Polyphenols in foods: Classification, methods of identification, and nutritional aspects in human health

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Abstract

Polyphenols widely exists in various foods, including main crops, fruits, beverages and some wines. Famous representatives of polyphenols, such as resveratrol in red wine, (−)-epigallocatechin gallate in green tea, chlorogenic acid in coffee, anthocyanins in colored fruits, procyanidins in grape seed have become hot research topics in food science and nutrition. There have been thousands of papers on the biochemistry, chemistry, nutritional values and population-based investigations of dietary polyphenols. In this chapter, we reviewed the published articles and database of dietary polyphenols to draw a profile for the classification, structural identification, and biological activities mainly based on enzymes, cell bioassay and animal models, as well as the population-based investigation results. The typical compound and its health benefits for each category of polyphenols was also introduced. The identification of dietary polyphenols could be solved by combined spectroscopy methods, of which the liquid chromatography tandem mass spectrometry is highlighted to greatly increase the efficiency

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on structural identification. Although the population-based investigation showed some controversial results for health benefits, the multi-functions of dietary polyphenols on preventing metabolic syndromes, various cancers and neurodegenerative disease have attracted much attention.

Abbreviations

ACC	acetyl-CoA carboxylase
ACE	angiotensin-converting enzyme
AMPK	AMP-activated protein kinase
CcO	cytochrome *c* oxidase
CD	circular dichroic
EC	(−)-epicatechin
ECG	(−)-epicatechin gallate
EGC	(−)-epigallocatechin
EGCG	(−)-epigallocatechin gallate
HDL-C	high density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
IFN-γ	interferon gamma
IUPAC	International Union of Pure and Applied Chemistry
LC-MS	liquid chromatography tandem mass spectrometry
LDL-C	low density lipoprotein cholesterol
NMR	nuclear magnetic resonance
PPAR	peroxisome proliferator-activated receptors

1. Introduction

Polyphenols is a type of functional ingredients in foods, beverages and wines. Using "polyphenols" as keyword, we can see the tendency of developing of food polyphenols worldwide as shown in Fig. 1. The phenolic compounds are mainly structural components of cell walls, and most of them are toxins and antifeedants of plant defense, coloring ingredients of flowers and fruits, antioxidants of bark and seeds. They are mainly derived from phenylpropanoid and phenylpropanoid-acetate backbones. During the growth of plants, the secondary metabolism produces a large and diverse class of flavonoids and suberin to protect the plant from environmental stresses, such as UV irradiation and desiccation.

With the development of food science and technology, food polyphenols have gradually walked into the industrial production and health application. The basic theory of food polyphenols involves organic chemistry, nutrition, analytical chemistry and medicine. In this chapter, we

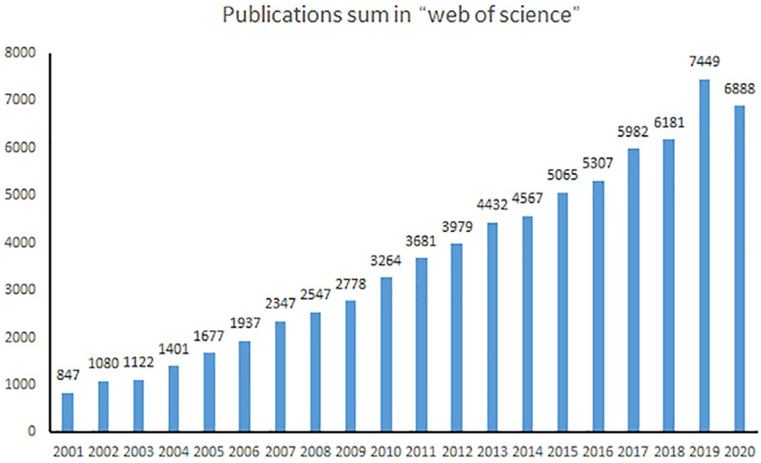

Fig. 1 The publication sum with the topic "polyphenol" in web of science.

mainly summarized and introduced the basis including classification, structural identification and health benefits of dietary polyphenols. The health benefits of dietary polyphenols have attracted much attention, because it is accessible by daily food intake. Thousands of papers have explored the biological activities of dietary polyphenols, like antioxidant, anti-inflammation, promoting apoptosis of tumor cells, estrogen-like action and neuroprotective effects. Based on the activities studies, some population-based studies including randomized, double-blind placebo-controlled clinical trial, cohort investigation, retrospective study and meta-analysis have been carried out to reveal the health benefits of dietary polyphenols.

2. Classification

Polyphenols are the critical secondary metabolites of many tea plants, apart from the primary metabolites such as carbohydrates, fatty acids and proteins. They usually do not provide the energy for human body, but possess various health benefits through many biological activities such as anti-oxidant and anti-inflammation. With the developing of polyphenols, the food polyphenols have garnered the most public interest because of their high presence in various food, including vegetable, fruits, seeds and beverages (Tylewicz, Nowacka, Martín-García, Wiktor, & Gómez Caravaca, 2018). Polyphenols have common structural characteristics, with at least one hydroxyl moiety, sometimes also with carboxyl moiety. Usually, food polyphenols are classified into hydroxybenzoic acids, hydroxycinnamic acids, flavonoids, stilbenes, lignans, flavonols, flavones, isoflavones, flavanones, anthocyanidins, flavanols, hydrolysable tannins and condensed tannins. Different from other natural products, polyphenols' structures are not complicated and usually have at least one hydroxyl moiety in the molecule.

So far, over 50,000 diverse polyphenols have been identified in plants. According to the regulation of IUPAC, one hydroxyl group on a benzene ring or other arene ring is defined as "phenols." It was also suggested that "polyphenols" was defined as plant secondary metabolites derived from the shikimate derived phenylpropanoid and/or the polyketide pathways. Among these polyphenol compounds, http://phenol-explorer.eu/foods reviewed almost all types of polyphenols (Neveu et al., 2010). In total, 501 polyphenols in various foods were reviewed. Basically, these polyphenols mainly contain 279 flavonoids, 108 phenolic acids, 10 stilbenes, 29 lignans, and 80 other polyphenols (Rothwell et al., 2012). If classified based on food types, most polyphenols were detected in fruit and fruit products, beverages, seeds and vegetables. Based on the chemical structures, flavonoids have 15-carbon skeletons, represented as the C6-C3-C6 system. Their skeletons are constructed by two benzene rings and a chain of three carbon atoms of their heterocyclic systems. Flavonoids could be further classified into anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavanols, flavanones, flavones, flavonols and isoflavonoids.

Usually, the flavonoids have different color because of their structural characteristics. For example, the anthocyanins often show the color of blue, red or violet, while flavones and flavonols present pale yellow. Other flavonoids including flavanols, isoflavones and flavanones are colorless. The spectrum information of these flavonoids are similar. The representative flavonoids aglycones are quercetin, kaempferol, myricetin and their glycosides. These compounds have been widely detected in onion, blueberry, clack currant, apple, black grape, tomato, and tea infusions.

Phenolic acids is also widely presented in berries, fruits and beverages. The phenolic acids could be divided into soluble and insoluble (bound form) types. The first type is low-molecular weight phenolic acids with water-soluble properties during processing and digestion. The phenolic acids can be condensed into insoluble high-molecular weight molecules with glucose, caffeic and quinic acids. The most common phenolic acid is hydroxycinnamic acids, including *p*-coumaric, caffeic, ferulic, and sinapic acids. The other usual phenolic acids is hydroxybenzoic acid, which could be

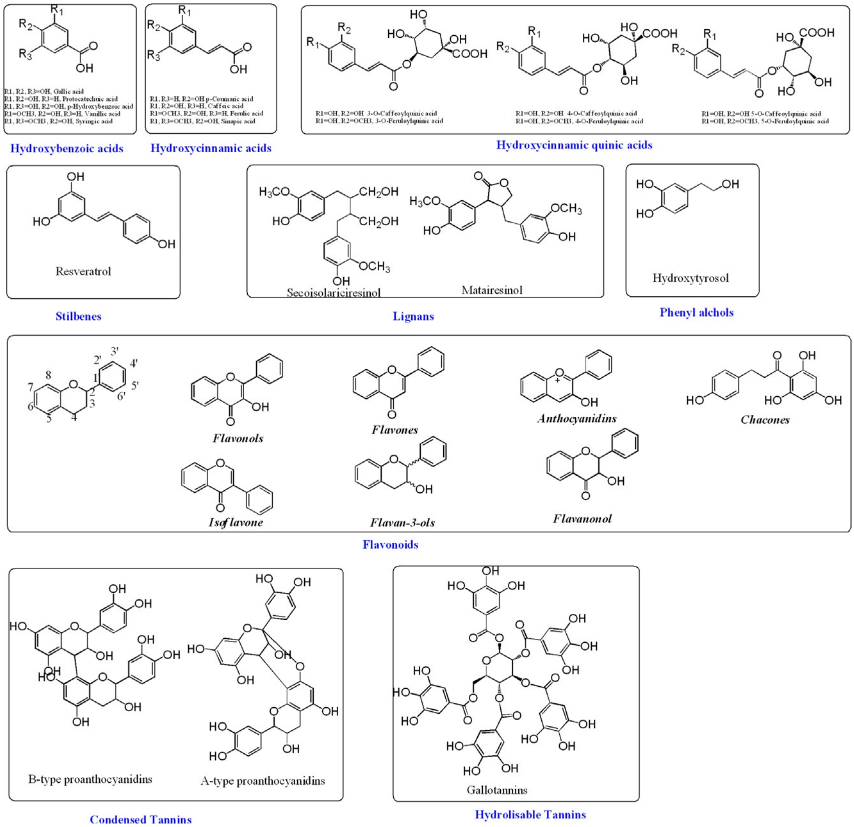

Fig. 2 The classification of dietary polyphenols based on chemical structures.

further named as p=hydroxybenzoic, protocatechuic, vanillic and syringic acids. Mattila et al. analyzed the content of phenolic acids in various plant-sourced foods. Chokeberry has the highest content of phenolic acids among all berries, of which dark plum and cherry are rich in caffeic acids (Mattila, Hellström, & Törrönen, 2006) (Fig. 2).

There are mainly three types of non-alcoholic beverages worldwide, tea, coffee and cocoa. In tea and cocoa, flavanols are very important polyphenols such as (+)-catechin, (−)-epicatechin, procyanidins dimer B2 and procyanidin trimer C1. In dark chocolate, the content of (+)-catechin is about 20 mg/100 g fresh weight, which is higher than that of tea. In the beverages of green tea and oolong tea, the typical flavanols are 2R, 3R-configuration flavanols, such as (−)-epigallocatechin gallate. For coffee, the typical polyphenols are hydroxycinnamic acids, including dicaffeoylquinic acid, mono-caffeoylquinic acid and geruloylquinic acid. The 5-caffeoylquinic acid, also named as neochlorogenic acid is also distributed in blueberry, apple, loquat, plum and sunflower seeds. Meanwhile, the typical flavanols epicatechin also abundantly exists in wine, raw broad ben seed and raw broad ben pod.

Flavan-3-ols and their oligomers are the most commonly consumed type of polyphenols, and are widely distributed in different foods. Tea is a typical beverage rich in flavan-3-ols in Asian countries, but in many Western countries, the flavan-3-ols are consumed from fruits. The catechins, especially (−)-epigallocatechin gallate is the abundant polyphenol in un-fermented teas, like green, white and yellow teas, but the oxidation products of flavan-3-ols, theaflavins were main components of black tea, which is the main form of tea consumed in Europe and USA. Cacao is very rich in flavan-3-ols monomers and oligomers, such as procyanidins.

Under the catalog of flavonoids, isoflavonoids are a unique subgroup of plant polyphenols with over 5000 compounds, mainly exists and reported in soybean. The main isoflavonoids in soybean are genistein and daidzein, which can bind with estrogen receptor so that they are referred as phyto-estrogens. Al-Maharik reviewed the novel isoflavonoids from 2012 to 2017 (Al-Maharik, 2019). Isoflavonoids are particularly concentrated in the legumes (Fabaceae) such as kudzu (*Pueraria lobata* (Willd.) Ohwi) or red clover (*Trifolium pratense* L.) or of course soy (*Glycine* max (L.) Merr.) (Franke, Halm, Kakazu, Li, & Custer, 2009).

Lignans is different from lignins which are polymers as the cell wall components of plant. They are a group of diphenolic compounds derived from shikimic acid biosynthetic pathway, structurally constructed by the combination of two phenylpropanoid C6–C3 units at the β and β′ carbon, and can be linked to additional ether, lactone, or carbon bonds. The plant lignans are a type of food polyphenols widely distributed in many foods, including flaxseed, rapeseed, sesame oils, whole-grain cereals, legume, vegetables and fruits (Milder, Arts, Putte, Venema, & Hollman, 2005; Peñalvo, Haajanen, Botting, & Adlercreutz, 2005). Secoisolariciresinol, lariciresinol, matairesinol, pinoresinol, medioresinol and syringaresinol are common lignans.

Stilbenes, is another class of phenolic compounds in various plants and foods. Like other polyphenols, it mainly acts as defensive secondary metabolite for protecting plant from pathogens and ultraviolet radiation. The basic skeleton is C6-C2-C6, in which two aromatic rings are linked by ethylene bridge (Neveu et al., 2010). Compared to other polyphenols, such as flavan-3-ols and chlorogenic acid, the content of stilbenes acquired from foods is limited. Some herbal medicines from *Polygonum* genus, like *Polygonum cuspidatum*, contains high content of stilbenes, but have not been used as dietary sources (Nonaka, Miwa, & Nishioka, 1982). The red wine is usually recognized as source for stilbenes, which are resveratrol, piceid, piceatannol, astringin and pterostilbene and their dimers (Vitrac et al., 2005; Vitrac, Monti, Vercauteren, Deffieux, & Mérillon, 2002).

3. Identification

In the history of polyphenols, the chromatographic separation contributed to the isolation and purification of many diverse polyphenols from the complicated food matrix or other secondary metabolites. In the past 100 years, the separation of polyphenols went through paper and silica gel partition chromatography, thin layer chromatography, molecular-exclusion chromatography, affinity chromatography, ion exchange chromatography and high speed countercurrent chromatography. The natural polyphenols have different color because of their structural properties. For example, the flavan-3-ols including catechin, galloylated catechins are colorless, but the oligomers and oxidation products of catechins are yellow, such as procyanidins and theaflavins, flavanones, flavonols and flavones are pale yellow or yellow (Balentine, Wiseman, & Bouwens, 1997; Senanayake, 2013).

The identification techniques for structures of polyphenols are not complicated and could be identified by UV-visible spectrum, infrared spectroscopy, mass spectrum, optical rotatory dispersion, circular dichroism and nuclear magnetic resonance spectrum (Power, Chapman, Chandra, & Cozzolino, 2019). With the developing of mass spectrum, more and more polyphenols could be directly identified by liquid-chromatography tandem mass spectrometry (Kontogianni, 2014). Furthermore, some liquid chromatography combining nuclear magnetic resonance (NMR) technique was also used in polyphenols structural identification.

Because of the basic skeleton of polyphenols, the novel structures of food polyphenols were less than other secondary metabolites of plants or marine organism. However, more and more novel quinic acid derivatives were isolated and identified. Hofmann group identified a series of *N*-phenylpropenoyl amino acids as the key astringent compounds of cocoa beans (Stark & Hofmann, 2005). Some caffeoylquinic acid is converted into bitter-tasting chlorogenic acid lactones by liquid chromatography tandem mass spectrometry (LC-MS) and NMR experiments (Frank, Blumberg, Krümpel, & Hofmann, 2008). Some flavan-3-ol oligomers are not stable and it is difficult to obtain purified compounds, but with high resolution mass spectrometry, ethyl-bridged flavan-3-ol dimers and trimers could be identified by specific fragment ions (Fayeulle et al., 2018). It was suggested that condensation of flavan-3-ols and acetaldehyde produced by microbial fermentation led to the formation of ethyl-bridged flavan-3-ols dimers and oligomers. Furthermore, flavanl-3-ol glycosides, including (+)-catechin-7-O-β-glucoside, (+)-catechin 3-O-glucoside, (+)-catechin 5-O-, 7-O-, 3′-O-, and 4′-O-glucosides, (+)-catechin 7-O-β- and 4′-O-β-glucosides, (+)-catechin 5-O-β-glucoside and (−)-catechin 7-O-β-glucosides have been identified in many foods, like buckwheat, cowpea, barley, lentils, and some herbal medicines (Castillo-Muoz, Gómez-Alonso, García-Romero, Gómez, & Hermosín-Gutiérrez, 2009; Cui et al., 2012; Delcambre & Saucier, 2012). The specific MS/MS fragmentations of flavan-3-ol dimer hexosides were explored and confirmed in grade and red wines by mass spectrometry (Marie, et al., 2018).

The tea polyphenols is one of the hottest research topics. The identification of tea catechin was firstly isolated and identified as (−)-epicatechin. Its separation techniques mainly relied on the chemical precipitation method and crystallization process. After that, other tea catechins were separated and purified by silica gel. Davis reviewed the ^{1}H and ^{13}C NMR assignments of main green tea polyphenols (Davis, Cai, Davies, & Lewis, 1996). The typical chemical shift data for all catechins are similar, but the C-2, C-3, C-4α and C-4β of (2*R*, 3*R*)-epicatechins and (2*R*, 3*S*)-catechins showed minor differences, which was caused by the different spatial shielding effect.

The NMR was also applied in the characterization, quality control, and metabolomics of other food polyphenols. Anthocyanins contain a flavylium cation on the C-ring, and attract much attention for being natural colorant and health-promoting benefits. The NMR is not only used in the identification of unknown compounds, but also in the quantitative analysis, metabolomics, geographical origin traceability, and authentication of food (Ye, Wang, & Xu, 2015). Anastasiadi et al. studied the NMR-based metabolomics to discriminate the wineries, production zones and vintages (Anastasiadi, Zira, Magiatis, Haroutounian, & Mikros, 2009). The quercetin glycosides, syringic, *trans*-caffeic acid, *trans*-catraric acid were the critical factors associated with different wineries. Apple have many cultivars with different features and flavor. Metabolome analysis and NMR spectroscopy also revealed the cultivar-specific differences.

Using NMR, the phenolic compounds of wine could be detected to identify the production region of German white wines. Furthermore, the main natural colorants of wine, anthocyanins could be identified by 1D and 2D NMR spectroscopy. Ferrari et al. reported the multivariate statistical analysis, Fourier transform near-infrared spectroscopy and NMR spectroscopies could discriminate the wines containing anthocyanins from black rice or grapevine (Ferrari, Foca, Vignali, Tassi, & Ulrici, 2011). NMR was also applied in the research of wine-making, cultivars, geographical origin and vintage (Anastasiadi et al., 2009). However, the sensitivity of NMR technique limited its application in the trace or minor metabolites' qualification and quantitative analysis. Only few compounds could be identified by referencing the chemical shift of standards. Other compounds were hard to be detected or characterized by NMR.

Therefore, Jaitz et al. used LC-MS/MS to explore the chemical differences of red wine according to geographic origin, grape cultivars and vintage (Jaitz et al., 2010). The detection limit of LC-MS could achieve the level of μg/mL. Ma et al. also applied the ultrafast polyphenol metabolomics of red wine to successfully find the different metabolites of six red wines (Ma, Tanaka, Vaniya, Kind, & Fiehn, 2016). LC-MS has a main advantage of allowing much shorter time consumed, and more detectable metabolites. In this study, 165 polyphenols were detected by ultrafast LC-MS metabolomics. Because of the speed, efficiency, selectivity and sensitivity of ultra-high performance liquid chromatography coupled to mass spectrometry, the qualitative and quantitative analysis of food polyphenols have been significantly improved.

Kuhnert used the LC-MS^n to study the mass profiling of chlorogenic acids and hydroxycinnamoyl shikimate esters (Jaiswal, Sovdat, Vivan, & Kuhnert, 2010). In total, 51 phenolic acids were identified by parent ion, MS^2 fragments and MS^3 fragments. The original structure of quinic acid has three hydroxyls in C-3, 4, 5 and one pair hydroxyl and carboxyl in C-1 position. Usually, the C-3,4,5 hydroxyls could be esterified by caffeoyl, feruloyl, coumaroyl and sinapoyl. To identify these quinic acid derivatives, the parent ion could be observed at [M-H]$^-$ of [quinic acid + n × caffeic acid or other moiety-n × 18–1]. For example, monocaffeoyl, dicaffeoyl, tricaffeoyl of quinic acid presented the negative parent ions *m/z* at 353 $[192+180-18-1]$, $[192+2\times180-2\times18-1]$ and $[192+3\times180-3\times18-1]$ (Clifford, Stoupi, & Kuhnert, 2007). To further explore the structure, the parent ion *m/z* at 677 of tri-caffeoyl quinic acid could continuously produce MS^2 ion at 515 by losing 162, MS^3 ion at 353 by losing 162 and MS^4 ion at 191. Other hydroxycinnamic acids could also be identified through the similar way.

The glycosylated flavonoids and phenolic compounds were identified by a same analytical scheme based on aqueous methanol extraction, reverse phase liquid chromatography, diode array and mass spectrometric detection (Lin & Harnly, 2007). According to the structural differences, the λ_{max} UV/vis absorbance of hydroxycinnamoyl quinic acids were 240, 298, 326 nm, while the glycosylated flavonols including quercetin, isorhamnetin, kaempferol were 256, 266, 352 nm.

Lin did a more comprehensive study on the identification of flavanols, proanthocyanidins, isoflavones, flavanones, dihydrochalcones, stilbenes, benzoic acids by LC-MSn (Lin & Harnly, 2012). All these polyphenols have a maximum absorbance wavelength at 260–288 nm in ultraviolet spectrum analysis. To identify the structures of flavonoids, usually, the LC-MS/MS has been widely applied in structural analysis. The regular flavanols include 2*R*,3*R*- or 2*R*,3*S* configuration catechins and their gallate (Zhou et al., 2018). During the mass fragmentation of these compounds, the galloyl moiety could be firstly lost to produce a neutral loss of 152. Furthermore, the flavan-3-ols dimers, trimers even oligomers has a typical fragments ions at 425[−152], 407 [−170] (Zhang, Li, Ma, & Tu, 2011; Zhang, Tai, Wang, Meng, & Wan, 2017). Therefore, the mono and oligomer flavan-3-ols could be distinguished and identified by their different parent ion and fragment ions.

However, during the processing of black tea, fermentation produces more complicated flavan-3-ol oxidation products. For example, the B-ring of flavan-3-ols couple was oxidized into benzotropolone moiety, in the form of theaflavins, isotheaflavins, theaflagallins, theaflavates, theaflavic acids and their derivatives (Drynan, Clifford, Obuchowicz, & Kuhnert, 2010).

In terms of the structure of stilbenes, *trans*- and *cis*-resveratrol were both presented in red wine. The chemical shift of the two isomers are slightly different in C-7,8, in which *trans*-molecule has a higher chemical shift value for protons at C-7,8 (Wu et al., 2004). LC-MS was applied to qualitatively and quantitatively determine the content of resveratrol in grapes juice, cranberry juice and wine (Wang, Catana, Yang, Roderick, & van Breemen, 2002). The red wine contained higher content of resveratrol than other fruit juices. Tisserant et al. used ^{13}C NMR, 2D-NMR and LC-MS to identify the resveratrol dimer, hydroxylated resveratrol dimer, dihydroxylated resveratrol dimer and resveratrol trimer in elicited grapevine hairy root cultures (Tisserant, Hubert, Lequart, Borie, & Courot, 2016) (Table 1).

Table 1 The mass fragmentation ions of various dietary polyphenols under soft ionization techniques.

Classification type	Compounds	Molecular weight	Parention (-MS)	Productions
Hydroxybenzoic acid	Benzoic acid	122	121	77
	Gallic acid	170	169	125, 79
Hydrolisable Tannins	HHDP-glucose	482	481	301, 275
	Mono-galloyl glucose	332	331	169, 151
	HHDP-galloyl glucose	634	633	375, 301
	Bis-HHDP glucose	785	786	301, 481
	Galloyl-bis-HHDP glucose	936	935	633, 783, 301
	Tris-galloyl-HHDP glucose	952	951	907, 783, 605, 301
Hydroxycinnamic acids	Caffeic acid	180	179	135
	Caffeoylquinic acid	354	353	191, 179, 135, 173
	Feruloylquinic acid	368	367	193, 191, 173, 149
	Coumaroylquinic acid	338	337	191, 163, 119, 173
	Trihydroxycinnamoylquinic acid	370	369	195, 191, 151
	Di-caffeoylquinic acid	516	515	353, 191, 173, 161, 135
	Tri-caffeoylquinic acid	678	677	515, 497, 353, 191, 179
Flavan-3-ols	(+)-catechin	290	289	245, 205
	(−)-catechin	290	289	245, 205, 179
	(−)-gallocatechin	306	305	261, 221, 219, 179
	(−)-epigallocatechin	306	305	261, 221, 219, 179
	(−)-epicatechin gallate	442	441	331, 289, 169
	(−)-epigallocatechin gallate	458	457	331, 305, 169

Continued

Table 1 The mass fragmentation ions of various dietary polyphenols under soft ionization techniques.—cont'd

Classification type	Compounds	Molecular weight	Parention (-MS)	Productions
Isoflavone	Genistein	270	269	269, 195, 133
Flavonone	Hesperetin	302	301	163.7
	Naringenin	272	271	151, 119
Flavones	Luteolin	286	285	217, 151, 133
Flavonols (glycosides)	Quercetin-3-galactoside	464	463	301
	Quercetin-rhamnosylgalactoside	610	609	301
	Quercetin-rutinoside	610	609	301
	Quercetin-rhamnose-hexose-rhamnose	756	755	609, 301
	Kaempferol-3-glucoside	448	447	285
	Kaempferol-3-rutinoside	594	593	285
	Kaempferol-rhamnose-hexose-rhamnose	740	739	593, 431, 285
Theaflavins	Theaflavin-3-monogallate	716	715	697, 577, 563, 545, 527, 483, 407, 389
	Theaflavin-3′-monogallate	716	715	577, 563, 545, 527, 483, 389
	Theaflavin-3,3′-digallate	868	867	697, 577, 563, 545, 527, 483, 407, 389
Condensed tannins	Procyanidins B2	578	577	451, 425, 407, 289, 287
	Procyanidin trimer	866	865	847, 695, 739, 577, 425, 289
	A-type procyanidin dimer	576	575	539, 449, 423, 407, 289
Anthocyanidins	Pelargonidin-3-glucoside	433	433(+MS)	271.6
	Peonidin-3-O-glucoside	463	463(+MS)	301
	Cyanidin-3-O-glucoside	449.4	449.2(+MS)	287

The circular dichroic (CD) is a necessary and powerful tool for the configuration confirmation of many flavonoids, like flavan-3-ols. The flavan-3-ols exhibited two absorption bands in the 240 and 280 nm range of UV spectra. The 1La and 1Lb transition was correlated to the absolute configuration of C2, C3 of the C-ring of flavan-3-ols (Rensburg, Steynberg, Burger, Heerden, & Ferreira, 1999). The natural catechins of tea leaves are mainly divided into two types, (2*R*, 3*R*)-flavan-3-ols including (−)-EGCG, (−)-EC, (−)-EGC and (−)-ECG, (2*S*, 3*R*)-flavan-3-ols including (−)-GCG and (−)-GC, (2*R*, 3*S*)-flavan-3ols including (+)-catechin and (−)-CG. For the flavan-3-ol derivatives, the configuration of new carbon could be clarified by subtracting one CD spectrum from the flavan-3-ols without substituent group (Wang et al., 2014).

4. Health benefits

Food polyphenols are mainly accessed by the types, frequency, and amount of food consumed. The average total polyphenol intake could be calculated by questionnaires and chemical analysis. In Japan, elderly population consumed about 1.5 g/day total polyphenols (Chie et al., 2015). There have been many reports on the health benefits of food polyphenols, such as chronic degenerative diseases, metabolic syndrome, cardiovascular diseases, cancer prevention, anti-aging and anti-diabetes. The well-known effects of food polyphenols are antioxidant, anti-inflammatory, anti-hypertensive, anti-diabetic. Furthermore, polyphenols also involved in carcinogenesis and then showed chemo preventive effects.

Dihydrochalcone is a typical polyphenol in Malus species, in total about 265 diverse dihydrochalcones have been identified in many plants and foods (Gutierrez, Zhong, & Brown, 2018). In the apple fruits, although hydroxycinnamic acids and flavnonols accounted for large proportion of total polyphenols, dihydrochalcones are also representative compounds in apple. Phloretin 2′-xyloglucose and phloridzin are two main dihydrochalcones in apple (Puel et al., 2005). Phlorizin inhibits sugar transport, improve insulin sensitivity to prevent diabetes 2. It normalizes the insulin sensitivity without changing the insulin levels, and strongly inhibits the sodium-coupled glucose transporter 1 (SGLT1) and increases the renal glucose loss (Schulze et al., 2014).

Lariciresinol and Secoisolariciresinol are the most reported lignans with many biological activities, such as anti-cancer, antifungal, anti-inflammatory, and anti-oxidant activities. Both oral administration and subcutaneous injection of (−)-secoisolariciresinol suppressed the gain of body weight, increased serum adiponectin level and decreased gene expression of fatty acid synthase and sterol regulatory element-binding protein-1c, promoted gene expression of acyl-CoA oxidase, carnitine palmitoyl transferase-1, and peroxisome proliferator-activated receptor α (Tominaga et al., 2012). Secoisolariciresinol diglucoside also improved the vascular endothelial function, endothelial NO synthase and haeme oxygenase-1-mediated myocardial angiogenesis, reduced low density lipoprotein cholesterol (LDL-C), maalnodialdehyde and increased high density lipoprotein cholesterol (HDL-C), so that to prevent the progression of atherosclerosis (Penumathsa et al., 2008; Prasad, 2005, 2007).

Except for the tea catechins, the methyl-catechins also showed many health benefits including anti-allergy, anti-obesity and prevention of cardiovascular disease risks. Methylated tea catechins inhibit mast cell degranulation by suppressing FcεRI expression in the cell surface, inhibit extracellular signal-regulated kinase 1/2 phosphorylation, and bind to the surface of KU812 cell to alleviate allergic disorders (Man, Xin, Qingrong, & Huang, 2018). Methyl catechin demonstrates stronger inhibitory effect on ACE compared with other major tea catechins, such as EC, ECG and EGC. Methyl catechins also influence the transcriptional factors and expression of related protein in adipocytes in preventing obesity.

In coffee and tea, chlorogenic acids are main phenolic acids compounds with many biological activities including antioxidant activity, antibacterial, hepatoprotective, cardioprotective, anti-inflammatory, antipyretic, neuroprotective, anti-obesity, antiviral, anti-microbial, anti-hypertension, free radicals scavenger and a central nervous system stimulator (Naveed et al., 2018). They include 3/4/5-caffeoylquinic acid, 3/4/5-feruloylquinic and 3,4/3,5/4,5-dicaffeoylquinic acid, 4/5-O-*p*-coumaroylquinic acid. The absorbed chlorogenic acids has a higher oral-bioavailability than other flavan-3-ols. The metabolites of chlorogenic acid are ferulic, isoferulic and caffeic acid in the systemic circulation after consumption of chlorogenic acid. Chlorogenic acid exhibited anti-inflammatory and anti-tumor activity by inhibiting matrix metalloproteinase-9. They also reduced fasting plasma glucose level and increased insulin sensitivity by inhibiting α-amylase and α-glucosidase (Williamson, 2013). It was suggested that chlorogenic acid inhibit glucose-6-phosphate translocase. To sum up, chlorogenic acid has three main biological activities, which are enhancing antioxidant properties, regulating metabolic syndrome and glucose metabolism. Chlorogenic acid upregulated the expression of peroxisome proliferator-activated receptors (PPAR)α, free fatty acid β-oxidation, adiponectin, AMP-activated protein kinase (AMPK) phosphorylation and downregulated Liver X Receptor α, PPARγ, acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (Naveed et al., 2018). Furthermore, chlorogenic acid showed preventive effects of rat hepatotoxicity induced by methotrexate, an anti-cancer drug used in clinical applications. The mechanism was related to its antioxidant activities (Ali et al., 2017). Cheng et al. also reported the protective effects on aluminum chloride induced hepatotoxicity and hepatotoxicity at dose of 30mg/kg (Cheng et al., 2017). It also showed that 40mg/kg BW of chlorogenic acid protected against Isoproterenol-induced myocardial infarction by restore the activities of heart mitochondrial enzymes isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase and malate dehydrogenase. The activities of lysosomal enzymes (β-glucosidase, β-glucuronidase, α-galactosidase, β-galactosidase, cathepsin-B and cathepsin-D) were increased significantly in the heart tissue (Akila, Asaikumar, & Vennila, 2017).

Wine is widely reported for its resveratrol with respect to anti-oxidant capacity. However, the real functions of resveratrol in red wine is still in debate. In addition, other phenolic acids including gallic acid, caffeic acid, *p*-coumaric acid, flavonoids were also distrusted in red wine (Anli, Vural, & Kizilet, 2008). There have been hundreds of papers about the biological activities, mainly regarding anti-cancer, anti-obesity, preventing non-alcoholic fatty liver disease, cardiovascular diseases, diabetes, metabolic syndrome, blood pressure. It is concluded that resveratrol may have positive effects on cellular proliferation, migration and apoptosis, act as inflammatory markers, lower LDL-cholesterol and restore insulin sensitivity. The most probable effects of resveratrol may focus on cardiovascular by population intervention study.

In red wine, resveratrol is also a famous compound in red wine with many potential health benefits, including antiaging and antidiabetogenic activities (Pastor et al., 2017). In 2003, Howitz et al. reported resveratrol can promote cell survival by stimulating sirtuin 1 (Howitz et al., 2003). Further study indicated resveratrol increased cAMP levels by activation of AMPK. Epac1 is essential for resveratrol to activate AMPK in HeLa cells. Resveratrol activates CamKKb-AMPK via the Epac1-PLC-Ryr pathway as a nonselective phosphodiesterase inhibitor (Park et al., 2012). To support the health benefits of red wine, resveratrol, at concentrations attainable moderate wine intake, activates platelet eNOS and in this way blunts the proinflammatory pathway linked to 38MAPK, thus inhibiting ROS production and ultimately platelet function (Gresele et al., 2008).

There are two isoforms of resveratrol, *cis* and *trans*, but the *trans* form of resveratrol presented more potent antiproliferative activities than its *cis* form (Anisimova et al., 2011). Like flavan-3-ol compounds, the oral bioavailability is low but they can be rapidly absorbed within 0.5 h. To regulate diabetes, resveratrol mainly target pancreases, adipose tissue, muscles and liver. The mechanisms are correlated with regulating glucose transporter-4 mediated glucose transport and IR phosphorylation, SIRT-1 and AMPK activation, mitochondrial β-oxidation, mitochondrial biogenesis, glycogen synthase and downregulating macrophage infiltration, adiponectin, lipogenic enzymes, oxidative stress and cytokine mediated inflammation, AMPK mediated FAS, ACC, gluconeogenesis. Like many polyphenols, resveratrol inhibit the formation of bovine serum albumin and advanced glycation end products (Shen, Xu, & Sheng, 2017). Resveratrol declined the cerebrospinal fluid Aβ 40 and plasma Aβ 40 levels in a randomized placebo controlled double blind phase 2 trial (Turner et al., 2015).

In terms of the anthocyanidins in plants, over 600 anthocyanins have been identified, with the most mentioned anthocyanidins, pelargonidin, cyaniding, peonidin, delphinidin, petunidin and malvidin (He & Giusti, 2010). The epidemiological evidences between anthocyanin-rich food and cancers have been convinced. Anthocyanins can inhibit the initiation, promotion and progression of many cancers, like breast, prostate, liver, colorectal and intestinal cancers (Wang et al., 2019). Anthocyanins are also colored water-soluble pigments widely used in food additives. Cyanidin-3-glucoside is the main anthocyanin in many plants. The color of anthocyanin is transformed from red to blue with the increase of pH value. Anthocyanidins and anthocyanins possess antioxidative and antimicrobial activities, improve visual and neurological health, and protect against various non-communicable diseases.

Hydroxycinnamic acids are more common than hydroxybenzoic acids, as being the predominate metabolites in many foods. In the *Rosaceae* fruits, hydroxycinnamic acids widely exist in almond, cherries, peach, pear, berries, apples, and plums (Määttä-Riihinen, Kamal-Eldin, & Törrönen, 2004). In apples, the main compounds are 3, 4, and 5-caffeoylquinic acid and 3-coumarylquinic acid. Flavonols and their glycosides are also detected in these Rosaceae fruits, with the main aglycones kaempferol, quercetin, and isorhamnetin, the last one of which is mainly detected in pears. However, most of these phenolic acids exist in fruits with the conjugated forms, like condensed and hydrolysable tannins. Therefore, actually, most of these phenolic acids are not released and absorbed in intestinal tract during digestion, mainly recognized as prebiotics.

Although flavonoids are scarcely absent in rice, biologist introduced phenylalanine ammonia lyase and chalcone synthase genes into rice and then highly increased the content of naringenin, kaempferol, genistein and other flavonoids in rice. This strategy is an effective tool to increase the accessibility of polyphenols by main staple food grain (Ogo, Ozawa, Ishimaru, Murayama, & Takaiwa, 2013).

Flavan-3-ols is one of the most important polyphenols in many foods and beverages. In tea, cocoa, grapes and berries, flavan-3-ols is the main compound. During the absorption and metabolism of flavan-3-ols, the oral-bioavailability is very limited because most of absorbed flavan-3-ols were transformed into glucuronidated and sulfonated conjugates; therefore, most of flavan-3-ols were less directly detected in the plasma or liver. However, during the digestion and microbial metabolism of flavan-3-ols, most of flavan-3-ols could be further metabolized or catabolized into low-molecular weight phenolic acids (Zhang et al., 2016). Many articles reported that colonic bacteria play a critical role in the absorption and catabolism of flavan-3-ols. The presence of flavan-3-ols could also affect the colon health, such as anti-inflammatory, also its microbiota.

The antioxidant effects of polyphenols have been widely confirmed by cell and animal models *in vivo* and *in vitro*. The common reactive oxygen species include superoxide anion ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2), nitrogen species (NO), hydroxyl ($OH-$), and alkoxyl radicals which are hazardous factors to cells, which can active the natural until antioxidant enzyme systems to catabolized reactive oxygen species into its less toxic substances. The polyphenols present antioxidant effects by attenuating the free radicals-induced damage by scavenging these radicals, and binding with the anti-oxidant enzymes to activate their activities. Furthermore, lipids especially polyunsaturated fatty acids (PUFA) produce 4-hydroxy-3-nonenal (HNE), which was involved in the onsets of degenerative diseases like diabetes.

The most reported mechanism should be regulating nuclear transcription factors, lipids biosynthesis, lipids oxidation, modulating inflammatory mediators including cytokines tumor necrosis factor α, interleukin

(IL)-1β. Furthermore, most of polyphenols could inhibit the bioactivities of glycosidase, amylase and lipase, leads to the decrease of the co-administered food main nutrients and the increase of blood glucose level. This strategy has been recognized as an effective way for many Asian diabetes 2 patients.

Food polyphenols also showed protective effects on delaying neuronal cell loss in many progress neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease (Singh, Mandal, & Khan, 2016). Up to now, the factors that trigger these neurodegenerative diseases still remain unknown. Oxidative stress and the abnormal antioxidant defense system may contribute to the formation of toxic proteins in the neuros. Polyphenols synthesized by plant protect plants against reactive oxygen species, and also have same benefits on human body. Most polyphenols can enhance the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase, thus catalyze the reactive oxygen species into less toxic molecules. Similarly, polyphenols can protect the neuronal cells from undergoing neurodegeneration.

As a typical flavan-3-ol compound, (−)-epigallocatechin gallate presents as an agonist of the main cellular energy sensor, adenosine monophosphate-activated protein kinase. EGCG can increase cell viability, scavenge reactive oxygen species and inhibit the expression of endoplasmic reticulum stress markers and apoptotic markers. Abib et al. reported EGCG also form chemical complex with Cd^{2+} and then inhibit Cd^{2+}-induced mitotoxicity (Abib et al., 2011). The oral-bioavailability of EGCG was still in debate, but Lin et al. reported that EGCG can partly penetrate the blood–brain barriers at a low rate (Lin, Wang, Tseng, Sung, & Tsai, 2007). Thus, it suggested the possibility of EGCG on preventing neurodegenerative diseases by directly affect the neurocyte. Castellano-González et al. reported that EGCG can induce energy turnover of adenine triphosphate purine by targeting cytochrome *c* oxidase (CcO) activity in cultured human neurons and astrocytes (Castellano-González, Pichaud, Ballard, Bessede, & Guillemin, 2016). Beyond the common antioxidant enzymes, EGCG firstly showed effects on CcO activity. It was suggested that EGCG can interact with its physiological regulators or directly act as electron donor. On the other side, Wang et al. also reported that EGCG can significantly increase the number of 5-bromo-2′-deoxyuridine (BrdU)-labeled cells *in vivo* and *in vitro*. The mechanism of EGCG in enhancing adult hippocampal neurogenesis was related to triggering robust upregulation of sonic hedgehog (Shh) receptor mRNA and protein expression and downstream Shh transcriptional target Gli1 (Wang et al., 2012).

The published studies and prospective cohort studies reported that flavan-3-ols exerts positive effects on cardiovascular results for diabetes, hypertension and hyperlipidemia (Osakabe, 2013). The epidemiological researches are important to assess the health benefits of flavan-3-ols and other polyphenols. Although there have been many correlation analysis between flavan-3-ols and diseases, the interpretation and analysis on the published results, biomarkers are necessary. The known health benefits mainly relied on the lipids, glucose, inflammatory factors, etc. analysis, but lack more confirmed disease risk reduction or prevention data, though the epidemiological investigations were usually unstable and affected by lifestyles or food intake. For example, to calculate the flavan-3ol intake by food composition databases is very limited, but clinical intervention experiment is short time and hard to provide more risk-related data of diseases.

Epidemiologic and experimental studies suggested the preventive effects of isoflavones on osteoporosis, cardiovascular diseases, and breast, prostate, colorectum cancers. As estrogen-like molecule, genistein has been recently shown to bind to the estrogen receptor beta (ERβ) with an affinity as that of 17β-estradiol (Kuiper et al., 1997).

Many studies have reported dark chocolate can inhibit the metabolic syndromes risk factors, like hypertension, hyperlipidemia and glucose intolerance. Recent epidemiological evidence suggested that flavan-3-ols could prevent the cardiovascular diseases, the relationship analysis revealed that intake of catechins are inversely correlated to the death of cardiovascular diseases. It also indicated dark chocolate reduced the risk of stroke and other cardio metabolic diseases. A series of meta-analysis on cocoa and its products on cardiovascular diseases indicated that cocoa can improve the homeostasis model assessment of insulin resistance (HOMA-IR), low density lipoprotein (LDL), systolic Blood Pressure, low density lipoprotein (HDL), diastolic blood pressure and total cholesterol.

5. Population based investigation of polyphenols

Most of population investigation studies of food polyphenols belong to epidemiological studies, but the dietary polyphenols frequencies, intake content, polyphenols types, interaction with other co-consumed compounds may affect the epidemiological results. In some studies, the strict double-blind, cross-over, placebo-controlled studies may provide more convincing results by designed protocol. Therefore, for the same type of food polyphenols, the results of population investigation may give different statics, especially for the significance between treated or non-treated groups.

For example, resveratrol is one typical dietary polyphenol by red wine which has been widely consumed in Europe. A large population investigation over 40,685 subjects aged from 35 to 64 years reported that resveratrol and piceid intake were 100 and 933 μg/day, respectively, mainly by wines and grape and its juices (Zamora-Ros et al., 2008). Because resveratrol is less directly used in population studies, many studies focused on the Mediterranean diet. The recent meta-analysis and cohort investigation indicated that Mediterranean diet could decrease the overall cancer risk by 4.7% for men and 2.4% for women (Couto et al., 2011). Other large longitudinal investigation for healthy individuals reported that Mediterranean diet was not correlated to the protection of cognitive decline (Cherbuin & Anstey, 2012). The correlation of obesity and Mediterranean are in debate, because part of cohort and intervention studies could decrease weight loss, but other did not show evidence of this association (Buckland, Bach, & Serra-Majem, 2010). Mediterranean-type diet had 6%–16% lower risk for the cardiovascular disease than other people with poor adherence (Wise, 2016).

As one of the most consumed beverages in Western countries, coffee has been evaluated regarding its health benefits on population. Because coffee is usually consumed in combination with sugar, and some subjects have the habit of smoking, so the evaluation of coffee is also controversial to some extent. An investigation in 1985 reported coffee consumption did not affect the plasma cholesterol (Mathias, Garland, Barrett-Connor, & Wingard, 1985). A similar result was confirmed by a 12-week double-blind trial (van Dusseldorp, Katan, & Demacker, 1990). A dose-response meta-analysis reported that every 2 cups/day increment in coffee intake can decrease 12% of incidence of type 2 diabetes, but it may be related to the caffeine intake (Jiang, Zhang, & Jiang, 2014). Qi et al. reviewed the coffee, tea and caffeine consumption and Parkinson's disease. They also reported that 3 cups/day coffee consumption can decrease Parkinson's diseases (Qi & Li, 2014).

A prospective study also revealed that intake of coffee was negatively associated with breast cancer (Oh et al., 2015).

Grape seed extract is rich in flavan-3-ol monomers, and proanthocyanidins oligomers. Martins et al. reported a randomized, double-blind placebo-controlled clinical trial on grape juice. Consumption of grape juice significantly reduced lipid peroxidation and deoxyribonucleic acid damage, which are indicator of oxidation stress by intermittent physical exercise (Martins et al., 2020). Grape seed supplement also increased the antioxidant capacity to reduce urine redox potential for healthy volunteers (Grases et al., 2015; Zhu & Du, 2020). Recently, we reviewed the health benefits of various teas, and found tea consumption can effectively decrease the risk of colorectal, gastric, and prostate cancer (Zhang et al., 2019).

In some investigations, it showed green coffee extract was beneficial to the body weight, body mass index (BMI) and waist circumference, but chlorogenic acid, one of the main phenolic of coffee was not correlated with these eanthropometric measures (Asbaghi et al., 2020). For subjects with $\text{BMI} > 25\,\text{kg/m}^2$ significant reduction in body weight and BMI was observed (Gorji et al., 2019). A randomized, double-blind, placebo-controlled trial reported that chlorogenic acids increased Congnitrax domain scores for motor speed, psychomotor speed and executive function, as well as the levels of apolipoproteins A1 and transthyretin (Saitou et al., 2018). A meta-analysis revealed that chlorogenic acids statistically decreased the systolic and diastolic blood pressure, although the mean differences were -4.31 and -3.68, which were not significant (Onakpoya, Spencer, Thompson, & Heneghan, 2015).

Quercetin is the typical flavonoid existed in many fruits and beverages. There have been many dietary supplements or health-care foods containing quercetin. A systematic review and meta-analysis studied the effects of quercetin on the plasma lipid profiles, blood pressure and glucose levels. It reported that quercetin significantly lowered systolic and diastolic blood pressure by -3.09 and -2.86 mmHg, respectively, but its effects on the levels of total triglycerides, high-density lipoprotein cholesterol (HDL-C) is limited (Huang, Liao, Dong, & Pu, 2020). A double-blind randomized clinical trial also suggested that quercetin had statistically significant improvement on high sensitivity C-reactive protein, iron, transferrin saturation and transferrin, but the total iron binding capacity was not affected (Sajadi Hezaveh, Azarkeivan, Janani, Hosseini, & Shidfar, 2019).

When quercetin is in combination with α-linolenic acid, they showed significant decreasing on total cholesterol, apolipoprotein B, low-density lipoprotein cholesterol (Burak et al., 2019).

As a mainly consumed food, soybean containing isoflavones is also studied regarding its health benefits to human. In the Pubmed database, there are in total 580 research publications about the clinical researches on isoflavones. It was reported that 8 weeks of isoflavones at the dose of 100 mg of soy isoflavones would reduce serum lipoprotein by 10%, and increase HDL-C by 11.5% (Yari, Tabibi, Najafi, Hedayati, & Movahedian, 2020). A randomized, double-blind, placebo-controlled trial used 108 mg/day of isoflavones genistein for postmenopausal women. It showed genistein supplement significantly reduced fasting blood glucose, glycated hemoglobin, serum triglyceride, increased serum high-density lipoprotein cholesterol and other antioxidant indexes (Braxas, Rafraf, Karimi Hasanabad, & Asghari Jafarabadi, 2019).

Anthocyanin mainly exists in colorful fruits, flowers and leaves. The pure anthocyanin single compound is hard to obtain, so most of anthocyanin is co-existed with other polyphenols like flavan-3-ols, procyanidins, hydroxycinnamic acids. The purple potatoes extract containing acylated anthocyanin alleviates postprandial glycemia and insulinemia, and affects postprandial inflammation (Jokioja et al., 2020). Açaí (*Euterpe oleracea* Mart.) berries predominantly contain anthocyanins, and consumption of 325 mL of berry juice for 12 weeks can decrease plasma level of interferon gamma and urinary level of 8-isoprostane, but other lipids and glucose related biomarkers were not changed (Kim et al., 2018). Blueberry is also a famous fruit. Curtis et al. designed and carried out a comprehensive double-blind, randomized controlled trail based on adults with metabolic syndromes. After 1/2 and 1 cup consumption of blueberry for 6 months, the main lipids and glucose metabolism indexes including serum glucose, insulin, blood pressure, NO, overall plasma were not affected, but endothelial function, high-density lipoprotein cholesterol, apolipoprotein A-I was improved (Curtis et al., 2019) (Table 2).

Based on the population researches, a clearer health benefits of various dietary polyphenols will impress us. Most of dietary polyphenols had effects on the lipids, glucose metabolism, and some biomarkers of tumorigenesis, but the risk reduction data of polyphenols is hard to evaluate under clinical or cohort investigations.

Table 2 The health benefits of various dietary polyphenols based on population investigation.

Compounds	Subjects	Dosage and duration	Main biomarkers	
Hydroxytyrosol, Punicalagin	Healthy adults	9.9 mg and 195 mg; 20 weeks	oxLDL (−28.74 ng/mL); Systolic pressure (−15.75 ± 9.9 mmHg); diastolic pressure (−6.36 ± 8.7 mmHg)	Quirós-Fernández, López-Plaza, Bermejo, Palma-Milla, and Gómez-Candela (2019)
Flavonoids coco drink	Subjects with Fatigue	350 mg, 120 mg GAE/day	No effects	Coe et al. (2017)
Gallic acid	Diabetic patients	15 mg/day, 7 days	Oxidized purines −31%; pyrimidines −2%; oxidized-LDL −24%; C-reactive protein −39%	Ferk et al. (2018)
Procyanidins (French maritime pine bark extract)	Postmenopausal osteopenic women	250 mg/day, 12 weeks	Procollagen type 1 amino-terminal propeptide; C-terminal telopeptide of type I collagen	Panahande et al. (2019)
Procyanidins (apple polyphenols)	Glucose tolerance in high-normal and borderline human subjects	600 mg/day, 12 weeks	Plasma glucose level	Shoji et al. (2017)
Procyanidins (French Maritime Pine bark extract)	Stage-1-hypertension subjects	150 mg/day, 5 weeks	Increase HDL-C 14.06%, apolipoprotein A-1 8.12%; decrease ratio of apolipoprotein B-100/A-1, 10.26%; systolic blood pressue −6.36 mmHg, decrease oxLDL-C;	Valls et al. (2016)

Continued

Table 2 The health benefits of various dietary polyphenols based on population investigation.—cont'd

Compounds	Subjects	Dosage and duration	Main biomarkers	
Green tea extract	Patients with malignant oral disorders	800 mg/day, 3 months	Downregulation of p53, Ki67, and cyclin D1 expression	Neetha, Panchaksharappa, Pattabhiramasastry, Shivaprasad, and Venkatesh (2020)
Green tea extract	T2MD patients	400 mg/day, 12 weeks	Decreased cAIx75, other biomarkers of lipids, glucose and blood pressure no changes	Quezada-Fernández et al. (2019)
EGCG (Polyphenon E)	Patients with bladder cancer	800, 1200 mg/day, 2–4 weeks	Reduced proliferating cell nuclear antigen and clusterin	Gee et al. (2017)
Chlorogenic acid, luteolin (Altilix®)	Metabolic syndrome patients	150 mg/day, 6 months	Weight, BMI, waist circumference, HbA1c, HOMA-IR, HOMA-β, total cholesterol, triglycerides, LDL-C, fatty liver index, AST, ALT, Flow-mediated dilation, carotid intima-media thickness	Castellino et al. (2019)
Anthocyanins (blackcurrant extract)	Old adults	300 mg/g, 7 days	Reduces central arterial stiffness and central blood pressure	Okamoto, Hashimoto, Kobayashi, Nakazato, and Willems (2020)
Blackcurrant Anthocyanins (apple polyphenols (AE), blackcurrant anthocyanins (BE))	Healthy volunteers	1200AE mg/day, 600AE + 600BE mg/day	Incremental areas under the curve (iAUC) of plasma glucose	Castro-Acosta et al. (2017)

Resveratrol	T2MD patients	1000 mg/day, 8 weeks	Decreased serum levels of asymmetric de-methyl-arginine (ADMA) and paraoxonase-1 (PON1) activity	Tabatabaie et al. (2020)
Resveratrol	T2MD patients	1000 mg/day, 8 weeks	Decreased fasting blood sugar (−7.97 ± 13.6 mg/dL) and increased high density lipoprotein (3.62 ± 8.75 mg/dL) levels	Abdollahi et al. (2019)
Genistein	Obese patients	50 mg/day, 2 months	Decreased metabolic endotoxemia, increased 5′-adenosine monophosphate-activated protein kinase phosphorylation, increased fatty acid oxidation and glucose tolerance	

6. Perspectives and conclusions

Polyphenols has become one of the hottest topics of food science and nutrition. More and more scientists and food technologists concern the biological activities, health benefits of dietary polyphenols. Some pre-clinical, clinical, population investigations also confirmed the preventative effects of food extracts, polyphenol-rich extracts and single compound on metabolic syndromes including hyperglycemia, hyperlipidemia, hypertension, neurodegenerative diseases and various cancers. Furthermore, the utilization and recycling of polyphenols from agricultural wastes, like fruits peels also expands the research and application of dietary polyphenols. Polyphenols not only affects the nutritional values, but also influences the food color, aroma and taste. Especially, the polyphenol-protein, polyphenol-Maillard reaction, can contribute to the flavor chemistry of various foods containing polyphenols.

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