

Review

# Chrononutrition and Polyphenols: Roles and Diseases

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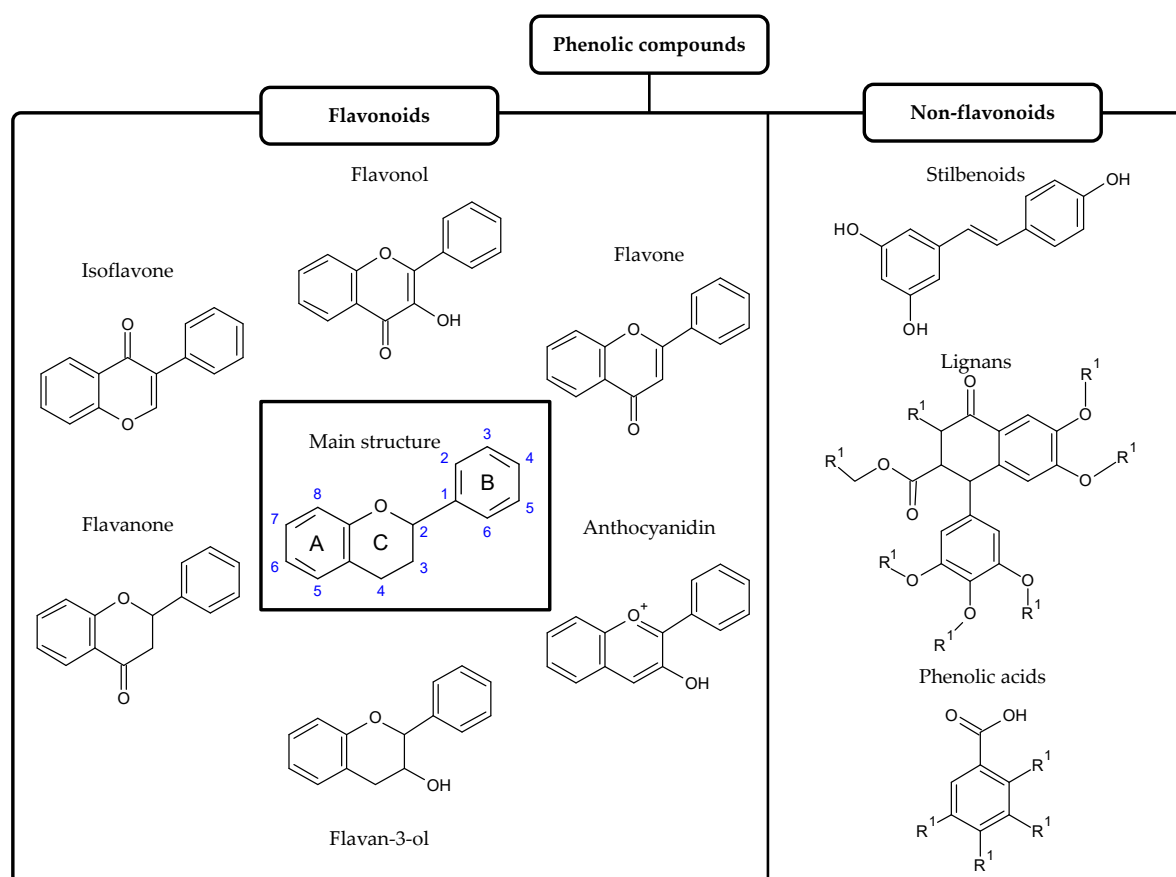
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**Supplementary Materials:** The following are available online at [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1), Figure S1: Basic chemical structures of the main classes of phenolic compounds. According to their structure, phenolic compounds can be classified into two major families: flavonoids and nonflavonoids, and they can be further divided into several subclasses, Table S1: Total phenolic contents of relevant plant products, their most important bioactive phenols and their health benefits.



**Figure S1.** Basic chemical structures of the main classes of phenolic compounds. According to their structure, phenolic compounds can be classified into two major families: flavonoids and nonflavonoids, and they can be further divided into several subclasses.

**Table S1.** Total phenolic contents of relevant plant products, their most important bioactive phenols and their health benefits.

Plant product	Scientific name	Total content of phenolic compounds (mg/100 g FW)*	Most important bioactive phenols	Benefits to human health	References
Apple (whole, raw)	<i>Malus domestica</i>	200.96	(+)-Catechin (-)-Epicatechin Quercetin Kaempferol	Anti-ulcer, Anti-allergy, Antioxidant, Antihypertensive, Anticancer, Antidiabetic, Anti-inflammatory, Cardioprotective	[1–8]
Apricot (raw)	<i>Prunus armeniaca</i> L.	133.00	Quercetin Kaempferol	Antioxidant, Anticancer, Antidiabetic, Anti-inflammatory	[4–8]
Broccoli (raw)	<i>Brassica oleracea</i> var. <i>italica</i>	198.55	Quercetin Myricetin	Anticancer	[9]
Cocoa, powder	<i>Theobroma cacao</i>	5624.23	(+)-Catechin (-)-Epicatechin	Antioxidant, Antihypertensive, Antidiabetic, Anti-inflammatory	[3,4]
Coffee (beverage, filtered)	<i>Coffea arabica</i> L.	266.70 mg/100 mL	Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid	Antioxidant, Anti-inflammatory, Cardioprotective	[10–14]
Common beans (whole)	<i>Phaseolus vulgaris</i> L.	1234.38	(+)-Catechin Quercetin Vanillin acid Ellagic acid Caffeic acid Ferulic acid Gallic acid Chlorogenic acid Sinapic acid	Antidiabetic, Anti-obesity, Antioxidant, Anti-inflammatory, Chemoprotective	[15]
Grape (black)	<i>Vitis vinifera</i> L.	184.97	(+)-Catechin (-)-Epicatechin Quercetin Kaempferol Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid Resveratrol Proanthocyanidins	Anti-ulcer, Anti-allergy, Antiproliferative, Antioxidant, Antihypertensive, Antidiabetic, Anti-inflammatory, Anticancer, Anti-obesity, Cardioprotective	[1,2,12–14,16–18,3–8,10,11]

Lemon	<i>Citrus limon</i>	59.80	Hesperidin Naringenin	Antioxidant, Anti-inflammatory, Anticancer, Cardioprotective	[4,8,19–21]
Mango	<i>Mangifera indica</i> L.	144.77	Mangiferin	Antioxidant, Anticancer, Antidiabetic, Anti-allergic, Anti-obesity	[22,23]
Nectarine (whole)	<i>Prunus persica</i> var. <i>nucipersica</i>	55.44	Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid	Antioxidant, Anti-inflammatory, Cardioprotective	[10–14]
Olive (green, raw)	<i>Olea europaea</i> L.	161.24	Tyrosol Hydroxytyrosol	Anticancer, Anti-inflammatory, Antioxidant, Cardioprotective	[24–28]
Onion (red, raw)	<i>Allium cepa</i> L. var. <i>cepa</i>	102.83	Quercetin Kaempferol	Anti-ulcer, Anti-allergy, Antiproliferative, Antioxidant, Anticancer, Antidiabetic, Anti-inflammatory, Cardioprotective	[2,4–8,24]
Orange (blond)	<i>Citrus sinensis</i> L.	278.59	Hesperidin Naringenin	Antioxidant, Anti-inflammatory, Anticancer, Cardioprotective	[4,8,19–21]
Parsley (fresh)	<i>Petroselinum crispum</i> Mill.	89.27	Apigenin	Antioxidant, Anticancer, Anti-inflammatory, Cardioprotective	[4,29,30]
Peach (whole)	<i>Prunus persica</i> L.	279.08	Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid	Antioxidant, Anti-inflammatory, Cardioprotective	[10–14]
Pear (whole)	<i>Pyrus communis</i>	107.91	(+)-Catechin Chlorogenic acids	Antioxidant	[2]
Pomegranate (peel, juice, seed)	<i>Punica granatum</i> L.	410.03 <sup>a</sup>	Anthocyanidins	Antioxidant, Cardioprotective	[31,32]
Plum (fresh)	<i>Prunus domestica</i> L.	409.79	Chlorogenic acids Caffeic acid <i>p</i> -Coumaric acid	Antioxidant Anti-inflammatory Cardioprotective	[10–14]
Raspberry (red, raw)	<i>Rubus idaeus</i> L.	154.65	Cyanidin Malvidin Gallic acid	Antioxidant, Anti-obesity, Anti-inflammatory, Anticancer, Antidiabetic, Cardioprotective	[1,4,33–41]
Soybean (seed)	<i>Glycine Max</i> L. Merr.	354.00 <sup>b</sup>	Genistein Daidzin	Antioxidant, Anticancer, Antihyperlipidemic	[4,42–44]

Spinach (raw)	<i>Spinacia oleracea</i> L.	248.14	Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid	Antioxidant, Anti-inflammatory, Cardioprotective	[10–14]
Strawberry (raw)	<i>Fragaria</i> L.	289.20	Cyanidin Malvidin Gallic acid	Proapoptotic effects, Antiproliferative, Antioxidant, Anti-obesity, Anti-inflammatory, Anticancer, Antidiabetic, Cardioprotective	[4,24,41,45 ,33–40]
Sweet cherry (raw)	<i>Prunus avium</i> L.	174.90	(+)-Catechin Quercetin Cyanidin Malvidin Chlorogenic acid Caffeic acid <i>p</i> -Coumaric acid	Antioxidant, Anti-obesity, Anti-inflammatory, Cardioprotective	[2,4,10– 14,34–36]
Tangerine	<i>Citrus tangerina</i>	192.00	Hesperetin Naringenin	Antioxidant, Anti-inflammatory, Anticancer, Cardioprotective	[4,8,19–21]
Tea (infusion)	<i>Camellia sinensis</i> L. <i>Kuntze</i>	104.48 (black) 61.86 (green) mg/100 mL	Gallic acid (+)-Catechin (-)-Epicatechin	Antioxidant, Anticancer, Antidiabetic, Antihypertensive, Anti-inflammatory, Cardioprotective	[3,4,33,37– 41]
Walnut	<i>Juglans regia</i> L.	1574.82	Ellagic acid Gallic acid	Antidiabetic, Antioxidant	[46,47]

\*Data from the Phenol-Explorer database [48–50]. <sup>a</sup>[51]. <sup>b</sup>[52]

## References

- Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev.* **2009**, *2*, 270–278.
- Rasouli, H.; Farzaei, M.H.; Khodarahmi, R. Polyphenols and their benefits: A review. *Int. J. Food Prop.* **2017**, *20*, 1700–1741.
- Bladé, C.; Aragonès, G.; Arola-Arnal, A.; Muguerza, B.; Bravo, F.I.; Salvado, M.J.; Arola, L.; Suárez, M. Proanthocyanidins in health and disease. *BioFactors* **2016**, *42*, 5–12.
- Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.E.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* **2013**, *18*, 1818–1892.
- Kawabata, K.; Mukai, R.; Ishisaka, A. Quercetin and related polyphenols: new insights and implications for their bioactivity and bioavailability. *Food Funct.* **2015**, *6*, 1399–1417.
- Calderón-Montaño, J.M.; Burgos-Morón, E.; Pérez-Guerrero, C.; López-Lázaro, M. A Review on the Dietary Flavonoid Kaempferol | BenthamScience. *Mini Rev. Med. Chem.* **2011**, *11*, 298–344.

7. Dragovic-Uzelac, V.; Pospíšil, J.; Levaj, B.; Delonga, K. The study of phenolic profiles of raw apricots and apples and their purees by HPLC for the evaluation of apricot nectars and jams authenticity. *Food Chem.* **2005**, *91*, 373–383.
8. Erlund, I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. *Nutr. Res.* **2004**, *24*, 851–874.
9. Heneman, K.; Zidenberg-Cherr, S. Nutrition and Health Info Sheet: Flavonols. *Univ. Calif.* **2008**, 1–5.
10. Sato, Y.; Itagaki, S.; Kurokawa, T.; Ogura, J.; Kobayashi, M.; Hirano, T.; Sugawara, M.; Iseki, K. In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. *Int. J. Pharm.* **2011**, *403*, 136–138.
11. dos Santos, M.D.; Almeida, M.C.; Lopes, N.P.; de Souza, G.E.P. Evaluation of the Anti-inflammatory, Analgesic and Antipyretic Activities of the Natural Polyphenol Chlorogenic Acid. *Biol. Pharm. Bull.* **2006**, *29*, 2236–2240.
12. Clifford, M.N. Chlorogenic acids and other cinnamates – nature, occurrence, dietary burden, absorption and metabolism. *J. Sci. Food Agric.* **2000**, *80*, 1033–1043.
13. Möller, B.; Herrmann, K. Quinic acid esters of hydroxycinnamic acids in stone and pome fruit. *Phytochemistry* **1983**, *22*, 477–481.
14. Clifford, M.N.; Jaganath, I.B.; Ludwig, I.A.; Crozier, A. Chlorogenic acids and the acyl-quinic acids: discovery, biosynthesis, bioavailability and bioactivity. *Nat. Prod. Rep.* **2017**, *34*, 1391–1421.
15. Ganesan, K.; Xu, B. Polyphenol-Rich Dry Common Beans (*Phaseolus vulgaris* L.) and Their Health Benefits. *Int. J. Mol. Sci.* **2017**, *18*, 2331.
16. Savouret, J.F.; Quesne, M. Resveratrol and cancer: a review. *Biomed. Pharmacother.* **2002**, *56*, 84–87.
17. Smoliga, J.M.; Baur, J.A.; Hausenblas, H.A. Resveratrol and health—a comprehensive review of human clinical trials. *Mol. Nutr. Food Res.* **2011**, *55*, 1129–1141.
18. Nicoletti, I.; Bello, C.; De Rossi, A.; Corradini, D. Identification and quantification of phenolic compounds in grapes by HPLC-PDA-ESI-MS on a semimicro separation scale. *J. Agric. Food Chem.* **2008**, *56*, 8801–8808.
19. Roohbakhsh, A.; Parhiz, H.; Soltani, F.; Rezaee, R.; Iranshahi, M. Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. *Life Sci.* **2015**, *124*, 64–74.
20. Tomás-Barberán, F.A.; Clifford, M.N. Flavanones, chalcones and dihydrochalcones – nature, occurrence and dietary burden. *J. Sci. Food Agric.* **2000**, *80*, 1073–1080.
21. Parhiz, H.; Roohbakhsh, A.; Soltani, F.; Rezaee, R.; Iranshahi, M. Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models. *Phytother. Res.* **2015**, *29*, 323–331.
22. Masibo, M.; He, Q. Major Mango Polyphenols and Their Potential Human Health. *Compr. Rev. Food Sci. Food Saf.* **2008**, *7*, 309–319.
23. Imran, M.; Arshad, M.S.; Butt, M.S.; Kwon, J.H.; Arshad, M.U.; Sultan, M.T. Mangiferin: a natural miracle bioactive compound against lifestyle related disorders. *Lipids Health Dis.* **2017**, *16*, 1–17.

24. Renard, C.M.G.C. Extraction of bioactives from fruit and vegetables: State of the art and perspectives. *Lwt* **2018**, *93*, 390–395.
25. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P.E. Polyphenols and human health: Prevention of disease and mechanisms of action. *Nutrients* **2010**, *2*, 1106–1131.
26. D'Archivio, M.; Filesi, C.; Di Benedetto, R.; Gargiulo, R.; Giovannini, C.; Masella, R. Polyphenols, dietary sources and bioavailability. *Ann. Ist. Super. Sanita* **2007**, *43*, 348–361.
27. Rigacci, S.; Stefani, M. Nutraceutical Properties of Olive Oil Polyphenols. An Itinerary from Cultured Cells through Animal Models to Humans. *Int. J. Mol. Sci.* **2016**, *17*, 843.
28. Martin-Pelaez, S.; Covas, M.I.; Fito, M.; Kusar, A.; Pravst, I. Health effects of olive oil polyphenols: recent advances and possibilities for the use of health claims. *Mol. Nutr. Food Res.* **2013**, *57*, 760–771.
29. Singh, M.; Kaur, M.; Silakari, O. Flavones: An important scaffold for medicinal chemistry. *Eur. J. Med. Chem.* **2014**, *84*, 206–239.
30. El Gharras, H. Polyphenols: Food sources, properties and applications - A review. *Int. J. Food Sci. Technol.* **2009**, *44*, 2512–2518.
31. Davidson, M.H.; Maki, K.C.; Dicklin, M.R.; Feinstein, S.B.; Witchger, M.S.; Bell, M.; McGuire, D.K.; Provost, J.C.; Liker, H.; Aviram, M. Effects of Consumption of Pomegranate Juice on Carotid Intima-Media Thickness in Men and Women at Moderate Risk for Coronary Heart Disease. *Am. J. Cardiol.* **2009**, *104*, 936–942.
32. Lansky, E.P. Pomegranate products useful in improving health and methods of use thereof 2002, WO 02/0943.
33. Gruz, J.; Novák, O.; Strnad, M. Rapid analysis of phenolic acids in beverages by UPLC-MS/MS. *Food Chem.* **2008**, *111*, 789–794.
34. Kong, J.M.; Chia, L.S.; Goh, N.K.; Chia, T.F.; Brouillard, R. Analysis and biological activities of anthocyanins. *Phytochemistry* **2003**, *64*, 923–933.
35. Prior, R.L.; Wu, X. Anthocyanins: Structural characteristics that result in unique metabolic patterns and biological activities. *Free Radic. Res.* **2006**, *40*, 1014–1028.
36. Kuntz, S.; Asseburg, H.; Dold, S.; Römpf, A.; Fröhling, B.; Kunz, C.; Rudloff, S. Inhibition of low-grade inflammation by anthocyanins from grape extract in an in vitro epithelial-endothelial co-culture model. *Food Funct.* **2015**, *6*, 1136–1149.
37. Jin, L.; Piao, Z.H.; Sun, S.; Liu, B.; Kim, G.R.; Seok, Y.M.; Lin, M.Q.; Ryu, Y.; Choi, S.Y.; Kee, H.J.; et al. Gallic Acid Reduces Blood Pressure and Attenuates Oxidative Stress and Cardiac Hypertrophy in Spontaneously Hypertensive Rats. *Sci. Rep.* **2017**, *7*, 1–14.
38. Hsu, C.L.; Yen, G.C. Effect of gallic acid on high fat diet-induced dyslipidaemia, hepatosteatosis and oxidative stress in rats. *Br. J. Nutr.* **2007**, *98*, 727–735.
39. Verma, S.; Singh, A.; Mishra, A. Gallic acid: Molecular rival of cancer. *Environ. Toxicol. Pharmacol.* **2013**, *35*, 473–485.
40. Punithavathi, V.R.; Prince, P.S.M.; Kumar, R.; Selvakumari, J. Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats. *Eur. J.*

- Pharmacol.* **2011**, *650*, 465–471.
41. Tomás-Barberán, F.A.; Clifford, M.N. Dietary hydroxybenzoic acid derivatives – nature, occurrence and dietary burden. *J. Sci. Food Agric.* **2000**, *80*, 1024–1032.
  42. McCue, P.; Shetty, K. Health benefits of soy isoflavonoids and strategies for enhancement: A review. *Crit. Rev. Food Sci. Nutr.* **2004**, *44*, 361–367.
  43. Tham, D.M.; Garner, C.D.; Haskell, W.L. Potential health benefits of dietary phytoestrogens: A review of clinical, epidemiological, and mechanistic evidence. *J. Clin. Endocrinol. Metab.* **2011**, *83*, 2223–2235.
  44. Ganesan, K.; Xu, B. A critical review on polyphenols and health benefits of black soybeans. *Nutrients* **2017**, *9*, 1–17.
  45. Pereira Lima, P.G.; Vianello, F.; Corrêa, C.R.; da Silva Campos, R.A.; Galhardo Borguini, M. Polyphenols in Fruits and Vegetables and Its Effect on Human Health. *Food Nutr. Sci.* **2014**, *5*, 1065–1082.
  46. Vinson, J.A.; Cai, Y. Nuts, especially walnuts, have both antioxidant quantity and efficacy and exhibit significant potential health benefits. *Food Funct.* **2012**, *3*, 134–140.
  47. Ma, Y.; Njike, V.Y.; Millet, J.; Dutta, S.; Doughty, K.; Treu, J.A.; Katz, D.L. Effects of walnut consumption on endothelial function in type 2 diabetic subjects. *Diabetes Care* **2010**, *33*, 227.
  48. Rothwell, J.A.; Urpi-Sarda, M.; Boto-Ordóñez, M.; Knox, C.; Llorach, R.; Eisner, R.; Cruz, J.; Neveu, V.; Wishart, D.; Manach, C.; et al. Phenol-Explorer 2.0: a major update of the Phenol-Explorer database integrating data on polyphenol metabolism and pharmacokinetics in humans and experimental animals. *Database (Oxford)* **2012**, *2012*, bas031.
  49. Rothwell, J.A.; Perez-Jimenez, J.; Neveu, V.; Medina-Remón, A.; M'Hiri, N.; García-Lobato, P.; Manach, C.; Knox, C.; Eisner, R.; Wishart, D.S.; et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. *Database* **2013**, *2013*, bat070.
  50. Neveu, V.; Perez-Jiménez, J.; Vos, F.; Crespy, V.; du Chaffaut, L.; Mennen, L.; Knox, C.; Eisner, R.; Cruz, J.; Wishart, D.; et al. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database (Oxford)*. **2010**, *2010*, bap024.
  51. Gözlekçi, S.; Saraçoğlu, O.; Onursal, E.; Özgen, M.; Gozlekci, S.; Saracoglu, O.; Onursal, E.; Ozgen, M. Total phenolic distribution of juice, peel, and seed extracts of four pomegranate cultivars. *Pharmacogn. Mag.* **2011**, *7*, 161–164.
  52. Nam, J.; Kang, S.; Hong, S.; Kim, S.; Jin, Y. Analysis of the Phenolic Content and Antioxidant Activities of Soybean Extracts from Different Regions and Cultivars. **2014**, *27*, 610–621.

