Lipid reducing activity and toxicity profiles of a library of polyphenol derivatives. *European Journal of Medicinal Chemistry, 151*, 272–284. https://doi.org/10.1016/j.ejmech.2018.03.036.

Vilela, C., Pinto, R. J. B., Coelho, J., Domingues, M. R. M., Daina, S., Sadocco, P., ... Freire, C. S. R. (2017). Bioactive chitosan/ellagic acid films with UV-light protection for active food packaging. *Food Hydrocolloids, 73*, 120–128. https://doi.org/10.1016/J.FOODHYD.2017.06.037.

Vinha, A. F., Rodrigues, F., Nunes, M. A., & Oliveira, M. B. P. P. (2018). Natural pigments and colorants in foods and beverages. *Polyphenols: Properties, Recovery, and Applications* (pp. 363–391). Elsevier. https://doi.org/10.1016/B978-0-12-813572-3.00011-7.

Vuolo, M. M., Lima, V. S., & Maróstica Junior, M. R. (2019). *Phenolic compounds: Structure, classification, and antioxidant power. In Bioactive Compounds: Health Benefits and Potencial Applications.* Woodhead Publishing33–50.

Xing, J., Yu, Z., Zhang, X., Li, W., Gao, D., Wang, J., ... Wang, W. (2019). Epicatechin alleviates inflammation in lipopolysaccharide-induced acute lung injury in mice by inhibiting the p38 MAPK signaling pathway. *International Immunopharmacology, 66*, 146–153. https://doi.org/10.1016/J.INTIMP.2018.11.016.

Yang, H., Wang, C., Zhang, L., Lv, J., & Ni, H. (2019). Rutin alleviates hypoxia/reoxygenation-induced injury in myocardial cells by up-regulating SIRT1 expression. *Chemico-Biological Interactions, 297*, 44–49. https://doi.org/10.1016/J.CBI.2018.10.016.

Yu, M., Chen, X., Liu, J., Ma, Q., Zhuo, Z., Chen, H., ... Hou, S.-T. (2019). Gallic acid disruption of Aβ1–42 aggregation rescues cognitive decline of APP/PS1 double transgenic mouse. *Neurobiology of Disease, 124*, 67–80. https://doi.org/10.1016/J.NBD.2018.11.009.

Zaitone, S. A., Ahmed, E., Elsherbiny, N. M., Mehanna, E. T., El-Kherbetawy, M. K., ElSayed, M. H., ... Moustafa, Y. M. (2019). Caffeic acid improves locomotor activity and lessens inflammatory burden in a mouse model of rotenone-induced nigral neurodegeneration: Relevance to Parkinson's disease therapy. *Pharmacological Reports, 71*(1), 32–41. https://doi.org/10.1016/J.PHAREP.2018.08.004.

Zhang, J., Zou, X., Zhai, X., Huang, X., Jiang, C., & Holmes, M. (2019). Preparation of an intelligent pH film based on biodegradable polymers and roselle anthocyanins for monitoring pork freshness. *Food Chemistry, 272*, 306–312. https://doi.org/10.1016/J.FOODCHEM.2018.08.041.

Zhang, X.-K., He, F., Zhang, B., Reeves, M. J., Liu, Y., Zhao, X., & Duan, C.-Q. (2018). The effect of prefermentative addition of gallic acid and ellagic acid on the red wine color, copigmentation and phenolic profiles during wine aging. *Food Research International, 106*, 568–579. https://doi.org/10.1016/J.FOODRES.2017.12.054.

Zhao, Y., & Saldaña, M. D. A. (2019). Use of potato by-products and gallic acid for development of bioactive film packaging by subcritical water technology. *The Journal of Supercritical Fluids, 143*, 97–106. https://doi.org/10.1016/J.SUPFLU.2018.07.025.

Zheleva-Dimitrova, D., Simeonova, R., Gevrenova, R., Savov, Y., Balabanova, V., Nasar-Eddin, G., ... Danchev, N. (2019). *In vivo* toxicity assessment of *Clinopodium vulgare* L. water extract characterized by UHPLC-HRMS. *Food and Chemical Toxicology, 134*, Article 110841. https://doi.org/10.1016/j.fct.2019.110841.

Zhou, B., Li, Q., Wang, J., Chen, P., & Jiang, S. (2019). Ellagic acid attenuates streptozocin induced diabetic nephropathy via the regulation of oxidative stress and inflammatory signaling. *Food and Chemical Toxicology, 123*, 16–27. https://doi.org/10.1016/J.FCT.2018.10.036.

Zhu, L., Gu, P. Q., & Shen, H. (2019). Gallic acid improved inflammation via NF-κB pathway in TNBS-induced ulcerative colitis. *International Immunopharmacology, 67*, 129–137. https://doi.org/10.1016/j.intimp.2018.11.049.

Zou, B., Nie, R., Zeng, J., Ge, Z., Xu, Z., & Li, C. (2014). Persimmon tannin alleviates hepatic steatosis in L02 cells by targeting miR-122 and miR-33b and its effects closely associated with the A type ECG dimer and EGCG dimer structural units. *Journal of Functional Foods, 11*(C), 330–341. https://doi.org/10.1016/j.jff.2014.10.016.

(2014). KR20150143698A.

宮泽利男浅井泰贵山口弘俊上杉高志村西修一. (2014). CN102481004B.