PREGLEDNI RAD

UDK BROJEVI:
616-036.1
615.279:547.56
DOI: https://doi.org/10.5937/zdravzast50-33638

ZNAČAJ POLIFENOLA U PREVENCIJI HRONIČNIH NEZARAZNIH BOLESTI

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SAŽETAK

Polifenoli su spojevi koji u svojoj strukturi sadrže jednu ili više hidroksilnih skupina vezanih izravno na jedan ili više aromatskih ugljovodonika. Predstavljaju jednu od najbrojnijih i najrasprostranjenijih skupina sekundarnih biljnih metabolita sa više od 8000 polifenolnih struktura. Polifenoli su antioksidansi koji smanjuju disfunkciju endotela i krvni pritisak, unapređuju imunološku odbranu, ublažavaju upalni odgovor, blokiraju agregaciju trombocita i oksidaciju lipoproteina male gustine. Neke studije ukazuju na postojanje indirektne veze između unosa flavonoida i obolevanja od infarkta miokarda i umiranja od koronarne bolesti. Crna čokolada, orašasti plovodi, grožđe, crveno vino i mediteranska dijeta (bazirana na voću i povrću, ribi i maslinovom ulju) su bogati polifenolima i ključni su u prevenciji kardiovaskularnih bolesti. Polifenoli sprečavaju neurodegenerativne promjene povezane s cerebralnom ishemijom. Antocijanini iz borovnica imaju antiaterogena i protivupalna svojstva tako da djeluju neuroprotektivno. Ekstrakt crnog vina, bogat antocijaninom, smanjuje ozljede izazvane cerebralnom ishemijom. Unošenje polifenola hranom može redukovati hipertenziju, protivupalnim i antioksidativnim efektima, kao i povećanom proizvodnjom oksida azota. Posebno se ukazuje na značaj crnog i zelenog čaja u snižavanju vrednosti krvnog pritiska. Neophodna su dalja istraživanja polifenola u cilju donošenja što jasnijih preporuka za njihovu opštu preventivnu primenu.

Ključne riječi: polifenoli, hronične nezarazne bolesti, prevencija, ishrana

Uvod

Prema hemijskim obilježjima, polifenoli su spojevi koji u svojoj strukturi sadrže jednu ili više hidroksilnih skupina vezanih izravno na jedan ili više aromatskih ugljikovodika (1,2). Predstavljaju jednu od najbrojnijih i najrasprostranjenijih skupina sekundarnih biljnih metabolita sa više od 8000 polifenolnih struktura (2,3). Cijela skupina ima naziv po osnovnom predstavniku, fenolu (1,2). Polifenoli nastaju od zajedničkog intermedijera, fenilalanina, odnosno bliskog prekursora, šikiminske kiseline (3). Klasifikacija polifenola se temelji na strukturi, biološkoj aktivnosti i biosintetskom putu (2). Generalno, razlikujemo flavonoide i neflavonoide (4). Flavonoidi pripadaju klasi nisko-molekularnih bioaktivnih fenolnih jedinjenja (5,6). Imaju zajedničku osnovnu strukturu s dva aromatična prstena i tri atoma ugljika povezana u oksigenirani heterocikl (4). Na temelju varijacije u tipu heterocikla podijeljeni u šest glavnih potklasa: flavonoli, flavanoni, flavanoli, flavoni, antocijani i izoflavoni (4). Ostale grupe flavonoida uključuju manje prisutne halkone, dihidrohalkone, dihidroflavonole, flavan-3,4-diole, kumarine i aurone (2). Unutar svake grupe postoje pojedinačne razlike u broju i rasporedu hidroksilnih grupa i njihovog stepena alkilacije i/ili glikozilacije (4). Flavonoidi se pojavljuju i kao hidroksilirani i metoksirani derivati, glikozilirani s monosaharidima ili oligosaharidima, esterificirani s organskim kiselinama (2).

Prehrambeni izvori polifenola

Voće, povrće i pića, poput čaja i crnog vina, predstavljaju glavne izvore polifenola (tabela 1) (7-9). Određeni polifenoli, poput kvercetina, nalaze se u svim biljnim proizvodima (voće, povrće, žitarice, mahunarke, voćni sokovi, čaj, vino), dok su drugi specifični za određenu hranu (flavanoni u citrusnom voću, izoflavoni u soji) (7). Flavanoni su prisutni u začinskim biljkama (kapari, šafran, sušeni meksički origano) i povrću (luk, špinat), a izoflavoni

REVIEW ARTICLE

UDK NUMBERS:
616-036.1
615.279:547.56
DOI: https://doi.org/10.5937/zdravzast50-33638

THE IMPORTANCE OF POLYPHENOLS IN THE PREVENTION OF CHRONIC NON-COMMUNICABLE DISEASES

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SUMMARY

Polyphenols are compounds that contain in their structure one or more hydroxyl groups attached directly to one or more aromatic hydrocarbons. They represent one of the most numerous and widespread groups of secondary plant metabolites with more than 8000 polyphenolic structures. Polyphenols are antioxidants that reduce endothelial dysfunction and blood pressure, improve the immune defense, alleviate the inflammatory response, block platelet aggregation and oxidation of low-density lipoproteins. Some studies suggest that there is an indirect link between flavonoid intake and myocardial infarction and coronary heart disease. Dark chocolate, nuts, grapes, red wine and the Mediterranean diet (based on fruits and vegetables, fish and olive oil) are rich in polyphenols and are key in preventing cardiovascular disease. Polyphenols prevent neurodegenerative changes associated with cerebral ischemia. Blueberry anthocyanins have antiatherogenic and anti-inflammatory properties so they have a neuroprotective effect. Red wine extract, rich in anthocyanin, reduces injuries caused by cerebral ischemia. Food intake of polyphenols can reduce hypertension, anti-inflammatory and antioxidant effects, as well as increased production of nitric oxide. The importance of black and green tea in lowering blood pressure is especially pointed out. Further research on polyphenols is needed in order to make as clear recommendations as possible for their general preventive use.

Key words: polyphenols, chronic noncommunicable diseases, prevention, diet

Introduction

According to their chemical characteristics, polyphenols are compounds that contain in their structure one or more hydroxyl groups attached directly to one or more aromatic hydrocarbons (1,2). They represent one of the most numerous and widespread groups of secondary plant metabolites with more than 8000 polyphenolic structures (2,3). The whole group was named after its main representative, phenol (1,2). Polyphenols arise from a common intermediate, phenylalanine, that is, a close precursor, shikimic acid (3). The classification of polyphenols is based on their structure, biological function and biosynthetic pathway (2). Generally, they are classified into flavonoids and non-flavonoids (4). Flavonoids belong to a class of low-molecular bioactive phenolic compounds (5,6). They have a common basic structure consisting of two aromatic rings that are bound together by three carbon atoms that form an oxygenated heterocycle (4). They are classified into six main sub-groups according to the variations of the type of heterocycle: flavonols, flavanones, flavanols, flavones, anthocyanins and isoflavones (4). The other groups of flavonoids include the less present chalcones, dihydrochalcones, dihydroflavonols, flavan-3,4-diols, coumarin and aurone (2). Within each group, there are individual differences regarding the number and location of hydrohyl groups and their degree of alkylation and/or glycosylation (4). Flavonoids appear as hydroxylated and methoxylated derivatives, glycosylated with monosaccharides or oligosaccharides, esterified with organic acids (2).

Food sources of polyphenols

Fruit, vegetables and beverages, such as tea and red wine, represent the main sources of polyphenols (Table 1) (7-9). Certain polyphenols, such as quercetin, are present in all plant products

Tabela 1. Prehrambeni izvori polifenola (7)

Polifenoli u hrani	Izvor polifenola	Sadržaj polifenola mg/kg (mg/l)
Hydroxybenzoic acids	Kupina	80–270
Protokatekuinska kiselina	Malina	60–100
Galna kiselina	Crna ribizla	40–130
p -hidroksibenzojeva kiselina	Jagoda	20–90
Hidroksicinamske kiseline	Borovnica	2000–2200
Kofeinska kiselina	Kivi	600–1000
Klorogenska kiselina	Trešnja	180–1150
Kumarna kiselina	Šljiva	140–1150
Ferulinska kiselina	Patlidžan	600–660
Sinapinska kiselina	Jabuka	50–600
	Kruška	15–600
	Cikorija	200–500
	Artičoka	450
	Krompir	100–190
	Kukuruzno brašno	310
	Brašno	70–90
	Jabukovača	10–500
	Kafa	350–1750
Antocijani	Patlidžan	7500
Cianidin	Kupina	1000–4000
Pelargonidin	Crna ribizla	1300–4000
Peonidin	Borovnica	250–5000
Definidin	Crno grožđe	300–750
Malvidin	Trešnja	350–4500
	Rabarbara	2000
	Jagoda	150–750
	Crno vino	200–350
	Šljiva	20–250
	Crveni kupus	250
Flavonoli	Žuti luk	350–1200
Kvercetin	Uvijeni kelj	300–600
Kaempferol	Praziluk	30–225
Miricetin	Šeri paradajz	15–200
	Brokoli	40–100
	Crna ribizla	30-70
	Borovnica	30–160
	Kajsija	25–50
	Jabuka	20–40
	Pasulj, zeleni ili beli	10–50
	Crno grožđe	15–40
	Paradajz	2–15
	Zeleni čaj	20–35
	Crni čaj	30–45
	Crno vino	2–30
Flavoni	Peršun	240–1850
Apigenin	Celer	20–140
Luteolin	Paprika	5–10
Flavanoni	Sok od naranče	215–685
Hesperetin	Sok od grejpfruta	100–650
Naringenin	Sok od limuna	50–300
Eriodiktiol		
Izoflavoni	Sojino brašno	800–1800
Daidzein	Soja, kuvana	200–900
Genistein	Tofu	80–700
Glicitein	Miso	250-900
	Sojino mlijeko	30–175

Table 1. Food sources of polyphenols (7)

Polyphenols in foods	Source	Polyphenol content mg/kg (mg/l)
Hydroxybenzoic acids	Blackberry	80–270
Protocatechuic acid	Raspberry	60–100
Gallic acid	Black currant	40–130
p-Hydroxybenzoic acid	Strawberry	20–90
Hydroxycinnamic acids	Blueberry	2000–2200
Caffeic acid	Kiwi	600–1000
Chlorogenic acid	Cherry	180–1150
Coumaric acid	Plum	140–1150
Ferulic acid	Aubergine	600–660
Sinapic acid	Apple	50–600
	Pear	15–600
	Chicory	200–500
	Artichoke	450
	Potato	100–190
	Corn flour	310
	Flour: wheat, rice, oat	70–90
	Jabukovača	10–500
	Coffee	350–1750
Anthocyanins	Aubergine	7500
Cyanidin	Blackberry	1000–4000
Pelargonidin	Black currant	1300–4000
Peonidin	Blueberry	250–5000
Delphinidin	Black grape	300–750
Malvidin	Cherry	350–4500
	Rhubarb	2000
	Strawberry	150–750
	Red wine	200–350
	Plum	20–250
	Red cabbage	250
Flavonols	Yellow onion	350–1200
Quercetin	Curly kale	300–600
Kaempferol	Leek	30–225
Myricetin	Cherry tomato	15–200
	Broccoli	40–100
	Black currant	30-70
	Blueberry	30–160
	Apricot	25–50
	Apple	20–40
	Beans, green or white	10–50
	Black grape	15–40
	Tomato	2–15
	Green tea infusion	20–35
	Black tea infusion	30-45
	Red wine	2–30
Flavones	Parsley	240–1850
Apigenin	Celery	20–140
Luteolin	Capsicum pepper	5–10
Flavanones	Orange juice	215–685
Hesperetin	Grapefruit juice	100–650
Naringenin	Lemon juice	50–300
Eriodictyol		
Isoflavones	Soy flour	800–1800
Daidzein	Soybeans, boiled	200–900
Genistein	Miso	250-900
Glycitein	Tofu	80–700
	Soy milk	30–175

Tabela 1. Prehrambeni izvori polifenola (7) - nastavak

Polifenoli u hrani	Izvor polifenola	Sadržaj polifenola mg/kg (mg/l)
Monomerni flavanoli	Čokolada	460–610
Katehin	Pasulj	350–550
Epikatehin	Kajsija	100–250
	Trešnja	50–220
	Grožđe	30–175
	Breskva	50–140
	Kupina	130
	Jabuka	20–120
	Zeleni čaj	100–800
	Crni čaj	60–500
	Crno vino	80–300
	Jabukovača	40

u mahunarkama i njihovim prerađenim proizvodima (značajna količina daidzeina i genisteina) (8). Flavoni su široko rasprostranjeni u sušenom bilju i agrumima, dok su antocijanini prisutni u obojenom voću i povrću (bobičasto voće, šljive, trešnje, crveni kupus, patlidžan, crveni luk i crvena rotkva) (8). Flavanoli se nalaze u voću (jagoda, jabuka i breskva), proizvodima od kakaa, crnom i zelenom čaju (8). Voće (jagoda, malina, brusnica, nar) i orašasti plodovi (kesten) su bogati fenolnim kiselinama, sjemenke (predominantno lan) i žitarice lignanima, grožđe i crno vino stilbenima (resveratrol) (8).

Bioraspoloživost polifenola

Bioraspoloživost polifenola određuju pedoklimatski i agronomski uslovi, kao i stepen zrelosti (7). Sa sa zrelošću plodova masline smanjuje se koncentracija fenolnih spojeva (10). Zrenje povećava koncentraciju antocijanina (10). Homogenizacija, liofilizacija, kuhanje i termička obrada različito utiču na sadržaj i količinu apsorbiranih polifenolnih spojeva (10). Termička obrada uzrokuje značajno smanjenje ukupnog sadržaja fenola u grahu i mahunarkama (10,11). Polifenoli u mrkvi se u potpunosti gube s ključanjem (10). Kuhanje na pari i prženje ima manje negativan učinak (10). S druge strane, kuhanje na pari brokuli povećava sadržaj polifenola (10). Homogenizacije povrća povećava bioraspoloživost polifenola (10). Skladištenje u mraku u trajanju od sedam mjeseci rezultuje smanjenjem sadržaja antocijana za 88% (10). Bioraspoloživost određuju izravne interakcije između polifenola i nekih sastojaka hrane, poput proteina, ugljikohidrata, vlakana, masti i alkohola (14). Prisustvo masti u ishrani pojačava apsorpciju flavonoida (10). S druge strane, dijetalna vlakna usporavaju resorpciju polifenola (10). Fitohemijske osobine polifenola (strukture molekula, lipofilnost, konstanta disocijacije i topljivost) imaju značajnu ulogu u apsorpciji istih (7). Molekule veće molekulske mase se sporije resorbuju (7). Stepen glikolizacije i tip šećerne jedinice znatno utječu na apsorpciju flavonoida u tankom crijevu (izuzev flavan-3ola koji nisu prisutni u obliku glikozida) (7). Katehini esterificirani s galnom kiselinom pokazuju značajno manju bioraspoloživost od pripadajućih slobodnih oblika (7). Faktori domaćina (crijevni i sistemski) su značajni u apsorpciji polifenola (10). Ograničena apsorpcija u probavnom sustavu predstavlja uzrok relativno niske bioraspoloživosti polifenola (2).

Metabolizam polifenola

Polifenoli u tanko crijevo uglavnom dospijevaju u nepromijenjenom obliku (slika 1) (7). U istom polifenoli podliježu hidroksilaciji djelovanje laktaze floridzin hidrolaze i citosolne β-glukozidaze (10,12,17). Laktaza floridzin hidrolaza ima dva katalitička mjesta, jedno za hidrolizu laktoze, a drugo za deglikozilaciju hidrofobnih supstrata (10,11). Nastali aglikoni pasivnom difuzijom ulaze u epitelnu ćeliju (povećana lipofilnost) (10). Citosolna β-glukozidaza učestvuje u transportu polarnih glukozida (prenos aktivnim, natrijum zavisnim, transporterom glukoze) (10). Polifenoli koji se ne apsorbuju u tankom crijevu (95%) u debelom crijevu prolaze kroz značajne strukturne modifikacije (10). Mikroflora debelog crijeva hidrolizira glikozide do aglikona i jednostavnih fenolnih kiselina (10). Prije ulaska u krvotok, jednostavni aglikoni

Table 1. Food sources of polyphenols (7) - continued

Polyphenols in foods	Source	Polyphenol content mg/kg (mg/l)
Monomeric flavanols	Chocolate	460–610
Catechin	Beans	350–550
Epicatechin	Apricot	100–250
	Cherry	50–220
	Grape	30–175
	Peach	50–140
	Blackberry	130
	Apple	20–120
	Green tea	100–800
	Black tea	60–500
	Red wine	80–300
	Cider	40

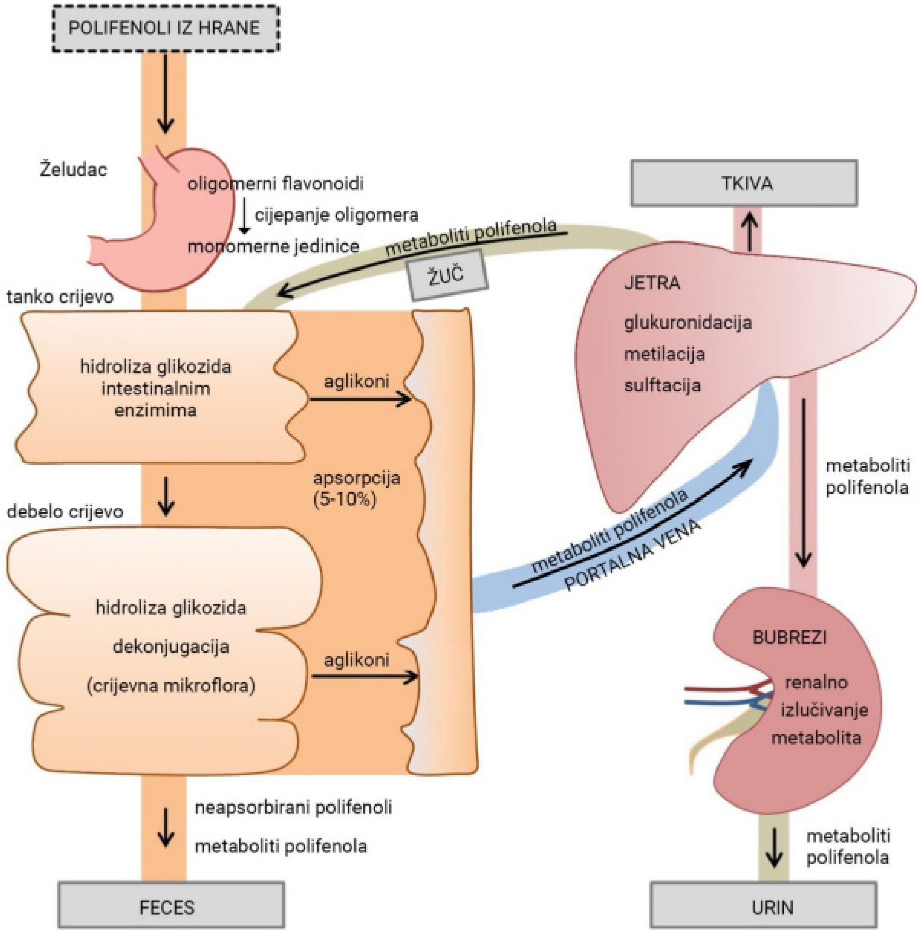
(fruit, vegetables, cereals, leguminous plants, fruit juices, tea, wine), while other products are specific to particular food (flavanones in citrus fruit, isoflavones in soybean) (7). Flavanones are present in spices (cappar, saffron, dried Mexican oregano) and vegetables (onions, spinach), while isoflavones are present in legumes and their processed products (significant amount of daidzein and genistein) (8). Flavones are widely present in dried herbs and citrus fruit, while anthocyanins are present in colored fruit and vegetables (berries, plums, cherries, red cabbage, aubergine, red onion and radish) (8). Flavanols are present in fruit (strawberry, apple and peach), cacao products, black and green tea (8). Fruit (strawberry, raspberry, cranberry and pomegranate) and nuts (chestnut) are rich in phenol acids, seeds (predominantly flax) and cereals are rich in lignans, while grapes and red wine are rich in stilbenes (resveratrol) (8).

Bioavailability of polyphenols

The bioavailability of polyphenols is determined by pedoclimatic and agronomic conditions, as well as by the degree of ripeness (7). The concentration of phenol compounds decreases with the ripeness of olives (10). During ripening, anthocyanin concentrations increase (10). Homogenization, lyophilisation, cooking and thermal processing influence the content and the quantity of absorbed polyphenolic compounds in different ways (10). Thermal processing causes a significant decrease in the total amount of phenols in peas and leguminous plants (10,11). Polyphenols in carrots are completely lost during boiling (10). Steaming and frying have a less negative effect (10). On the other hand, the amount of polyphenols increases when steaming broccoli (10). Homogenization of vegetables increases the bioavailability of polyphenols 910). Storage over seven months in the dark caused a decrease in anthocyanins for 88% (10). Bioavailability is determined by direct interaction between polyphenols and some ingredients, such as proteins, carbohydrates, fibers, fat and alcohol (14). The presence of fat in diet increases the absorption of flavonoids (10). On the other hand, dietary fibers slow down the absorption of polyphenols (10). Phytochemical properties of polyphenols (molecular structure, lipophilic properties, dissociation constant and melting point) have a significant role in their absorption (7). Molecules of higher molecular mass are absorbed more slowly (7). The degree of glycosylation and the type of glucose unit significantly influence the absorption of flavonoids in small intestines (except flavan-3-ols which are not present in the form of glycosides) (7). Catechins which are esterified with gallic acid show significantly reduced bioavailability than the affiliated free forms (7). Factors belonging to the host (intestinal and systemic) are also important for the absorption of polyphenols (10). Limited absorption in the digestive system is a cause of relatively low bioavailability of polyphenols (2).

Metabolism of polyphenols

Polyphenols reach the small intestine in their unchanged form (Picture 1). There polyphenols are subject to hydroxylation under the influence of lactase phlorizin hydrolase and cytosolic ß-glucosidase (10,12,17). Lactase phlorizin hydrolase has two catalytic sites, one



Slika 1. Apsorpscija i metabolizam polifenola (2)

se podvrgavaju procesu konjugacije koji se odvija u tankom crijevu i jetri (predominantno) (10). Konjugacija (metilacija, sulfacija i glukuronidacija) predstavlja metabolički proces detoksikacije zajednički mnogim ksenobiotičkim spojevima koji ograničava potencijalne toksične efekte i olakšava uklanjanje istih iz žuči i urina (10). Katehol-O-metiltransferaza katalizira prijenos metilne grupe iz adenozil-metionina u polifenole s difenolnom sekvencom, poput kvercetina, katehina, kafene kiseline i cijanidina (10). Enzim je prisutan u širokom spektru tkiva, s najvećom aktivnošću u jetri i bubrezima (10). Sulfotransferaze kataliziraju transfer sulfatnog dijela iz fosfoadenozin-fosfosulfata u hidroksilnu grupu polifenola (10,13). Sulfacija se predominantno odvija u jetri (10,13). Uridin 5 difosfat glukuroniziltransferaze unutar endoplazmatskog retikuluma kataliziraju transfer glukuronske kiseline iz uridin difosfat glukuronske kiseline u polifenole (10). Glukuronidacija polifenola u enterocitima prethodi konjugaciji u jetri (10). Proces konjugacije s jedne strane stvara aktivne metabolite dijetalnih polifenola, s druge strane smanjuje ukupnu količinu polifenola u krvotoku, povećavajući njihovo izlučivanje (10). Ekskrecija polifenola se odvija putem bubrega i manjim dijelom žuči (5).

Polifenoli i kardiovaskularne bolesti

Polifenoli smanjuju kardiovaskularni rizik (14). Redukuju biosintezu lipida, povećavaju fekalnu ekskreciju holesterola, inhibiraju lipoprotein male gustine (engl. *Low-density lipoprotein* - LDL), povećavaju koncentraciju lipoproteina visoke gustine (engl. *High-density lipoprotein* - HDL), smanjuju agregaciju lipoproteina male gustine, posljedičnu fagocitozu makrofaga i stvaranje pjenastih stanica, održavaju elastičnost stijenke krvnih žila i inhibiraju trombocitnu aktivnost (5).

Brojna istraživanja ukazuju na protektivnu ulogu polifenola koji se unose ishranom. Konzumiranje tamne čokolade s visokim udjelom flavonoida povećava koncentraciju epikatehina u plazmi kod zdravih odraslih osoba uzrokujući endotel zavisnu vazodilataciju (15). Konzumiranja grožđa i crvenog vina rezultuje porastom cikličnog guanozin monofosfata (aktivaciju endotelne dušik oksid

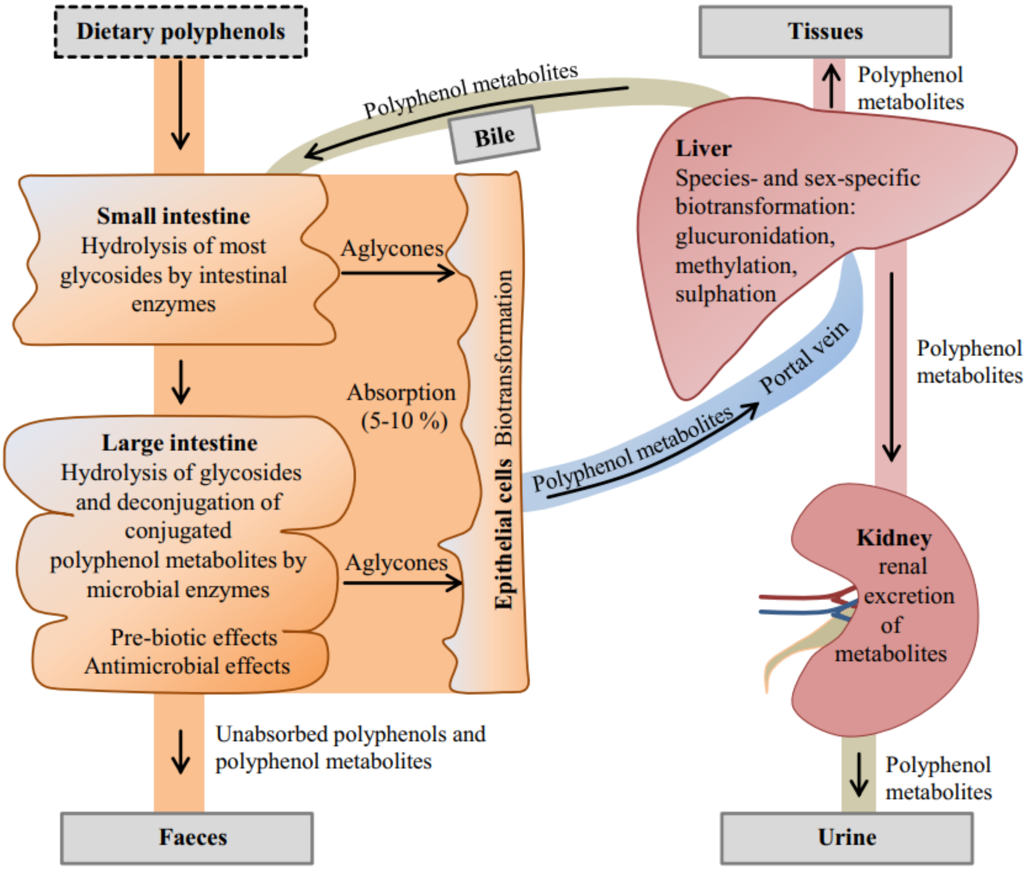


Figure 1. Absorption and metabolism of polyphenols (2)

for the hydrolysis of lactose, and the other for the deglycosylation of hydrophobic substrates (10,11). Aglycones that are caused by passive diffusion reach the epithelial cell (lipophility increases) (10). Cytosolic ß-glucosidase participates in the transport of polar glucosides (transport with the active, sodium-dependent glucose transporter) (10). Polyphenols that are not absorbed in the small intestine (95) undergo significant structural modifications in the large intestine (10). The microflora of the large intestine hydrolyzes glycosides to aglycones and simple phenolic acids (10). Prior to passage into the blood stream, simple aglycones undergo the process of conjugation in the small intestine and liver (predominantly) (10). The conjugation (methylation, sulfation and glucuronidation) is a metabolic process of detoxication that is common in many xenobiotic compounds and that limits the potential toxic effects and alleviates the excretion from the gall bladder and urine (10). Catechol-O-methyltransferase catalyzes the transfer of methyl group from adenosyl-methionine into polyphenols with diphenolic sequence, such as quercetin, catechin, caffeic acid, cyanidin (10). The enzyme is present in many tissues, with the greatest activity in the liver and kidneys (10). Sulfotransferase catalyze the transfer of sulfate part from phosphoadenosine-phosphosulfate into the hydroxyl group of polyphenols (10,13). Sulfation is predominant in the liver (10,13). Uridine-5-diphosphate glucuroniziltransferase within the endoplasmic reticulum catalyze the transfer of glucuronic acid from uridine diphosphate glucuronic acid into polyphenols (10). Glucuronidation of polyphenols in enterocytes is prior to the conjugation in the liver (10). The process of conjugation creates active metabolites of dietary polyphenols on the one hand, while on the other hand, it reduces the total amount of polyphenols in the blood stream, by increasing their excretion (10). Polyphenols are excreted via kidneys and to a lesser extent, via gallbladder (5).

Polyphenols and cardiovascular diseases

Polyphenols reduce the cardiovascular risk (14). They reduce the biosynthesis of lipids, increase the fecal excretion of cholesterol, sintaze) i opuštanjem vaskularnih glatkih mišića (16). Oksidacija LDL-a ima značajnu ulogu za nastanak ateroskleroze (16). Fenoli u crvenom vinu inhibiraju oksidaciju LDL-a kataliziranu bakrom (16).

Upotreba čokolade bogate procijanidinom rezultuje povećanjem plazmatskog antioksidativnog kapaciteta i odlaganjem LDL oksidacije (17). Katehini zelenog čaja se ugrađuju u čestice LDL-a i redukuju oksidaciju istih (18). Listovi hibiskusa sabdarife su bogati flavonoidima, posjeduju antioksidativno i antiaterosklerotsko djelovanje (19).

Proliferacija i migracija vaskularnih glatkih mišićnih ćelija indukuje progresivno zadebljanje intime i razvoj skleroze arterijskog zida (16). Polifenoli crvenog vina i borovnice inhibiraju receptor aktiviran proliferatorom peroksizoma γ koja redukuje aktivnost signalnog puta proliferacije (16).

Makrofagi igraju ključnu ulogu u aterogenezi svojim proinflamatornim djelovanjem (20). Polifenoli mogu smanjiti proupalne medijatore hronične upale (22). Resveratrol, izorhamnetin, kurkumin i vanilinska kiselina mogu smanjiti oslobađanje proupalnog citokina iz T limfocita (16).

Aterosklerozu karakteriše pojačana aktivacija trombocita (16). Resveratrol smanjuje aktivaciju trombocita izazvanu kolagenom, adenozin difosfatom i trombinom i agregaciju istih. Polifenoli u naru smanjuju agregaciju trombocita (inhibiraju proizvodnju tromboksana A2, kolagena i arahidonske kiseline) (16).

Kohortna studija sprovedena u Finskoj među 2748 muškaraca i 2385 žena uzrasta od 30 do 69 godina (bez poznate koronarne bolesti), u trajanju od 26 godina, identifikovala je značajan inverzni gradijent unosa flavonoida u ishrani i ukupnog i koronarnog mortaliteta (21). Istraživanje sprovedeno u Grčkoj unutar 30 muškaraca starosti preko 70 godina, s nedavnim (< 2 mjeseca) akutnim koronarnim sindromom ili bajpasom koronarne arterije i fibrilacijom atrija pokazuje da ekstrakt polifenola crvenog grožđa uzrokuje vazodilataciju posredovanu protokom (vrhunac za 60 minuta) (22). Rezultati petogodišnje studije u Holandiji ukazuju na obrnutu povezanost unosa flavonoida i obolevanja od infarkta miokarda i umiranja od koronarne bolesti (23). Dvostruko slijepo, placebo kontrolisano ispitivanje 40 pacijenata nakon infarkta, sprovedeno u Kavkazu uočilo je da resveratrol u osoba s bolestima koronarnih arterija poboljšava dijastoličku funkciju lijeve komore, funkciju endotela, smanjuje nivo LDL-holesterola i štiti od nepovoljnih hemodinamskih promjena (24). Kohortna studija sprovedena u Ujedinjenom Kraljevstvu među 30.458 žena (starosne dobi od 35 do 69 godina) u trajanju od 16,7 godina identifikovala je direktnu povezanost ukupnog unosa voća i smanjene smrtnosti od koronarne bolesti srca i kardiovaskularnih bolesti (smanjenje rizika za 6-7% za svaki konzumirani obrok od 80 g/dan) (25). Multicentrično, randomizirano, ispitivanje primarne prevencije (PREDIMEDIRANA studija) pružilo je snažne dokaze da orašasti plovodi i mediteranska dijeta na bazi povrća bogatog polifenolima predstaljaju idealan i održiv model prevencije kardiovaskularnih bolesti (26).

Polifenoli i moždani udar

Moždani udar je drugi uzrok smrtnosti u svijetu i glavni uzrok invaliditeta odraslih u zemljama sa srednjim (12,8%) i visokim prihodima (8,7%) (27). Oksidativni stres predstavlja ključni događaj u patogenezi cerebralne ishemije (27). Prekomjerna proizvodnja reaktivnih vrsta kiseonika u toku ishemije prouzrokuje neravnotežu oksidativnih i antioksidativnih procesa koja oštećuje lipide, proteine i nukleinske kiseline, indukujući apoptozu odnosno nekrozu (28). Polifenoli sprečavaju neurodegenerativne promjene povezane s cerebralnom ishemijom (28). Stimulišu redoks enzime, poput endotelne dušik oksid sintaze, katalaze, superoksid dizmutaze 1 i superoksid dizmutaze 2, te moduliraju imunološki odgovor inhibiranjem protivupalnih biomarkera (28).

Polifenoli zelenog čaja i epigalokatehin-3-galat mogu inhibirati apoptozu neurona regulacijom nivoa neurotrofina (16,27). Resveratrol i polifenoli zelenog čaja smanjuju reaktivne vrste kiseonika u mitohondrijima i edem endotelnih ćelija mozga (smanjenjem jonizovanog kalcijuma) (27). Resveratrol značajno smanjuje apoptozu, peroksidaciju mitohondrijskih lipida, zapreminu moždanog infarkta i edem (27). Mangiferin i morin, dva prirodna antioksidansa iz kore manga predstavljaju perspektivne neuroprotektore cerebrovaskularnog insulta, epilepsije, traume mozga i oštećenja kičmene moždine (antioksidativna i antiapoptotička aktivnost) (27). Neuroprotektor kvercetin smanjuje nivo matrične metalopeptidaze, pokazuje antilipidno, peroksidativno, antioksidativno i protivupalno djelovanje (27). Polifenoli iz grožđa inhibit low-density lipoprotein, increase high-density lipoprotein, decrease the aggregation of low-density lipoprotein, the consequential phagocytosis of macrophages and formation of foam cells, maintain blood vessel elasticity and inhibit thrombin activity (5).

Numerous studies point out the protective role of polyphenols that we get through certain foods. The consumption of dark chocolate with high percentage of flavonoids increases the concentration of epicatechin in plasma of healthy adults, thus inducing endothelium-dependent vasodilation (15). The consumption of grapes and red wine results in the increase of cyclic guanosine monophosphate (activation of endothelial nitric oxide synthase) and the relaxation of vascular smooth muscles (16). Oxidation of LDL has an important role in the occurrence of atherosclerosis (16). Phenols in red wine inhibit copper-catalyzed oxidation of LDL (16).

The use of chocolate rich in procyanidin increases plasma antioxidant capacity and postpones LDL oxidation (17). Catechins in green tea are incorporated into LDL particles and reduce their oxidation (18). Hibiscus sabdariffa leaves are rich in flavonoids, and they have antioxidant and antiatherosclerotic effects (19).

The proliferation and migration of vascular smooth muscle cells induce progressive intimal thickening and development of sclerosis of arterial walls (16). Polyphenols from red wine and blueberries inhibit the peroxisome proliferator-activated reactor that reduces the activity of signaling pathway of proliferation (16).

Macrophages have an important role in atherogenesis with their proinflammatory activity (20). Polyphenols can reduce proinflammatory mediators of chronic inflammation (22). Resveratrol, isorhamnetin, curcumin and vanillic acid can decrease the liberation of proinflammatory cytocine from T-lymphocytes (16).

Atherosclerosis is characterized by the increased thrombocyte activation (16). Resveratrol reduces thrombocyte activation caused by collagen, adenosine diphosphate and thrombin and their aggregation. Polyphenols in pomegranate reduce thrombocyte aggregation (they inhibit the production of thromboxane A2, collagen and arachidonic acid) (16).

A cohort study conducted in Finland, which included 2748 men and 2385 women aged 30-69 years (without known coronary disease) and which lasted 26 years, identified a significant inverse gradient between the flavonoid intake and total coronary mortality (21). A study conducted in Greece, which included 30 men older than 70 with a recent (<2 months) coronary syndrome or bypass of coronary artery and atrial fibrillation, showed that red grape polyphenol extract caused flow-mediated vasodilation (peaking at 60 minutes) (22). The results of five-year study conducted in the Netherlands showed the inverse relationship between the flavonoid intake and myocardial incidence and mortality associated with coronary disease (23). A double-blind, placebo-controlled trial of 40 patients after myocardial infarction, which was conducted in the Caucasus, found that resveratrol in patients with diseases of coronary arteries, improved the diastolic function of left ventricle, endothelial function and decreased the level of LDL cholesterol and protected from unfavorable chemodynamic changes (24). A cohort study conducted in the United Kingdom, which included 30458 women (aged 35 to 69 years) and lasted 16.7 years, identified a direct relationship between the total fruit intake and decreased mortality of coronary disease and cardiovascular disease (reduction of risk for 6-7% for each intake of 80g/daily) (25). A multicenter, randomized study of primary prevention (the PREDIMED study) proved that nuts and Mediterranean diet based on vegetables rich in polyphenols present an ideal and sustainable model of cardiovascular disease prevention (26).

Polyphenols and stroke

Stroke is the second leading cause of death worldwide and major cause of disability of adults in middle-income countries (12.8%) and high-income countries (8.7%) (27). Oxidative stress is a key event in the pathogenesis of cerebral ischemia (27). The excessive production of reactive oxygen species during ischemia causes the imbalance between the oxidative and antioxidative process that damages lipids, proteins and nucleic acids, thus inducing apoptosis, that is, necrosis (28). Polyphenols prevent neurodegenerative changes associated with cerebral ischemia (28). They stimulate redox enzymes, such as endothelial nitric oxide synthase, catalase, superoxide dismutase and 1 superoxide dismutase 2, and therefore, they modulate the immune response by inhibiting anti-inflammatory biomarkers (28).

u prahu, koji se daju kao dodatak prehrani, štite mozak od ishemijskih oštećenja (27). Antocijanini iz borovnica ima antiaterogena i protivupalna svojstva te djeluje neuroprotektivno (27). Ekstrakt crnog vina, bogat antocijaninom, smanjuje ozljede izazvane cerebralnom ishemijom, štiti od ekscitotoksičnosti izazvane ishemijom i energetskim zatajenjem i oksidativnim stresom (27,29).

Meta-analiza 11 prospektivnih studija utvrdila je da umjerana konzumacija kafe smanjuje rizik od nastanka moždanog udara (30). Kohortna studija sprovedena u Sjedinjenim Američkim Državama među 229.119 muškaraca i 173.141 žena uzrasta od 50 do 71 godine (bez prisustva karcinoma, srčanih bolesti i moždanog udara) identifikovala je postojanje obrnute veze između konzumiranja kafe i razvoja moždanog udara (31). Slični rezultati prikazani su u jednoj kohortnoj studiji koju je činilo 83.076 žena u Sjedinjenim Američkim Državama, a koje su bile praćene 24 godine (41). Meta-analiza osam studija, sa 5228 osoba sa moždanim udarom među 280.174 učesnika identifikovala je povezanost značajnog unosa flavonola i smanjenja rizika za nastanak moždanog udara (32). Unos flavonola veći od 20 mg/dan smanjuje rizik razvoja moždanog udara za 14% (32).

Polifenoli i hipertenzija

Arterijska hipertenzija predstavlja glavni faktor rizika za nastanak kardiovaskularnih bolesti (33). Polifenoli koji su unose ishranom mogu smanjiti ublažiti hipertenziju protivupalnim i antioksidativnim efektima, kao i povećanom proizvodnjom oksida azota (33). Protivupalni učinak nastaje kao rezultat smanjene ekspresije redoks-osjetljivog nuklearnog faktora-kB, dok je antioksidativni učinak povezan s poboljšanim enzimskim aktivnostima superoksid dismutaze, katalaze i glutation peroksidaze (33). Osim toga, polifenoli sudjeluju u aktivaciji redoks-osjetljivog puta fosfoinozitid 3- kinaze, što rezultuje povećanim stvaranjem oksida azota (33). Izoflavoni stimulišu endotelnu sintezu dušik oksida, što dovodi do povećanja endogene proizvodnje oksida azota (34). Antocijanini smanjuju ekspresiju NF-κB signalnog puta, aktivatora protein 1 (AP-1) i signalni put mitogen-aktivirane protein kinaze (34). Cijanidin 3-O-glukozid iz kupina aktivira endotelnu dušik oksid sintazu sprečava disfunkciju endotela i vaskularno zatajenje uklanjanjem peroksinitrata (jakog oksidansa odgovornog za oštećenje dezoksiribonukleinske kiseline i proteina) (34). Delfhinidin, antocijanin prisutan u crnom vinu, inhibira apoptozu ćelija endotela putem stvaranja dušikovog oksida i regulacije homeostaze kalcijuma (34).

Randomizirano, dvostruko slijepo, kontrolirano, unakrsno istraživanje sprovedeno u Australiji među 61 ispitanikom uzrasta od 24 do 72 godine utrdilo je hipotenzivni kapacitet ekstrakta lišća masline (35). Istraživanje koje je obuhvatilo 550 odraslih i starijih osoba u Sao Paulu identifikovalo je inverznu povezanost unosa lignana, stilbena, tirosola, alkilfenola i drugih polifenola i hipertenzije (36). Istraživanje u Poljskoj unutar prospektivne kohortne studije o zdravlju, alkoholu i psihosocijalnim faktorima u istočnoj Evropi (HAPIEE) sa 8.821 učesnika uzrasta od 45 do 69 godina u trajanju od pet godina utvrdio je zaštitni učinak fenolne kiseline na razvoj hipertenzije (37). Studija o mediteranskoj zdravoj ishrani, starenju i životnom stilu (MEAL) sprovedena među 2.044 muškarca i žena starijim od 18 godina u Italiji pokazuje linearnu inverznu povezanost unosa fenolne kiseline i hipertenzije u skupini odraslih osoba koje žive na mediteranskom ostrvu (38). Dijetalni unos fenolnih kiselina (hidroksibenzojeva i hidroksifeniloctena kiselina) u najvišim kvartilima (približno > 400 mg/dan) je bila obrnuto povezana sa hipertenzijom (38). Istraživanje sprovedeno u Koreji među 2.204 muškaraca i 3305 žena starijih od 40 godina koji nisu imali metabolički sindrom ukazuje na postojanje inverzne povezanosti konzumiranja izoflavona i hipertenzije kod žena (39). Metaanaliza osam kontrolisanih ispitivanja s ukupno 843 sudionika utvrdila je da konzumacija susama (bogatog fitosterolima i lignaninima) smanjuje krvni pritisak (40). Rezultati istraživanja sprovedenog u Kini koje je obuhvatilo 1.476 ispitanika uočilo je da konzumiranje crnog i zelenog čaja snižava krvni pritisak (41). Konzumacija zelenog čaja (u prosjeku 400 mL) rezultuje smanjenjem sistolnog krvnog pritiska za 2,1 mmHg i padom dijastolnog krvni pritisak za 1,7 mmHg (41). Konzumacija crnog čaja (u prosjeku 400 ml) uzrokuje pad sistolnog krvnog pritiska za 1,4 mmHg i dijastolnog krvnog pritiska za 1,1 mmHg (41).

Zaključak

Polifenoli smanjuju disfunkciju endotela, redukuju krvni pritisak, unapređuju antioksidativnu

Polyphenols in green tea and epigallocatechin-3-gallate may inhibit apoptosis of neurons by regulating the level of neurotrophin (16,27). Resveratrol and polyphenols in green tea reduce the reactive oxygen species in mitochondria and edema of endothelial brain cells (by decreasing the ionized calcium) (27). Resveratrol significantly reduces apoptosis, peroxidation of mitochondrial lipids, volume of stroke and edema (27). Mangiferin and morin, two natural antioxidants from mango peel, are promising neuroprotectors of cerebrovascular insult, epilepsy, brain trauma and damage of spinal cord (antioxidative and antiapoptotic activity) (27). Neuroprotector quercetin decreases the level of matrix metallopeptidase, shows antilipid, peroxidative, antioxidative and anti-inflammatory activity (27). Polyphenols from grapes in powder, which are given as food supplements, protect the brain from ischemic damage (27). Anthocyanins from blueberries have antiatherogenic and anti-inflammatory properties and neuroprotective effect (27). Red wine extract, rich in antocyanin, decreases damage caused by cerebral ischemia, protects from excitotoxicity caused by ischemia and reduced energy and oxidative stress (27,29).

A meta-analysis of 11 prospective studies found that moderate coffee consumption reduced the risk of stroke (30). A cohort study, which was conducted in the United States of America among 229,119 men and 173,141 women aged 50 to 71 (with no cancer, heart diseases and stroke) identified the inverse relationship between coffee consumption and development of stroke (31). Similar results were shown in a cohort study which included 83.076 women in the United States of America, who had been observed for 24 years (41). A meta-analysis of eight studies, which included 5228 persons with stroke among 280174 respondents, identified the relationship between the significant intake of flavonols and decrease of the risk for the appearance of stroke (32). The intake of flavonols higher than 20mg/daily reduces the risk of stroke development for 14% (32).

Polyphenols and hypertension

Arterial hypertension is the main risk factor for the appearance of cardiovascular diseases (33). Polyphenols that we get through food can alleviate hypertension with their anti-inflammatory and antioxidative effects, as well as the increased production of nitric oxide (33). Anti-inflammatory effect is caused by the decreased expression of redox-sensitive nuclear factor-kB, while the antioxidative effect is associated with the improved enzyme activities of superoxide dismutase, catalase and glutation peroxidase (33). In addition, polyphenols take part in the activation of redox-sensitive pathway phosphoinositide kinase, which results in the increased production of nitric oxide (33). Isoflavones stimulate the endothelial nitric oxide synthase, resulting in the increased endogen production of nitric oxide (34). Anthocyanins reduce the expression of NF-kB signaling pathway, activator of protein 1 (AP-1) and signaling pathway of mitogen-activated protein kinase (34). Cyanidin 3-O-glucoside from blackberries activates endothelial nitric oxide sintase, prevents endothelial dysfunction and vascular failure by removing peroxynitrite (strong oxidant responsible for the damage of deoxyribonucleic acid and proteins) (34). Delphinidin, anthocyanin present in red wine, inhibits endothelial cells apoptosis by creating nitric oxide and regulation of calcium homeostasis (34).

A randomized, double-blind, controlled, cross-sectional study, which was conducted in Australia and included 61 respondents aged 24 to 72 years, found the hypotensive capacity of extract of olive leaves (35). A study, which included 550 elderly adults in Sao Paolo, indentified the inverse relationship between the intake of lignans, stilbenes, tyrosol, alkifenol and other polyphenols and hypertension (36). A study from Poland, which was a prospective, cohort study about health, alcohol and psychosocial factors in Eastern Europe (HAPIEE) with 8821 respondents aged 45 to 69 years that lasted five years, found the protective effect of phenolic acid on the development of hypertension (37). A study about the Mediterranean healthy eating, ageing and lifestyle (MEAL) was conducted among 2044 men and women older than 18 years in Italy and it showed a linear inverse relationship between the intake of phenolic acid and hypertension among adults who lived in the Mediterranean (38). Dietary intake of phenolic acids (hydroxybenzoic and hydroxyphenyllactic acid) in highest quartiles (approximately > 400 mg/daily) was inversely related with hypertension (38). A study conducted in Korea among 2204 men and 3305 women older than 40 years, who did not have metabolic syndrome, pointed out odbranu, ublažavaju upalni odgovor, blokiraju agregaciju trombocita i oksidaciju lipoproteina male gustine. Snižena intrinzička aktivnost polifenola zbog otežane apsorpcije, visokog stepena biotransformacije i brze eliminacije iz organizma značajno limitira njihovo dejstvo. Brojne studije ukazuju na njihov ogroman značaj u prevenciji hroničnih nezaraznih bolesti, ali su neophodna dalja istraživanja koja bi precizirala dozvoljene protektivne doze koje se unose hranom i/ili suplementima.

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the existence of inverse relationship between the consumption of isoflavones and hypertension in women (39). A meta-analysis of eight controlled studies with 843 respondents found that sesame consumption (rich in phytosterols and lignans) decreases the blood pressure (40). The results of study conducted in China, which included 1476 respondents, found that the consumption of black and green tea lowers the blood pressure (41). The consumption of green tea (on average 400 ml) resulted in the decrease of systolic blood pressure for 2.1 mmHg and lowering of diastolic blood pressure for 1.7 mmHg (41). The consumption of black tea (on average 400 ml) causes lowering of systolic blood pressure for 1.4 mmHg and diastolic blood pressure for 1.1 mmHg (41).

Conclusion

Polyphenols decrease endothelial dysfunction and blood pressure, improve the antioxidative defense, alleviate the inflammatory response, block platelet aggregation and oxidation of low-density lipoproteins. Reduced intrinsic activity of polyphenols due to malabsorption, high level of biotransformation and fast elimination from the body, significantly limit their activity. Numerous studies point to their huge significance in the prevention of chronic non-contagious diseases. However, further research is needed that would state precisely the allowed preventive doses that are taken in with food and/or supplements.

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Sukob interesa: Nije prijavljen.
Primljen: 30.08.2021.
Revizija: 30.09.2021.
Prihvaćen: 03.10.2021.

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Conflict of interest: None declared.
Received: 08/30/2021
Revised: 09/30/2021
Accepted: 10/03/2021

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