Plant Polyphenols

Subjects: Allergy

Contributor: Qingbiao Xu

Plant polyphenols are the main category of natural active substances, and are distributed widely in vegetables, fruits, and plant-based processed foods. Polyphenols have a beneficial performance in preventing diseases and maintaining body health.

Keywords: polyphenols ; foodomics ; functional activity

1. Classification, Source and Function of Polyphenols

More than 8000 phenolic substances are commonly distributed in fruits, vegetables, tea, coffee, cocoa, beans, and grains (**Table 1**) [1]. Polyphenols have complex structures and can be divided into phenolic acids, lignans, stilbene, tannins, and flavonoids (e.g., isoflavones and anthocyanins). Polyphenols derived from various sources have many beneficial and specific therapeutic properties (**Table 1**). Phenolic acid has an extensive physiological activity, including anti-oxidation, scavenging free radicals, anti-ultraviolet radiation, and antibacterial and antiviral effects. Stilbene resveratrol has a preventive effect on atherosclerosis and cancer [2]. Stilbene and flavonoids can be used to prevent and treat cardiovascular and cerebrovascular diseases [3][4][5]. As the most common phytoestrogens, lignans are famous for its high anti-oxidant activity and inhibiting lipid peroxidation [6][7]. Lignans can also bind to estrogen receptors and interfere with cancer-promoting effects; therefore, it has a preventive effect on breast and colon cancer. As a kind of polyphenols, tannin can exert various activities, such as anti-oxidative, anti-microbial, anti-cancer, anti-hypertensive, and anti-inflammatory effects [8][9]. However, complexes can be formed by polyphenols with starch, protein, and enzymes; therefore, they are considered as anti-nutrients. Due to their carcinogenic and anti-nutritional effects, it is harmful for human and animal to have too many tannins [10].

Table 1. Classification, sources, and functions of polyphenols.

Polyphenols	Subclass	Sources	Function	Ref.
Phenolic acids		**Coffee, berries, kiwi, apple, cherry**	**Anti-inflammatory, anti-oxidant, antibacterial, antiviral, antiparasitic**	[11] [12] [13]
Stilbenes		**Grapes, wine**	**Anti-inflammatory, anti-oxidant, heart protection, anti-cancer, anti-obesity**	[14] [15] [16]
Lignans		**Linseed, sesame, wheat**	**Anti-tumor, scavenging free radicals, anti-oxidant**	[17] [18] [19]
Flavonoids				
	Isoflavones	**Soy, miso**	**Estrogenic activity, anti-inflammatory, anti-obesity, anti-diabetic, anti-oxidant, cholesterol lowering**	[20] [21] [22]
	Flavones	**Parsley, celery, capsicum pepper**	**Anti-inflammatory, anti-oxidant, regulating glucose and lipid metabolism, anti-virus, anti-bacterial, anti-parasitic**	[23] [24] [25]
	Flavanones	**Grapefruit, lemon, oranges**	**Anti-inflammatory, anti-oxidant, regulating glucose and lipid metabolism, preventing liver steatosis, anti-bacterial, anti-viral, anti-parasitic, anti-fungal**	[26] [27]
	Flavonols	**Berries, onion, broccoli, leek**	**Anti-inflammatory, anti-oxidant, anti-virus, anti-bacterial**	[28] [29] [30]

Polyphenols	Subclass	Sources	Function	Ref.
Tannins	Flavanols	Grapes, cocoa, wine, apricots, green tea, beans	Anti-inflammatory, anti-oxidant, antibacterial, antiviral, antiparasitic, anticancer	[31] [32] [33]
	Anthocyanins	Berries, black grapes, aubergine, red wine, rhubarb	Anti-inflammatory, anti-bacterial, anti-oxidant, anti-diabetic, anti-cancer, nerve protection, anti-allergic	[34] [35] [36]
	Condensed tannins	Cocoa, chocolate, apples, grapes	Anti-oxidant, eliminating free radicals, enhancing immunity, preventing cardiovascular and cerebrovascular diseases, improving hypoxia	[37] [38] [39]
	Hydrolyzable tannins	Mango, pomegranate	Anti-oxidant, anticancer, phytoestrogens activity	[40] [41]

Due to their extensive biological activities, plant polyphenols have become a study hotspot in the field of human nutrition and health. Similarly, polyphenols also have various positive effects on livestock and poultry. Plant polyphenol extracts and polyphenol monomer compounds can effectively improve animal intestinal microenvironment with various functional activities, such as immune regulation, bacteriostasis, anti-oxidation, and microbiota regulation [42][43].

2. Foodomics Applied in the Study of Polyphenols

As shown in **Figure 1**, foodomics is a collection of genomics, transcriptomics, proteomics, and metabolomics, and can be used to study polyphenols from multiple angles. The data obtained from various omics will be integrated to explore the molecular mechanism and novel pathways of plant polyphenols to predict and treat diseases of human and animals.

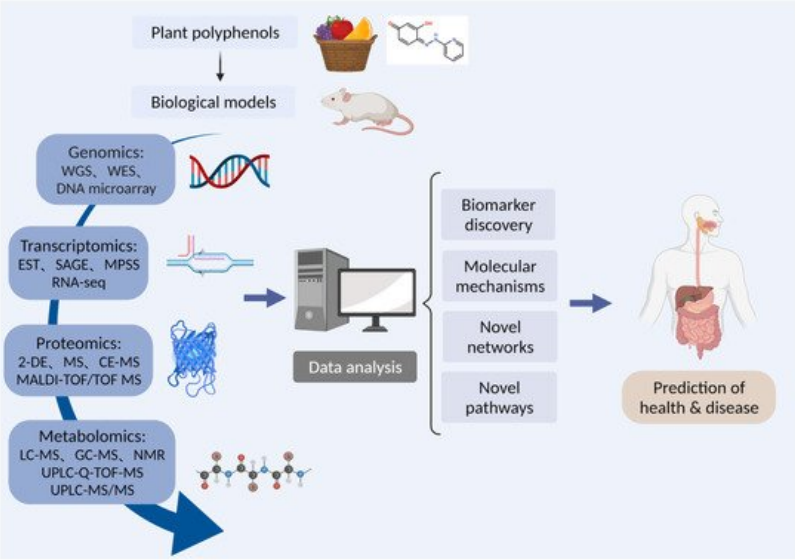

Figure 1. The strategy of foodomics to study the bioactivities of polyphenols. 2-DE: two-dimensional gel electrophoresis; CE-MS: capillary electrophoresis mass spectrometry; EST: expression sequence tags technology; GC: gas chromatography; LC: liquid chromatograph; MPSS: massively parallel signature sequencing; MALDI-TOF/TOF: matrix-assisted laser desorption ionization time-of-flight/time-of-flight; MS: mass spectrometry; NMR: nuclear magnetic resonance; RNA-seq: RNA sequencing; SAGE: serial analysis of gene expression; UPLC-Q-TOF: ultra-performance liquid chromatography to quadrupole time-of-flight; WES: whole exome sequencing; WGS: whole genome sequencing.

3. Microbiomics Involved in the Bioactivity of Polyphenols

3.1. Regulation of Polyphenols on Gut Microbiota

Microbiome refers to all microorganisms and genetic information in a specific environment and has beneficial effects in nutrition, metabolism, and immunity [44]. Gut microbiota mainly consists of *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Among them, *Firmicutes* and *Bacteroides* are the dominant microbiota [45]. Like prebiotics, the polyphenols in diet have received widespread attention for their functional regulatory effects on gut microorganisms, as shown in **Figure 2**. Polyphenols can inhibit harmful bacteria proliferation (e.g., *Escherichia coli* and *Salmonella*), while promoting the growth of probiotics (e.g., *Bifidobacterium* and *Lactobacillus*).

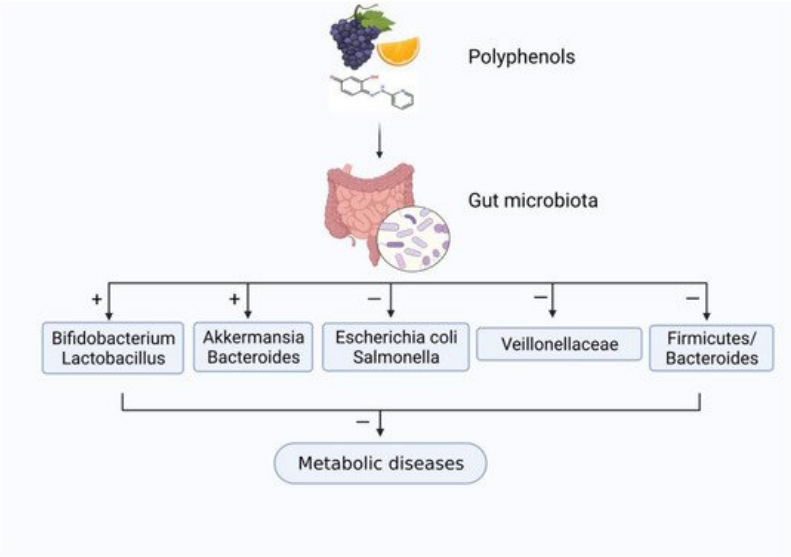

Figure 2. The influence of the interaction between plant polyphenols and gut microbiota on metabolic diseases. “+” means “enhance”; “−” means “weaken”.

Intestinal disorders can be inhibited by polyphenols via richening the abundance of beneficial bacteria and microbial diversity. Resveratrol has a promoting effect on *Lactobacillus* and *Bifidobacterium*, which can exert anti-inflammatory effects through reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines [46][47]. Alpha diversity of gut microbiota was changed, and relative abundances of *Bifidobacterium*, *Feacalibacterium*, *Eubacterium*, and *Coprococcus* were increased by the intake of polyphenols from green tea [48]. The abundance of *Bifidobacteria* and *Lactobacillus* in the gut were increased by the intake of blueberries [49]. In addition, it has been confirmed that inflammatory bowel disease (IBD) is influenced by multiple factors, including the host, microorganisms, and the environment, and the occurrence of IBD is related to gut microbes [50]. In our lab, we found that polyphenol taxifolin changed the composition of colonic microbial community by 16S rDNA sequencing. The change in *Bacteroides*, *Clostridium saccharogumia*, *Clostridium ramosum*, *Sphingobacterium multivorum*, and *Bacteroidetes*/*Firmicutes* ratio caused by dextran sulfate sodium was restored by taxifolin to relieve mice colitis [51]. In conclusion, plant polyphenols can promote beneficial bacteria in the process of regulating intestinal microbes. Once the polyphenols enter the intestinal tract, they will activate the gut microbiota and regulate gut microecology. Conversely, polyphenols can also be used by gut microbiota to produce bioactive molecules (e.g., phenolic acids), which may be the key biologically active effector [52][53], subsequently promoting the health of human and animals.

3.2. Combination of Microbiome and Metabolomics in Polyphenol Study

Currently, microbiome technologies mainly contain microbial metagenomics, metametabolomics, macrotranscriptomics, and macroproteomics, allowing us to analyze the microbiome at different levels (e.g., DNA, RNA, protein, and metabolites). At present, numbers of studies on polyphenols mainly focus on metagenomics and metametabolomics. In contrast, their combination to explore the metabolic process of polyphenols is still lacking. The combination of metabolomics and microbiome is a novel approach to explore the specific mechanism of polyphenols. Gut microbiota plays a critical role in health and nutritional status of human and animals [54]. In general, the method of the combination of microbiome and metabolomics is shown in **Figure 3**. By sequencing the metagenomics of gut microbiota, the corresponding microorganisms can be identified and metabolites can be analyzed using metabolomics technology to discover a novel pathway. In a previous study, primary bile acids were modified into secondary bile acids by clostridium species using 16S amplicon sequencing and metabolomics [55]. It has been verified that polyphenols have various biological activities with a positive influences on gut microbes [56][57][58]. Therefore, the combination of metabolomics and microbiome in the exploration of polyphenols is a trend in the future.

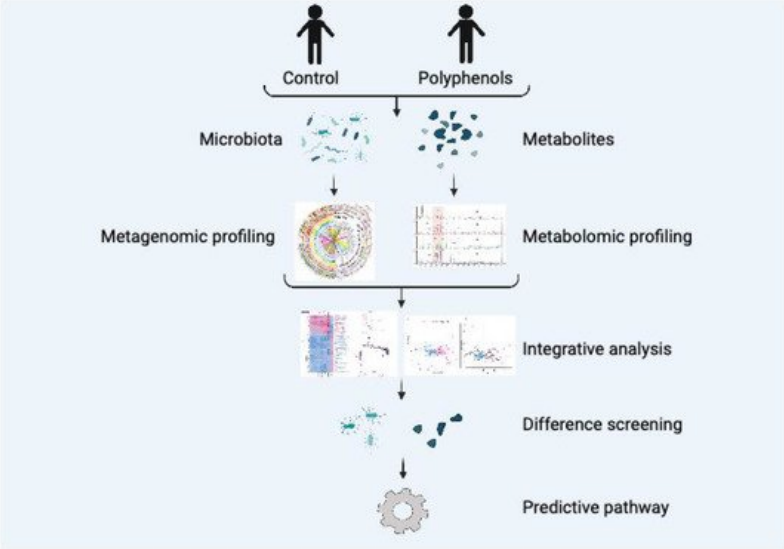

Figure 3. Combining microbiome and metabolomics to investigate the bioactivity of plant polyphenols.

The combination of microbiome and metabolomics has been used to study the effects of plant polyphenols on cardiovascular diseases. Through the metabolomics and genomics analysis of microorganisms in serum, urine, and feces, the risk of cardiovascular disease can be reduced by pomegranate polyphenols [59]. The influence of green tea polyphenols on gut microbiota and micronutrient metabolism was analyzed using metagenomics and metabolomics, and the metabolites of tricarboxylic acid and urea cycle were analyzed using metabolomics and 16S rRNA sequencing, showing that energy conversion was enhanced by green tea polyphenols via promoting the metabolism of gut microbiota in rat [60]. Moreover, the diversity and overall structure of gut microbiota were changed by polyphenols using 16S rRNA sequencing, indicating that polyphenols have an anti-cancer effect. Therefore, it has been speculated that polyphenols can regulate tumor growth by controlling certain bacteria and subsequently changing the cellular components and metabolites [61]. In conclusion, the positive effects of polyphenols on human gut health can be clarified through a microbiome approach. The underlying mechanisms of polyphenols on gut microbiota and metabolites using microbiomics, metabolomics, and multiple omics need to be further explored.

References

1. Ganesan, K.; Xu, B. A critical review on polyphenols and health benefits of black soybeans. Nutrients 2017, 9, 455.
2. Fukao, H.; Ijiri, Y.; Miura, M.; Hashimoto, M.; Yamashita, T.; Fukunaga, C.; Oiwa, K.; Kawai, Y.; Suwa, M.; Yamamoto, J. Effect of trans-resveratrol on the thrombogenicity and atherogenicity in apolipoprotein e-deficient and low-density lipoprotein receptor-deficient mice. Blood Coagul. Fibrinolysis 2004, 15, 441–446.
3. Mahmoud, A.M.; Bautista, R.J.H.; Sandhu, M.A.; Hussein, O.E. Beneficial effects of citrus flavonoids on cardiovascular and metabolic health. Oxidative Med. Cell. Longev. 2019, 2019, 5484138.
4. Vallance, T.M.; Ravishankar, D.; Albadawi, D.A.I.; Osborn, H.M.I.; Vaiyapuri, S. Synthetic flavonoids as novel modulators of platelet function and thrombosis. IJMS 2019, 20, 3106.
5. Ciumărnean, L.; Milaciu, M.V.; Runcan, O.; Vesa Ştefan, C.; Răchişan, A.L.; Negrean, V.; Perné, M.-G.; Donca, V.I.; Alexescu, T.-G.; Para, I.; et al. The effects of flavonoids in cardiovascular diseases. Molecules 2020, 25, 4320.
6. Owen, R.W.; Giacosa, A.; Hull, W.E.; Haubner, R.; Spiegelhalder, B.; Bartsch, H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. Eur. J. Cancer 2000, 36, 1235–1247.
7. Owen, R.W.; Mier, W.; Giacosa, A.; Hull, W.E.; Spiegelhalder, B.; Bartsch, H. Identification of lignans as major components in the phenolic fraction of olive oil. Clin. Chem. 2000, 46, 976–988.
8. Okuda, T.; Ito, H. Tannins of Constant structure in medicinal and food plants-hydrolyzable tannins and polyphenols related to tannins. Molecules 2011, 16, 2191–2217.
9. Koleckar, V.; Kubikova, K.; Rehakova, Z.; Kuca, K.; Jun, D.; Jahodar, L.; Opletal, L. Condensed and hydrolysable tannins as antioxidants influencing the health. Mini Rev. Med. Chem. 2008, 8, 436–447.
10. Chung, K.-T.; Wong, T.Y.; Wei, C.-I.; Huang, Y.-W.; Lin, Y. Tannins and human health: A review. Crit. Rev. Food Sci. Nutr. 1998, 38, 421–464.

11. Bento-Silva, A.; Koistinen, V.M.; Mena, P.; Bronze, M.R.; Hanhineva, K.; Sahlstrøm, S.; Kitrytė, V.; Moco, S.; Aura, A.-M. Factors affecting intake, metabolism and health benefits of phenolic acids: Do we understand individual variability? Eur. J. Nutr. 2020, 59, 1275–1293.
12. De Camargo, A.C.; Regitano-d'Arce, M.A.B.; Rasera, G.B.; Canniatti-Brazaca, S.G.; do Prado-Silva, L.; Alvarenga, V.O.; Sant'Ana, A.S.; Shahidi, F. Phenolic acids and flavonoids of peanut by-products: Antioxidant capacity and antimicrobial effects. Food Chem. 2017, 237, 538–544.
13. Szwajgier, D.; Borowiec, K.; Pustelniak, K. The neuroprotective effects of phenolic acids: Molecular mechanism of action. Nutrients 2017, 9, 477.
14. Berman, A.Y.; Motechin, R.A.; Wiesenfeld, M.Y.; Holz, M.K. The therapeutic potential of resveratrol: A review of clinical trials. NPJ Precis. Oncol. 2017, 1, 35.
15. Cheng, C.K.; Luo, J.-Y.; Lau, C.W.; Chen, Z.-Y.; Tian, X.Y.; Huang, Y. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. Br. J. Pharmacol. 2020, 177, 1258–1277.
16. Varoni, E.M.; lo Faro, A.F.; Sharifi-Rad, J.; Iriti, M. Anticancer molecular mechanisms of resveratrol. Front. Nutr. 2016, 3, 8.
17. Senizza, A.; Rocchetti, G.; Mosele, J.I.; Patrone, V.; Callegari, M.L.; Morelli, L.; Lucini, L. Lignans and gut microbiota: An interplay revealing potential health implications. Molecules 2020, 25, 5709.
18. Cui, Q.; Du, R.; Liu, M.; Rong, L. Lignans and their derivatives from plants as antivirals. Molecules 2020, 25, 183.
19. Rodríguez-García, C.; Sánchez-Quesada, C.; Toledo, E.; Delgado-Rodríguez, M.; Gaforio, J. Naturally lignan-rich foods: A dietary tool for health promotion? Molecules 2019, 24, 917.
20. Yu, J.; Bi, X.; Yu, B.; Chen, D. Isoflavones: Anti-inflammatory benefit and possible caveats. Nutrients 2016, 8, 361.
21. Zaheer, K.; Akhtar, M.H. An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. Crit. Rev. Food Sci. Nutr. 2017, 57, 1280–1293.
22. Umeno, A.; Horie, M.; Murotomi, K.; Nakajima, Y.; Yoshida, Y. Antioxidative and antidiabetic effects of natural polyphenols and isoflavones. Molecules 2016, 21, 708.
23. Hostetler, G.L.; Ralston, R.A.; Schwartz, S.J. Flavones: Food sources, bioavailability, metabolism, and bioactivity. Adv. Nutr. 2017, 8, 423–435.
24. Kilani-Jaziri, S.; Mustapha, N.; Mokdad-Bzeouich, I.; El Gueder, D.; Ghedira, K.; Ghedira-Chekir, L. Flavones induce immunomodulatory and anti-inflammatory effects by activating cellular anti-oxidant activity: A structure-activity relationship study. Tumor Biol. 2016, 37, 6571–6579.
25. Jiang, N.; Doseff, A.I.; Grotewold, E. Flavones: From biosynthesis to health benefits. Plants 2016, 5, 27.
26. Barreca, D.; Gattuso, G.; Bellocco, E.; Calderaro, A.; Trombetta, D.; Smeriglio, A.; Lagana, G.; Daglia, M.; Meneghini, S.; Nabavi, S.M. Flavanones: Citrus phytochemical with health-promoting properties. Biofactors 2017, 43, 495–506.
27. Testai, L.; Calderone, V. Nutraceutical value of citrus flavanones and their implications in cardiovascular disease. Nutrients 2017, 9, 502.
28. Martinez, V.; Mestre, T.C.; Rubio, F.; Girones-Vilaplana, A.; Moreno, D.A.; Mittler, R.; Rivero, R.M. Accumulation of flavonols over hydroxycinnamic acids favors oxidative damage protection under abiotic stress. Front. Plant Sci. 2016, 7, 838.
29. Scarano, A.; Butelli, E.; de Santis, S.; Cavalcanti, E.; Hill, L.; de Angelis, M.; Giovinazzo, G.; Chieppa, M.; Martin, C.; Santino, A. Combined dietary anthocyanins, flavonols, and stilbenoids alleviate inflammatory bowel disease symptoms in mice. Front. Nutr. 2018, 4, 75.
30. Aherne, S.A.; O'Brien, N.M. Dietary flavonols: Chemistry, food content, and metabolism. Nutrition 2002, 18, 75–81.
31. Mena, P.; Bresciani, L.; Brindani, N.; Ludwig, I.A.; Pereira-Caro, G.; Angelino, D.; Llorach, R.; Calani, L.; Brighenti, F.; Clifford, M.N.; et al. Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: Synthesis, analysis, bioavailability, and bioactivity. Nat. Prod. Rep. 2019, 36, 714–752.
32. Mena, P.; Dolores, G.; Brindani, N.; Esteban-Fernández, A.; Curti, C.; Moreno-Arribas, M.V.; Rio, D.D.; Bartolomé, B. 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone and its sulphate conjugates, representative circulating metabolites of flavan-3-ols, exhibit anti-adhesive activity against uropathogenic escherichia coli in bladder epithelial cells. J. Funct. Foods 2017, 29, 275–280.
33. Fayeulle, N.; Vallverdu-Queralt, A.; Meudec, E.; Hue, C.; Boulanger, R.; Cheynier, V.; Sommerer, N. Characterization of new flavan-3-Ol derivatives in fermented cocoa beans. Food Chem. 2018, 259, 207–212.

34. Khoo, H.E.; Azlan, A.; Tang, S.T.; Lim, S.M. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr. Res. 2017, 61, 1361779.

35. Ali, H.M.; Almagribi, W.; Al-Rashidi, M.N. Antiradical and reductant activities of anthocyanidins and anthocyanins, structure-activity relationship and synthesis. Food Chem. 2016, 194, 1275–1282.

36. Mudd, A.M.; Gu, T.; Munagala, R.; Jeyabalan, J.; Egilmez, N.K.; Gupta, R.C. Chemoprevention of colorectal cancer by anthocyanidins and mitigation of metabolic shifts induced by dysbiosis of the gut microbiome. Cancer Prev. Res. 2020, 13, 41–51.

37. Zhang, L.-L.; Lin, Y.-M.; Zhou, H.-C.; Wei, S.-D.; Chen, J.-H. Condensed tannins from mangrove species kandelia candel and rhizophora mangle and their antioxidant activity. Molecules 2010, 15, 420–431.

38. Smeriglio, A.; Barreca, D.; Bellocco, E.; Trombetta, D. Proanthocyanidins and hydrolysable tannins: Occurrence, dietary intake and pharmacological effects: Pharmacological aspects of tannins. Br. J. Pharmacol. 2017, 174, 1244–1262.

39. Tie, F.; Wang, J.; Liang, Y.; Zhu, S.; Wang, Z.; Li, G.; Wang, H. Proanthocyanidins ameliorated deficits of lipid metabolism in type 2 diabetes mellitus via inhibiting adipogenesis and improving mitochondrial function. IJMS 2020, 21, 2029.

40. Ismail, T.; Calcabrini, C.; Diaz, A.; Fimognari, C.; Turrini, E.; Catanzaro, E.; Akhtar, S.; Sestili, P. Ellagitannins in cancer chemoprevention and therapy. Toxins 2016, 8, 151.

41. Rasines-Perea, Z.; Jacquet, R.; Jourdes, M.; Quideau, S.; Teissedre, P.-L. Ellagitannins and flavano-ellagitannins: Red wines tendency in different areas, barrel origin and ageing time in barrel and bottle. Biomolecules 2019, 9, 316.

42. Theodorou, M.K.; Kingston-Smith, A.H.; Winters, A.L.; Lee, M.R.F.; Minchin, F.R.; Morris, P.; MacRae, J. Polyphenols and their influence on gut function and health in ruminants: A review. Environ. Chem. Lett. 2006, 4, 121–126.

43. Geng, D.; Fang, M.Y.; Deli, L.I.; Zheng, S.Q.; Lijun, D.U. Research progress in terms of interaction between chinese medicine components and intestinal microenvironment. Sci. Sin. 2018, 48, 379–389.

44. Luca, S.V.; Macovei, I.; Bujor, A.; Miron, A.; Skalicka-Wozniak, K.; Aprotosoaie, A.C.; Trifan, A. Bioactivity of dietary polyphenols: The role of metabolites. Crit. Rev. Food Sci. Nutr. 2020, 60, 626–659.

45. Gerritsen, J.; Smidt, H.; Rijkers, G.T.; de Vos, W.M. Intestinal microbiota in human health and disease: The impact of probiotics. Genes Nutr. 2011, 6, 209–240.

46. Larrosa, M.; Yanez-Gascon, J.M.; Selma, V.M.; Gonzalez-Sarrias, A.; Toti, S.; Ceron, J.J.; Tomas-Barberan, F.; Dolara, P.; Espin, J.C. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. J. Agric. Food Chem. 2009, 57, 2211–2220.

47. Kim, N.; Kunisawa, J.; Kweon, M.-N.; Ji, G.E.; Kiyono, H. Oral feeding of Bifidobacterium bifidum (BGN4) prevents CD4(+) CD45RB(High) T cell-mediated inflammatory bowel disease by inhibition of disordered T cell activation. Clin. Immunol. 2007, 123, 30–39.

48. Yuan, X.; Long, Y.; Ji, Z.; Gao, J.; Fu, T.; Yan, M.; Zhang, L.; Su, H.; Zhang, W.; Wen, X.; et al. Green tea liquid consumption alters the human intestinal and oral microbiome. Mol. Nutr. Food Res. 2018, 62, 1800178.

49. Vendrame, S.; Guglielmetti, S.; Riso, P.; Arioli, S.; Klimis-Zacas, D.; Porrini, M. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. J. Agric. Food Chem. 2011, 59, 12815.

50. Nishida, A.; Inoue, R.; Inatomi, O.; Bamba, S.; Naito, Y.; Andoh, A. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin. J. Gastroenterol. 2018, 11, 1–10.

51. Hou, J.; Hu, M.; Zhang, L.; Gao, Y.; Ma, L.; Xu, Q. Dietary taxifolin protects against dextran sulfate sodium-induced colitis via NF-KB signaling, enhancing intestinal barrier and modulating gut microbiota. Front. Immunol. 2020, 11, 631809.

52. Duda-Chodak, A.; Tarko, T.; Satora, P.; Sroka, P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. Eur. J. Nutr. 2015, 54, 325–341.

53. Edwards, C.A.; Havlik, J.; Cong, W.; Mullen, W.; Preston, T.; Morrison, D.J.; Combet, E. Polyphenols and health: Interactions between fibre, plant polyphenols and the gut microbiota. Nutr. Bull. 2017, 42, 356–360.

54. Li, W.; Deng, Y.; Chu, Q.; Zhang, P. Gut microbiome and cancer immunotherapy. Cancer Lett. 2019, 447, 41–47.

55. Ma, C.; Han, M.; Heinrich, B.; Fu, Q.; Zhang, Q.; Sandhu, M.; Agdashian, D.; Terabe, M.; Berzofsky, J.A.; Fako, V.; et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018, 360, eaan5931.

56. Tomás-Barberán, F.A.; Selma, M.V.; Espín, J.C. Interactions of gut microbiota with dietary polyphenols and consequences to human health. Curr. Opin. Clin. Nutr. Metab. Care 2016, 19, 471–476.

57. De Bruyne, T.; Steenput, B.; Roth, L.; de Meyer, G.R.Y.; Santos, C.N.D.; Valentová, K.; Dambrova, M.; Hermans, N. Dietary Polyphenols targeting arterial stiffness: Interplay of contributing mechanisms and gut microbiome-related metabolism. Nutrients 2019, 11, E578.
58. Sorrenti, V.; Ali, S.; Mancin, L.; Davinelli, S.; Paoli, A.; Scapagnini, G. Cocoa polyphenols and gut microbiota interplay: Bioavailability, prebiotic effect, and impact on human health. Nutrients 2020, 12, E1908.
59. Aviram, M.; Rosenblat, M. Pomegranate protection against cardiovascular diseases. Evid. Based Complement. Alternat. Med. 2012, 2012, 382763.
60. Zhou, J.; Tang, L.; Shen, C.-L.; Wang, J.-S. Green tea polyphenols boost gut-microbiota-dependent mitochondrial TCA and urea cycles in Sprague-Dawley rats. J. Nutr. Biochem. 2020, 81, 108395.
61. Yang, R.; Shan, S.; Zhang, C.; Shi, J.; Li, H.; Li, Z. Inhibitory effects of bound polyphenol from foxtail millet bran on colitis-associated carcinogenesis by the restoration of gut microbiota in a mice model. J. Agric. Food Chem. 2020, 68, 3506–3517.

Retrieved from https://encyclopedia.pub/entry/history/show/37936