EFFECTS OF POLYPHENOLS ON HUMAN HEALTH

Goran Belojević[1]

[1] Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Corresponding author:

Prof. dr Goran Belojević

Medicinski fakultet Univerziteta u Beogradu, Dr Subotića starijeg 8, Beograd, Srbija

goran.belojevic1956@gmail.com

Abstract

Polyphenols are nutrients that are classified as phytochemicals because they are found exclusively in foods of plant origin. They are divided into flavonoids (flavonols, flavanones, isoflavones, anthocyanins, flavan-3-ols, and flavones) and nonflavonoids (phenolic acids, hydrocinnamates, ellagitannins and ellagic acid, stilbenes, lignans, dihydrochalcones, and coumarins). Research shows that polyphenols have multiple positive health effects.

This paper aims to systematize recent scientific results on the effects of polyphenols on health.

A search of the scientific literature of the last 20 years in the English language on the health effects of polyphenols was performed in the "PubMed" database using the keywords: "polyphenols"; "microbiota"; "diabetes mellitus"; "cardiovascular diseases"; "cognitive functions"; "viral diseases"; "cancer"; "mental health" and "dyslipidemias".

There is a mutual positive influence of polyphenols and microbiota. Polyphenols affect the composition of the microbiota, especially the growth of beneficial microbiotic strains. In epidemiological studies, polyphenols have shown a protective effect concerning DM type 2 by lowering blood glucose and glycosylated hemoglobin, reducing insulinemia and increasing insulin sensitivity, reducing inflammation and oxidative stress in cells. By reducing arterial stiffness, oxidative stress, inflammation, and endothelial dysfunction, and regulating the production of nitrogen monoxide and cytokines, they reduce the risk of hypertension, myocardial infarction, and cerebral insult. Polyphenols have a positive effect on cognitive functions and executive functioning and reduce the risk of Parkinson's disease. Their antiviral effect is based on the inhibition of the enzyme helicase, which is necessary for viral replication and recombination, reduction of oxidative stress, virucidal effect, interaction with the structural proteins of the virus, and interference with the fusion of the virus with the cell membrane, reduction of inflammation and increase of immunity and reduction of dysbiosis in the intestines and lungs. The protective effect of polyphenols concerning cancer is based on induced apoptosis, inhibition of the matrix-metalloproteinase enzyme that enables metastases, inhibition of tumor growth, and inhibition of angiogenesis. In terms of mental health, polyphenols reduce the risk of depression and ADHD (Attention Deficit Hyperactivity Disorder) and have a beneficial effect on the reduction of tardive dyskinesia in patients with schizophrenia. They also have a positive effect on dyslipidemia, by reducing the level of LDL cholesterol and increasing the level of HDL cholesterol.

Polyphenols are phytochemicals with multiple positive health effects. They work synergistically with the gut microbiota. Epidemiological studies have shown that polyphenols reduce the risk of diabetes mellitus type 2, hypertension, myocardial infarction, cerebral insult, viral diseases, Parkinson's disease, cognitive disorders, cancer, depression, and dyslipidemia. Nutritional support or supplementation with polyphenols can be recommended in the primary and secondary prevention of the mentioned diseases.

Keywords: polyphenols, microbiota, diabetes mellitus, hypertension, myocardial infarction, cognition, virus diseases, cancer, depression, dyslipidemias

Introduction

Under the term polyphenols, we refer to nutrients that are classified as phytochemicals. Plant-based foods are the exclusive nutritional source of polyphenols. Their specific characteristic is that a relative deficiency in the body is not tied to specific symptoms. Therefore, there are no established values for recommended daily intake of polyphenols as is the case with vitamins and minerals.

DOI: 10.5937/Galmed2307046B

Each polyphenol has at least one aromatic ring and one or more attached hydroxyl functional groups[1].

Polyphenols are classified into five groups: flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols. In a narrower classification, polyphenols are categorized as flavonoid (flavonoids) and non-flavonoid (the other four groups)[2].

Flavonoid polyphenols are divided into flavonols (the main nutritional source is onion), flavanones (citrus fruits), isoflavones (soy), anthocyanins (blueberries), flavan-3-ols (black tea), and flavones (celery), as detailed in Table 1[3].

Table 1. Classification of Flavonoid Polyphenols (Flavonoids)

Subgroup of Flavonoids	Representatives	Best Nutritional Sources
Flavonols	Quercetin Myricetin	Onion, black tea, green tea, almonds
Flavanones	Hesperidin Eriodictyol	Citrus fruits, tomato
Isoflavones	Daidzein Genistein	Soy, tofu, legumes
Anthocyanins	Cyanidin	Blueberries, blackberries, raspberries, red wine
Flavan-3-ols	Catechin Epicatechin gallate	Black tea, green tea, dark chocolate, hazelnuts, almonds
Flavones	Luteolin Apigenin	Celery, vegetable oils, cereals

Source: Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA The effects of polyphenols and other bioactives on human health. Food Funct. 2019;10(2):514-28.

Non-flavonoid polyphenols include phenolic acids (the main nutritional source is pomegranate), hydroxycinnamates (coffee), ellagitannins and ellagic acid (tropical fruits), stilbenes (red wine), lignans (seeds), dihydrochalcones (apples), and coumarins (cinnamon), as shown in Table 2[4].

Table 2. Classification of Non-flavonoid Polyphenols

Non-flavonoid polyphenols	Representatives	Nutritional sources
Phenolic acids	Benzoic acid	Pomegranate, cereals, black tea
Hydroxycinnamates	Hydroxycinnamic acid, caffeic acid	Coffee, red wine, red fruits, vegetables, whole grains
Ellagitanins and ellagic acid	Punicalagin, castalagin	Tropical fruit, berries, nuts
Stilbenes	Resveratrol	Red wine, grapes
Lignans	Secoisolariciresinol	Seeds, cereals
Dihydrochalcones	Floretin	Apples
Coumarins	Coumarin	Cinnamon

Source: Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: chemistry, sources, mechanisms of action, and safety, J. Nutr. Gerontol. Geriatr., 2012, 31, 176-19.

This study aimes is to systematize the results of recent scientific research on the effects of polyphenols on human health.

A search of scientific literature published in the period 2002-2022 in the English language on the health effects of polyphenols was conducted using the "PubMed" database. The search keywords included: "polyphenols"; "microbiota"; "diabetes mellitus"; "cardiovascular diseases"; "cognitive functions"; "viral diseases"; "cancer"; "mental health"; and "dyslipidemias".

Microbiota and Polyphenols

After enzymatic deconjugation, polyphenols are absorbed to a lesser extent in the small intestine and to a greater extent in the colon. Preserved microbiota is crucial for the unimpeded absorption of polyphenols. The microbiota plays a role in further breaking down deconjugated polyphenols into phenolic acids, which are absorbed from the intestines in that form[5].

There is a mutual positive influence between polyphenols and the microbiota. Polyphenols affect the composition of the microbiota, particularly promoting the growth of beneficial microbial strains such as *Bifidobacterium*, *Lactobacillus*, *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii*[6]. If the diet is rich in blueberries, which are abundant in anthocyanins, there is an increase in the strains of *Lactobacillus acidophilus* and *Bifidobacterium* in the intestines[7]. On the other hand, for instance, to manifest a positive effect of isoflavones on the cardiovascular system, daidzein must be converted into equol in the colon under the influence of the microbiota. Therefore, the positive health effect of isoflavones is possible only if the microbiota composition includes bacteria that produce equol[8]. In synergy with the gut microbiota, polyphenols from green and black tea can slow down the growth of pathogenic microorganisms and influenza viruses, Hepatitis C virus, and HIV[9].

Polyphenols and Diabetes Mellitus Type 2

Polyphenols stimulate insulin secretion, promote beta-cell proliferation in the islets of Langerhans in the endocrine pancreas, and reduce insulin resistance, inflammation, and oxidative stress in cells. Epidemiological studies have demonstrated the protective effect of polyphenols on type 2 diabetes mellitus by lowering fasting blood glucose and glycosylated hemoglobin, reducing insulinemia, and increasing insulin sensitivity, especially anthocyanins, resveratrol, gallic acid, and flavanones[10, 11].

Floretin from apples is an inhibitor of the sodium-glucose cotransporter in the intestines (SGLT-1) and in the kidneys (SGLT-2), thereby reducing hyperglycemia[12]. In individuals with type 2 diabetes mellitus, polyphenols have a beneficial effect on regulating endothelial function, glucose metabolism, oxidative stress biomarkers, coagulation, cholesterol metabolism, and there are other indirect effects mediated through the gut microbiota. Polyphenols from coffee, tea, apples, and cocoa exhibit favorable effects in alleviating type 2 diabetes mellitus symptoms[13]. An increased intake of flavan-3-ols from legumes, chocolate, red wine, nuts, and tea also contributes to reducing the risk of developing type 2 diabetes mellitus[14]. Meta-analysis has demonstrated that regular consumption of dark chocolate rich in flavan-3-ols reduces the risk of developing type 2 diabetes mellitus by 31%[15]. Another meta-analysis has established that increased intake of anthocyanins from berries leads to a significant reduction in fasting blood glucose, postprandial glucose, and glycosylated hemoglobin[16]. Resveratrol has a favorable effect on glycemic control by increasing insulin sensitivity[17]. If polyphenol-rich fruit is consumed alongside fast food or bakery products, it reduces inflammation, postprandial glucose, and insulin levels[18, 19].

Polyphenols and Cardiovascular Diseases

A negative correlation has been found between the intake of polyphenols from olive oil, nuts, and red wine in the Mediterranean diet and cardiovascular events and overall mortality[20]. Flavan-3-ols from chocolate have a favorable impact on reducing the risk of myocardial infarction, hypertension, and hypercholesterolemia[21]. Regular consumption of chocolate rich in flavan-3-ols also exhibits a positive effect on reducing arterial stiffness, thereby reducing the risk of hypertension[22]. A meta-analysis has shown that individuals who consume higher amounts of dark chocolate with flavan-3-ols have a 37% lower risk of cardiovascular diseases and a 29% lower risk of stroke compared to those who do not consume these foods[15]. Another meta-analysis has demonstrated that increased intake of anthocyanins from berries and red wine significantly reduces LDL cholesterol levels and systolic blood pressure[16]. Resveratrol from red wine has anti-inflammatory and antioxidant effects based on the regulation of nitric oxide and cytokine production[23]. Another positive effect of resveratrol is the slowing of aging through the activation of yeast sirtuins[24]. In addition to consuming resveratrol-rich foods, supplementation with resveratrol also has a positive effect on the cardiovascular system by reducing total cholesterol, C-reactive protein, as well as systolic and diastolic blood pressure[25]. Quercetin has a favorable effect on endothelial function by regulating vasoactive nitric oxide and endothelin-1[26]. Supplementation with quercetin at a dose of ≥ 500 mg per day leads to a significant reduction in systolic and diastolic blood pressure, as well as LDL cholesterol[27, 28]. A meta-analysis of randomized controlled trials has shown that resveratrol significantly reduces blood levels of C-reactive protein (37%), making it a recommended nutritional support for the treatment of cardiovascular disease patients due to its anti-inflammatory effect[29]. Resveratrol exerts a favorable effect on endothelial function by increasing flow-mediated arterial dilation and reducing intracellular adhesion molecule, which can be utilized in supplementation for individuals with cardiovascular diseases[30]. A meta-analysis of 10 observational studies has demonstrated a dose-dependent favorable effect of green tea consumption on reducing the risk of intracerebral hemorrhage, with a 6% decrease for each cup of tea (120 mL)[31].

Polyphenols and Cognitive and Neurological Functions

A meta-analysis has shown that regular consumption of green tea, but not black tea, reduces the risk of cognitive disorders by 27%. There is also a dose-dependent effect, where the risk of cognitive disorders decreases by 6% with a daily intake of 100 mL of tea, by 19% with an intake of 300 mL, and by 29% with a consumption of 500 mL of tea per day[32]. If one cup of black or green tea is consumed daily, the risk of Parkinson's disease is reduced by 17%, without indications of a dose-dependent risk reduction with an increase in the number of consumed cups of tea per day[33]. It has been shown that supplementation with approximately 500 mg of flavan-3-ols per day leads to improvements in cognitive functions such as attention and executive functioning[34]. Flavan-3-ols increase levels of serum Brain-Derived Neurotrophic Factor (BDNF), which is important for the differentiation of new neurons and synapses in the brain and improved cognitive functions[35]. A meta-analysis encompassing 80 studies has demonstrated that the greatest effects on cognitive functions such as long-term memory, mental processing speed, and mood are attributed to polyphenols from cocoa, Ginkgo biloba, and blueberries[36].

Antiviral Effects of Polyphenols

The antiviral effects of polyphenols are based on multiple mechanisms, including inhibition of helicase enzymes (essential for viral replication and recombination), reduction of oxidative stress, virucidal effects, interaction with viral structural proteins, and disruption of virus-cell membrane fusion, reduction of inflammation, enhancement of immunity, and mitigation of dysbiosis in the gut and lungs through prebiotic roles[37]. Polyphenols from green tea (epigallocatechin gallate) and black tea (theaflavins) inhibit the RNA-dependent RNA polymerase, which is crucial for the replication and transcription of SARS-CoV-2. They also exhibit inhibitory effects on the structural proteins of SARS-CoV-2, ACE-2 receptors, and the receptor-binding domain on the spike protein[38]. Therefore, tea can be recommended as nutritional support for COVID-19 prevention and treatment. In addition to its effect on SARS-CoV-2, epigallocatechin also has inhibitory effects on hepatitis, Zika, Dengue, Ebola, influenza, rotavirus, and norovirus. Theaflavins exhibit inhibitory effects on HIV, rotavirus, influenza virus, and calicivirus[39]. Propolis contains polyphenols, including flavonoids, and exhibits an inhibitory effect on *Herpes simplex* virus type 1 and type 2 by preventing their penetration into cells[40].

DOI: 10.5937/Galmed2307046B

Anthocyanins from berries exert an inhibitory effect on the influenza virus by preventing replication within cells[41]. Similarly, resveratrol from berries acts by blocking the kinase C enzyme necessary for virus replication[42]. On the Zika virus, resveratrol from berries and red wine acts by inhibiting the virus from binding to the cell and its replication within the cell[43]. The inhibitory effect on the dengue virus is based on preventing its replication within the cell[44]. Resveratrol prevents the respiratory syncytial virus from binding to receptors on respiratory tract cells[45]. It also inhibits the intracellular replication of hepatitis C virus[46]. The inhibitory effect of resveratrol on HIV-1 is manifested through the obstruction of reverse transcription in CD4 T cells[47]. For the *Varicella-zoster virus*, it inhibits intracellular replication[48].

Polyphenols and Cancer

The anti-tumor effect of polyphenols is based on induced apoptosis, inhibition of matrix metalloproteinase enzymes that enable metastasis, inhibition of tumor growth, and inhibition of angiogenesis[49]. An anamnestic study conducted in Canada has shown that polyphenols have a protective effect against lung cancer. When comparing individuals in the highest and lowest quartiles of total flavonoid intake from food, those with a high flavonoid intake had a 37% lower risk of developing squamous cell lung cancer, while no association with flavonoid intake was observed for adenocarcinoma[50]. In terms of colorectal cancer, epidemiological studies have demonstrated a protective effect of dietary intake of total flavonoids and lignans. When comparing the upper and lower quartiles based on polyphenol intake from food, it has been shown that high intake of total flavonoids and lignans reduces the risk of colorectal cancer by as much as 41%[51]. A meta-analysis based on 40 epidemiological studies has demonstrated that a high dietary intake of isoflavones from soy reduces the risk of gastrointestinal cancers by 27%[52]. A meta-analysis based on 12 epidemiological studies has shown that the risk of breast cancer is reduced by 12% with a high intake of flavonols and by 17% with high intake of flavones. However, no protective effect was found for flavan-3-ols, flavanones, anthocyanins, or total flavonoids[53]. Polyphenols exhibit a protective effect against estrogen receptor-negative breast cancer, but not against estrogen receptor-positive breast cancer[54]. A meta-analysis of 19 studies from Europe and Asia has demonstrated that high polyphenol intake reduces the risk of gastric cancer by 29%, with a greater protective effect observed in women (35%) compared to men (21%)[55].

Polyphenols and Mental Health

The use of green tea extract at a dose of 400 mg, three times a day in mentally healthy individuals significantly acts preventively against the development of depressive symptoms compared to the placebo group[56]. When comparing individuals who regularly consume black or green tea with those who rarely or never consume tea, regular consumers exhibit a 31% lower risk of developing depression. Additionally, a dose-dependent effect is observed, where with each increase in daily tea consumption by three cups, the risk of depression decreases by 37%[57]. In individuals with schizophrenia, a 12-week administration of Ginkgo biloba extract at a dose of 240 mg daily resulted in a significant reduction of tardive dyskinesia symptoms (involuntary movements) compared to the placebo group[58]. It has been shown that after five weeks of administration at a dose of 240 mg daily, Ginkgo biloba has positive effects on reducing symptoms of ADHD and improving the quality of life in children[59].

Polyphenols and Dyslipidemias

An eight-week consumption of moderate amounts of blackberries leads to a significant increase in HDL cholesterol levels in individuals without medication but with present cardiovascular risk factors, compared to the placebo group[60]. A meta-analysis of 17 studies has demonstrated that the intake of epigallocatechin gallate polyphenols from green tea over 4-14 weeks, with a daily dose ranging between 107 and 856 mg, leads to a significant reduction in LDL cholesterol levels[61]. The administration of anthocyanins from Aronia extract at a dose of 500 mg daily for 12 weeks in former smokers led to a significant reduction of LDL cholesterol levels by 11%[62]. The administration of resveratrol at a daily dose of 500 mg for 12 weeks led to a significant reduction in the enzyme alanine aminotransferase and the degree of liver steatosis compared to the placebo group[63]. A meta-analysis of randomized controlled clinical trials has shown a significant dose-dependent effect of resveratrol on reducing LDL cholesterol levels in the blood. The effect on total cholesterol and triglyceridemia is also favorable, but without dose dependence[64].

Conclusion

Polyphenols are phytochemicals with multiple positive effects on health. They influence the composition of the microbiota, particularly by stimulating the growth of beneficial microbial strains such as *Lactobacillus* and *Bifidobacterium*. In individuals with type 2 diabetes mellitus, they stimulate insulin secretion, and beta cell proliferation in the Langerhans islets of the endocrine pancreas, reduce insulin resistance, inflammation, and oxidative stress in cells. With their anti-inflammatory and antioxidant actions, based on the regulation of nitric oxide production, cytokines, and the reduction of arterial stiffness and LDL cholesterol, polyphenols contribute to reducing the risk of myocardial infarction, hypertension, and stroke. They exhibit inhibitory effects on a wide range of viruses. The antitumor effect of polyphenols is based on induced apoptosis, inhibition of matrix metalloproteinase enzymes that enable metastasis, inhibition of tumor growth, and angiogenesis. In terms of neurological effects, polyphenols have a positive impact on cognitive functions, executive functioning, and a reduced risk of developing Parkinson's disease. They also provide protection against the development of depressive symptoms, symptoms of ADHD in children, and involuntary movements in individuals with schizophrenia. Polyphenols also have a favorable effect on dyslipidemia by reducing LDL cholesterol levels and increasing HDL cholesterol levels. Nutritional support or supplementation with polyphenols can be recommended in both primary and secondary prevention of the mentioned conditions.

Literature

1. (Lupton JR, Atkinson SA, Chang N, Fraga CG, Levy J, Messina M, et al. Exploring the benefits and challenges of establishing a DRI-like process for bioactives. Eur J Nutr. 2014 Apr;53 Suppl 1(Suppl 1):1-9.
2. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Funct. 2019 Feb 20;10(2):514-28.
3. Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: chemistry, sources, mechanisms of action, and safety. J Nutr Gerontol Geriatr. 2012;31(3):176-89.
4. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Funct . 2019;10(2):514-28.
5. Selma MV, Espín JC, Tomás-Barberán FA. Interaction between phenolics and gut microbiota: role in human health. J Agric Food Chem. 2009 Aug 12;57(15):6485-501.
6. Tomás-Barberán FA, Selma MV, Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health. Curr Opin Clin Nutr Metab Care. 2016 Nov;19(6):471-6.
7. 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 Dec 28;59(24):12815-20.
8. Frankenfeld CL. Cardiometabolic risk and gut microbial phytoestrogen metabolite phenotypes. Mol Nutr Food Res. 2017 Jan;61(1).
9. 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 Apr;54(3):325-41.
10. Cao H, Ou J, Chen L, Zhang Y, Szkudelski T, Delmas D, et al. Dietary polyphenols and type 2 diabetes: Human Study and Clinical Trial. Crit Rev Food Sci Nutr. 2019;59(20):3371-9.
11. Costabile G, Vitale M, Luongo D, Naviglio D, Vetrani C, Ciciola P, et al. Grape pomace polyphenols improve insulin response to a standard meal in healthy individuals: A pilot study. Clin Nutr. 2019 Dec;38(6):2727-34.
12. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev. 2005 Jan-Feb;21(1):31-8.
13. Wang D, Chen C, Wang Y, Liu J, Lin R. Effect of black tea consumption on blood cholesterol: a meta-analysis of 15 randomized controlled trials. PLoS One. 2014 Sep 19;9(9):e107711.
14. Greenberg JA. Chocolate intake and diabetes risk. Clin Nutr. 2015 Feb;34(1):129-33.
15. Buitrago-Lopez A, Sanderson J, Johnson L, Warnakula S, Wood A, Di Angelantonio E, et al. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ. 2011 Aug 26;343:d4488.
16. Yang L, Ling W, Du Z, Chen Y, Li D, Deng S, et al. Effects of Anthocyanins on Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Nutr. 2017 Sep 15;8(5):684-93.
17. Liu K, Zhou R, Wang B, Mi MT. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. Am J Clin Nutr. 2014 Jun;99(6):1510-9.
18. Joseph SV, Edirisinghe I, Burton-Freeman BM. Fruit Polyphenols: A Review of Anti-inflammatory Effects in Humans. Crit Rev Food Sci Nutr. 2016;56(3):419-44.
19. Nyambe-Silavwe H, Williamson G. Polyphenol- and fibre-rich dried fruits with green tea attenuate starch-derived postprandial blood glucose and insulin: a randomised, controlled, single-blind, cross-over intervention. Br J Nutr. 2016 Aug;116(3):443-50.
20. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, Martínez-González MA, de la Torre R, Corella D, et al; PREDIMED Study Investigators. Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. Nutr Metab Cardiovasc Dis. 2014 Jun;24(6):639-47.
21. Larsson SC, Åkesson A, Gigante B, Wolk A. Chocolate consumption and risk of myocardial infarction: a prospective study and meta-analysis. Heart. 2016 Jul 1;102(13):1017-22.
22. Crichton GE, Elias MF, Alkerwi A, Stranges S, Abhayaratna WP. Relation of Habitual Chocolate Consumption to Arterial Stiffness in a Community-Based Sample: Preliminary Findings. Pulse (Basel). 2016 Jul;4(1):28-37.
23. Tomé-Carneiro J, Larrosa M, González-Sarrías A, Tomás-Barberán FA, García-Conesa MT, Espín JC. Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. Curr Pharm Des. 2013;19(34):6064-93.
24. Bonkowski MS, Sinclair DA. Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. Nat Rev Mol Cell Biol. 2016 Nov;17(11):679-90.
25. Guo XF, Li JM, Tang J, Li D. Effects of resveratrol supplementation on risk factors of non-communicable diseases: A meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2018;58(17):3016-29.
26. Loke WM, Hodgson JM, Proudfoot JM, McKinley AJ, Puddey IB, Croft KD. Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. Am J Clin Nutr. 2008 Oct;88(4):1018-25.
27. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr. 2009 Oct;102(7):1065-74.

28. Bondonno NP, Bondonno CP, Rich L, Mas E, Shinde S, Ward NC, et al. Acute effects of quercetin-3-O-glucoside on endothelial function and blood pressure: a randomized dose-response study. Am J Clin Nutr. 2016 Jul;104(1):97-103.
29. Teimouri M, Homayouni-Tabrizi M, Rajabian A, Amiri H, Hosseini H. Anti-inflammatory effects of resveratrol in patients with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2022 Nov;70:102863.
30. Mohammadipoor N, Shafiee F, Rostami A, Kahrizi MS, Soleimanpour H, Ghodsi M, et al. Resveratrol supplementation efficiently improves endothelial health: A systematic review and meta-analysis of randomized controlled trials. Phytother Res. 2022 Sep;36(9):3529-39.
31. Cheng P, Zhang J, Liu W, Sun Q, Fu Z, Lin H, et al. Tea consumption and cerebral hemorrhage risk: a meta-analysis. Acta Neurol Belg. 2022 Oct;122(5):1247-59.
32. Liu X, Du X, Han G, Gao W. Association between tea consumption and risk of cognitive disorders: A dose-response meta-analysis of observational studies. Oncotarget. 2017 Jun 27;8(26):43306-21.
33. Li FJ, Ji HF, Shen L. A meta-analysis of tea drinking and risk of Parkinson's disease. ScientificWorldJournal. 2012;2012:923464.
34. Mastroiacovo D, Kwik-Uribe C, Grassi D, Necozione S, Raffaele A, Pistacchio L, et al. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study--a randomized controlled trial. Am J Clin Nutr. 2015 Mar;101(3):538-48.
35. Neshatdoust S, Saunders C, Castle SM, Vauzour D, Williams C, Butler L, et al. High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor: Two randomised, controlled trials. Nutr Healthy Aging. 2016 Oct 27;4(1):81-93.
36. Cheng N, Bell L, Lamport DJ, Williams CM. Dietary Flavonoids and Human Cognition: A Meta-Analysis. Mol Nutr Food Res. 2022 Nov;66(21):e2100976.
37. Levy E, Delvin E, Marcil V, Spahis S. Can phytotherapy with polyphenols serve as a powerful approach for the prevention and therapy tool of novel coronavirus disease 2019 (COVID-19)? Am J Physiol Endocrinol Metab. 2020 Oct 1;319(4):E689-E708.
38. Lung J, Lin YS, Yang YH, Chou YL, Shu LH, Cheng YC, et al. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. J Med Virol. 2020 Jun;92(6):693-7.
39. Mhatre S, Srivastava T, Naik S, Patravale V. Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. Phytomedicine. 2021 May;85:153286.
40. Yildirim A, Duran GG, Duran N, Jenedi K, Bolgul BS, Miraloglu M, et al. Antiviral Activity of Hatay Propolis Against Replication of Herpes Simplex Virus Type 1 and Type 2. Med Sci Monit. 2016 Feb 9;22:422-30.
41. Ikuta K, Hashimoto K, Kaneko H, Mori S, Ohashi K, Suzutani T. Anti-viral and anti-bacterial activities of an extract of blackcurrants (Ribes nigrum L.). Microbiol Immunol. 2012 Dec;56(12):805-9.
42. Palamara AT, Nencioni L, Aquilano K, De Chiara G, Hernandez L, Cozzolino F, et al. Inhibition of influenza A virus replication by resveratrol. J Infect Dis. 2005 May 15;191(10):1719-29.
43. Mohd A, Zainal N, Tan KK, AbuBakar S. Resveratrol affects Zika virus replication in vitro. Sci Rep. 2019 Oct 4;9(1):14336.
44. Zainal N, Chang CP, Cheng YL, Wu YW, Anderson R, Wan SW, et al. Resveratrol treatment reveals a novel role for HMGB1 in regulation of the type 1 interferon response in dengue virus infection. Sci Rep. 2017 Feb 20;7:42998.
45. Liu T, Zang N, Zhou N, Li W, Xie X, Deng Y, et al. Resveratrol inhibits the TRIF-dependent pathway by upregulating sterile alpha and armadillo motif protein, contributing to anti-inflammatory effects after respiratory syncytial virus infection. J Virol. 2014 Apr;88(8):4229-36.
46. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5:558-67.
47. Chan CN, Trinité B, Levy DN. Potent Inhibition of HIV-1 Replication in Resting CD4 T Cells by Resveratrol and Pterostilbene. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00408-17.
48. Docherty JJ, Sweet TJ, Bailey E, Faith SA, Booth T. Resveratrol inhibition of varicella-zoster virus replication in vitro. Antiviral Res. 2006 Dec;72(3):171-7.
49. Zhu Y, He W, Gao X, Li B, Mei C, Xu R, et al. Resveratrol overcomes gefitinib resistance by increasing the intracellular gefitinib concentration and triggering apoptosis, autophagy and senescence in PC9/G NSCLC cells. Sci Rep. 2015 Dec 4;5:17730.
50. Christensen KY, Naidu A, Parent MÉ, Pintos J, Abrahamowicz M, Siemiatycki J, et al. The risk of lung cancer related to dietary intake of flavonoids. Nutr Cancer. 2012;64(7):964-74.
51. Zamora-Ros R, Not C, Guinó E, Luján-Barroso L, García RM, Biondo S, et al. Association between habitual dietary flavonoid and lignan intake and colorectal cancer in a Spanish case-control study (the Bellvitge Colorectal Cancer Study). Cancer Causes Control. 2013 Mar;24(3):549-57.
52. Tse G, Eslick GD. Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis. Eur J Nutr. 2016 Feb;55(1):63-73.
53. Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z, Mantian M. Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One. 2013;8(1):e54318.
54. Wang Y, Gapstur SM, Gaudet MM, Peterson JJ, Dwyer JT, McCullough ML. Evidence for an association of dietary flavonoid intake with breast cancer risk by estrogen receptor status is limited. J Nutr. 2014 Oct;144(10):1603-11.
55. Fagundes MA, Silva ARC, Fernandes GA, Curado MP. Dietary Polyphenol Intake and Gastric Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 Nov 29;14(23):5878.
56. Zhang Q, Yang H, Wang J, Li A, Zhang W, Cui X, et al. Effect of green tea on reward learning in healthy individuals: a randomized, double-blind, placebo-controlled pilot study. Nutr J. 2013 Jun 18;12:84.
57. Dong X, Yang C, Cao S, Gan Y, Sun H, Gong Y, et al. Tea consumption and the risk of depression: a meta-analysis of observational studies. Aust N Z J Psychiatry. 2015 Apr;49(4):334-45.
58. Zhang WF, Tan YL, Zhang XY, Chan RC, Wu HR, Zhou DF. Extract of Ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011 May;72(5):615-21.
59. Uebel-von Sandersleben H, Rothenberger A, Albrecht B, Rothenberger LG, Klement S, Bock N. Ginkgo biloba extract EGb 761® in children with ADHD. Z Kinder Jugendpsychiatr Psychother. 2014 Sep;42(5):337-47.
60. Erlund I, Koli R, Alfthan G, Marniemi J, Puukka P, Mustonen P, et al. Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. Am J Clin Nutr. 2008 Feb;87(2):323-31.
61. Momose Y, Maeda-Yamamoto M, Nabetani H. Systematic review of green tea epigallocatechin gallate in reducing low-density lipoprotein cholesterol levels of humans. Int J Food Sci Nutr. 2016 Sep;67(6):606-13.
62. Xie L, Vance T, Kim B, Lee SG, Caceres C, Wang Y, et al. Aronia berry polyphenol consumption reduces plasma total and low-density lipoprotein cholesterol in former smokers without lowering biomarkers of inflammation and oxidative stress: a randomized controlled trial. Nutr Res. 2017 Jan;37:67-77.
63. Faghihzadeh F, Adibi P, Hekmatdoost A. The effects of resveratrol supplementation on cardiovascular risk factors in patients with non-alcoholic fatty liver disease: a randomised, double-blind, placebo-controlled study. Br J Nutr. 2015 Sep 14;114(5):796-803.
64. Cao X, Liao W, Xia H, Wang S, Sun G. The Effect of Resveratrol on Blood Lipid Profile: A Dose-Response Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022 Sep 11;14(18):3755.

Declaration of interest statement: None

Received: 22. 01. 2023.
Accepted: 20. 03. 2023.
Online: 01. 09. 2023.