Marijana C Jandrić-Kočič[1]

UTICAJ POLIFENOLA NA RAZVOJ ATEROSKLEROZE

Sažetak: Polifenoli predstavljaju jednu od najbrojnijih i najrasprostranjenijih skupina sekundarnih biljnih metabolita sa više od 8.000 polifenolnih spojeva. Voće, povrće i pića, poput čaja i crnog vina, glavni su izvori polifenola. Značajan broj istraživanja ukazuje na sposobnost određenih polifenola da odgode razvoj ateroskleroze. Prema istim, polifenoli smanjuju taloženje lipida, oksidativni stres, upalu zida krvnog suda, proliferaciju vaskularnih glatkih mišićnih ćelija i endotelnu disfunkciju. Široka upotreba polifenola zahtijeva dalja istraživanja biodostupnosti, apsorpcije i transformacije. Neophodno je utvrđivanje učinka pojedinačnih polifenola, kao i interakcije s drugim bioaktivnim jedinjenjima, definisanje dijetalnog referentnog unosa i sigurnost upotrebe u određenim subpopulacijama.

Ključne riječi: polifenoli, ateroskleroza, kardiovaskularne bolesti

Summary: Polyphenols represent one of the biggest and most widespread groups of secondary plant metabolites with more than 8000 polyphenolic compounds. Fruits, vegetables and beverages such as tea and red wine are the main sources of polyphenols. A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis. According to the same polyphenols reduce lipid deposition, oxidative stress, inflammation of the blood vessel wall, proliferation of vascular smooth muscle cells and endothelial dysfunction. The widespread use of polyphenols requires further research on bioavailability, absorption and transformation. It is necessary to determine the effect of individual polyphenols as well as the interaction with other bioactive compounds, define the dietary reference intake and the safety of use in certain subpopulations.

Keywords: polyphenols, atherosclerosis, cardiovascular diseases

[1] Marijana Jandrić-Kočić, Dom zdravlja Krupa na Uni, Banjaluka, Republika Srpska, e-mail: marijanajandrickocic@gmail.com

Uvod

Polifenoli su spojevi koji u svojoj strukturi sadrže jednu ili više hidroksilnih skupina vezanih izravno na jedan ili više aromatskih ugljikovodonika.[1,2] Predstavljaju jednu od najbrojnijih i najrasprostranjenijih skupina sekundarnih biljnih metabolita sa više od 8.000 polifenolnih spojeva.[2,3] Prema strukturi, biološkoj aktivnosti i biosintetskom putu razlikujemo flavonoide i neflavanoide.[4] Flavonoidi su podjeljeni u šest glavnih potklasa: flavonoli, flavanoni, flavanoli, flavoni, antocijani i izoflavoni.[4-6] Ostale grupe flavonoida uključuju manje prisutne halkone, dihidrohalkone, dihidroflavonole, flavan-3,4-diole, kumarine i aurone.[2] Neflavonoidi uključuju fenolne kiseline (benzojeva kiselina i cimetna kiselina), stilbene, lignane, tanine i druge polifenole (kurkumin, gingerol).[2] Glavne izvore polifenola predstavljaju voće, povrće i pića, poput čaja i crnog vina.[7,8,9] Njihov sadržaj u biljnim proizvodima određuju pedoklimatski i agronomski uslovi, kao i stepen zrelosti.[7] Apsorpcija polifenola je uslovljena fitohemijskim osobinama (struktura molekula, lipofilnost, konstanta disocijacije i topivost), izravnom interakcijom s komponentama hrane i faktorima domaćina (crijevnim i sistemskim).[7,9] Procjenjeni dnevni unos polifenola iznosi 1g.[7]

Ateroskleroza predstavlja vodeći uzrok morbiditeta i mortaliteta u Evropi i Sjedinjenim Američkim Državama.[8-11] Definiše se kao hronična upalna bolest zidova velikih i srednjih arterija (predominantno aorte, karotidne arterije, koronarne arterije i arterije donjih ekstremiteta).[8] Faktori rizika ateroskleroze su hiperholesterolemija, hipertenzija, pušenje cigareta, gojaznost, fizička neaktivnost, godine, porodična anamneza, dijabetes melitus, muški pol, ali i hipertrigliceridemija**,** hiperhomocisteinemija i hiperfibrinogenemije.[9,11,12] Aterosklerozu uzrokuje hronična upala u zidu krvnog suda indukovana neuravnoteženim metabolizmom lipida i narušenim imunološkim odgovorom.[8,9] Oksidativna modifikacija LDL holesterola (engl. Low-density lipoprotein, LDL) (posredovana reaktivnim oblicima kiseonika, mijeloperoksidazom, lipoperoksidazom, nikotinamid adenin dinukleotid fosfatom) u oksidovani lipoprotein niske gustine (engl. Oxidized low-density lipoprotein, Ox-LDL), unutar ekstracelularnog matriksa subendotelnog prostora, indukuje endotelnu disfunkciju, stvaranje pjenastih ćelija, migraciju i naknadnu proliferaciju glatkih mišićnih ćelija krvnog suda (engl. *smooth muscle cell*, SMC), adheziju i agregaciju trombocita.[8,10]
Kliničke manifestacije ateroskleroze su uslovljene mjestom razvoja plaka i prisustvom tromboembolijskih promjena (infarkt miokarda, prolazni ishemijski napad i moždani udar, intermitentna klaudikacija, infarkt crijeva).[9]

Značajan broj istraživanja ukazuju na sposobnost određenih polifenola da odgode razvoj ateroskleroze.[13-20] Prema istim, polifenoli smanjuju taloženje lipida, oksidativni stres, upalu zida krvnog suda, proliferaciju vaskularnih glatkih mišićnih ćelija i endotelnu disfunkciju.[13-20]

Uloga polifenola u razvoju ateroskleroze

Polifenoli modifikuju procese uključene u formiranje, napredovanje i eventualno puknuće aterosklerotskog plaka.[13-20] Polifenoli mogu značajno smanjiti apsorpciju lipida inhibiranjem emulzifikacije u tankom crijevu, inhibiranjem aktivnosti pankreasne lipaze, smanjenjem micelarne rastvorljivosti i precipitacije micelarnog holesterola.[13-16] Smanjena apsorpcija holestelola uzrokuje povećanu proizvodnju mitohondrijalne ribonukleinske kiseline za LDL receptor u jetri.[16] Smanjuju produkciju apolipoproteina B100 u jetri redukovanjem stvaranja estera holesterola, smanjenjem aktivnosti acil-CoA holesterol aciltransferaze i smanjenjem aktivnosti mikrosomalnog proteina za prenos triglicerida.[15] Samim tim, polifenoli redukuju koncentraciju LDL-a u ekstracelularnom matriksu subendotelnog prostora.[8,23] Smanjuju koncentraciju triglicerida putem smanjenja aktivnosti mikrosomalnog proteina za prenos triglicerida i mogućeg povećanja aktivnosti lipoproteinske lipase.[15] Smanjena koncentracija triglicerida modifikuje kaskadu delipidacije, te redukuje koncentraciju LDL-a u plazmi.[15]

Polifenoli ostvaruju antioksidativno djelovanje na nekoliko načina.[2] Najučinkovitiji podrazumjeva neutralizaciju slobodnih radikala (prenos atoma vodonika iz aktivne hidroksilne grupa polifenola na slobodni radikal).[2] Sposobnost neutralizacije slobodnih radikala je uslovljena rasporedom i ukupnim brojem hidroksilnih grupa, stepenom polimerizacije, glikozidacijom, O-metilacijom i 2-3 dvostrukom vezom u konjugaciji s 4-keto grupom.[2] Antiupalno djelovanje polifenola podrazumjeva inhibiciju proinflamatornih enzima (lipooksigenaza, ciklooksigenaza-2, inducibilna azot oksid sintaza, nuklearni faktor-κB, aktivirajući protein-1), te aktivaciju protein kinaze aktivirane mitogenom, protein kinaze-C, nuklearnog faktora eritroid 2-vezanog za faktor 2 i enzima faze-II detoksikacije antioksidansa.[16-18] Polifenoli mogu inhibirati proliferaciju vaskularnih glatkih mišićnih ćelija zaustavljanjem ćelijskog ciklusa u S fazi mitoze (lomljenje lanca dezoksiribonukleinske kiseline u prisustvu jona bakra) i apoptozom.[19] Nezavisno od svojih antioksidativnih efekata, polifenoli ostvaruju vazoprotektivno, antiagregaciono, antiaterogeno, vazorelaksantno i antihipertenzivno djelovanje aktiviranjem proizvodnje vazodilatacionih faktora (azotni oksid, hiperpolarizirajući faktor izveden iz endotela, prostaciklin), inhibiranjem sinteze vazokonstriktornog endotelina-1 u endotelnim ćelijama, te inhibiranjem ekspresije dva glavna proangiogena faktora, faktora rasta vaskularnog endotela i matriks metaloproteinaze-2 u glatkim mišićnim ćelijama.[20] U endotelnim ćelijama polifenoli povećavaju nivo kalcijuma, indukuju redoks-senzitivnu aktivacija fosfatidilinozitol 3 kinaza/Akt protein kinaza B puta i povećavaju ekspresiju sintaze azot oksida.[20] U glatkim mišićnim ćelijama,se odvija redoks-senzitivna inhibicija aktivacije puta protein kinaze aktivirane mitogenom p38 (inhibicija ekspresije gena vaskularnog endotelnog faktora rasta aktivirana faktorom rasta trombocita) i redoks-nezavisna inhibicija stvaranja matriks metaloproteinaze-2 indukovane trombinom.[20]

Fenoli crvenog vina inhibiraju oksidaciju LDL, proliferaciju vaskularnih glatkih mišićnih ćelija i aktiviraju endotelnu azot oksid sintazu.[21] Polifenoli nara smanjuju agregaciju trombocita.[21] Flavonoidi tamne čokolade povećavaju plazmatski antioksidativni kapacitet i uzrokuju endotel zavisnu vazodilataciju.[22,23] Katehini zelenog čaja se ugrađuju u čestice LDL i redukuju oksidaciju istih.[24] Flavonoidi u listovima hibiskusa sabdarife inhibiraju oksidaciju LDL-a.[25] Fenoli borovnice redukuju aktivnost signalnog puta proliferacije.[21] Polifenoli iz ekstradjevičanskog maslinovog ulja suprimiraju nastajanje reaktivnih vrsta kiseonika, pospješuju nastanak azotnog oksida, inhibiraju angiogenezu, migraciju i proliferaciju vaskularnih ćelija i sprečavaju vaskularne ozljede uzrokovane naprednim krajnjim produktima glikacije.[26] Resveratrol, izorhamnetin, kurkumin i vanilinska kiselina smanjuju oslobađanje proupalnih citokina.[21] Resveratrol smanjuje aktivaciju i agregaciju trombocita.[21] Kurkumin redukuje proliferaciju vaskularnih glatkih mišićnih ćelija i smanjuje oksidativni stress.[21]

Metoda

Literatura je pretražena korištenjem ključnih riječi: polifenoli, ateroskleroza i kardiovaskularne bolesti. Pretraživanje je sprovedeno za period od 2001. do 2022. godine u okviru sledećih baza podataka: PubMed, Emabase, Scopus, SCin-dex i Hrčak. Zbog ograničenog broja dostupnih studija u pretraživanju baza nisu korišteni dostupni filteri. Nakon pročitanih sažetaka, radovi su detaljnije proučeni, te su isključeni oni koji ne odgovaraju postavljenom cilju istraživanja.

Ateroprotektivni učinak polifenola

Značajan broj istraživanja na životinjama su utrvdili integralnu povezanost polifenola s razvojem ateroskleroze.[27-30] Istraživanje u Australiji ustanovilo je da specifični polifenoli u ishrani, predominantno kvercetin i teaflavin, mogu usporiti aterosklerozu kod miševa s uklonjenim genom za apolipoproteina E.[27] Prema istom, ateroprotektivni učinak ishrane bogate voćem i povrćem dijelom može biti rezultat učinka flavonoida.[27] Istraživanja na miševima s uklonjenim genom LDL receptora utvrdila su da upotreba voća i povrća ekvivalentna 8-9 porcija voća i povrća kod ljudi usporava razvoj aterosklerotskog plaka uzrokovanog aterogenim prehranom.[28] Slična istraživanja u Izraelu potvrdila su ateroprotektivno djelovanje polifenola grožđa.[29] Istraživanje s novozelandskim kunićima na aterosklerotičnoj ishrani u Španiji uočilo je ateroprotektivno djelovanje komponenti ekstradjevičanskog maslinovog ulja.[30] Hidroksitirozol je poboljšao funkciju endotela, dok je skvalen smanjio fibrozu plaka.[30]

Ateroprotektivni učinak polifenola bio je predmet mnogobrojnih istraživanja s ljudima.[31-38] Multicentrična, randomizovana, kontrolisana studija PREDIMED u

Španiji, u trajanju od 8 godina, u kojoj je učestvovalo 7.447 osoba s visokim rizikom za razvoj kardiovaskularnih bolesti, ustanovila je da mediteranska dijeta na bazi povrća bogatog nezasićenim masnim kiselinama, obogaćena maslinovim uljem, usporava progresiju supkliničke ateroskleroze (mjerene ultrazvukom karotidnih arterija).[31] Podstudija PREDIMED studije, u kojoj je učestvovalo 1.139 osoba s visokim rizikom za razvoj kardiovaskularnih bolesti, uočila je značajnu inverznu korelaciju između jednogodišnjeg unosa polifenola i cirkulišućih inflamatornih molekula povezanih s aterosklerozom.[32] Dvostruko slijepo randomizovano unakrsno kontrolisano istraživanje s 24 odrasle ženske osobe prosječne starosti 26 godina potvrdilo je ateroprotektivnu ulogu polifenola.[33] Prema istom, ishrana bogata polifenolima poboljšava funkciju endotela, čime se stimuliše sistem azot oksid sintaze i smanjuje oksidacija LDL (predominantno hidroksitirosol i njegovi derivati).[33] Prospektivna kohortna studija u Danskoj tokom 23 godine, u kojoj je učestvovalo 53.552 osobe, utvrdila je da je unos polifenola (1000 mg/dan) povezan s 14% manjim rizikom od aterosklerotskih kardiovaskularnih bolesti (9% ishemijska bolest srca, 9% ishemijski moždani udar i 32% bolest perifernih arterija).[34] Najsnažnija asocijacija je potvrđena bolest u bolesti perifernih arterija i aterosklerotske kardiovaskularne bolesti pušača i osoba s zloupotrebom alkohola.[34] Pretile osobe su imale nisku povezanost, što bi se moglo objasniti promjenom u crijevnom mikrobionu i narušenom biokonverzijom flavonoida u debelom crijevu.[34,35] Dvostruko slijepo randomizovano kontrolisano istraživanje u Mađarskoj među osobama sa infarktom miokarda ustanovilo je da unos resveratrola (bez konzumiranja alkohola) usporava razvoj ateroskleroze kod osoba sa koronarnom arterijskom bolešću.[36] Istraživanje među 558 muškaraca starosti 40–49 godina s povišenim ukupnim holesterolom u serumu i/ili visokim koronarnim rizikom utvrdilo je da konzumacija voća i bobičastog voća bogatog polifenolima može usporiti napredovanje ateroskleroze karotidnih arterija.[37] Metaanaliza 7 studija, koje su uključivale 133 učesnika koji su koristili raznovrsnu hranu i suplemente bogate hidroksitirosolom, kvercetinom i resveratrolom (45–1015 mg/100 g), u trajanju do 145 dana, ustanovile su redukciju lipida i inflamatornih markera.[38]

S druge strane, istraživanje miševa s uklonjenim genom Apolipoproteina E u Sjedinjenim Američkim Državama utvrdilo je da polifenoli crvenog vina ne smanjuju veličinu formiranog aterosklerotskog plaka, kao ni sadržaj kolagena u istim.[39] Slično istraživanje u Kanadi uočilo je da katehin u mladih miševa štiti od razvoja ateroskleroze.[40] U starijih miševa s razvijenim aterosklerotskim plakom katehin pogoduje daljoj endotelnoj disfunkciji i adheziji leukocita.[40] Sistematski pregled i metaanaliza 35 prospektivnih kohortnih istraživanja u Češkoj uočila je da umjereno pijenje crnog čaja, manje od 4 šolje dnevno, ima ateroprotektivan učinak, dok konzumacija od 4 do 6 šolja dnevno predisponira aterosklerozu.[40] Ovaj učinak je uslovljen sadržajem kofeina u crnom čaju.[41]U istom istraživanju je postojala značajna inverzna korelacija između pijenja zelenog čaja i razvoja ateroskleroze u azijskoj. ali ne i zapadnoj populaciji.[41]

Istraživanja u Kini utvrdila su da konzumiranje voća bogatog polifenolima nema ateroprotektivni učinak u osoba s visokim rizikom od kardiovaskularnih bolesti.[42] Jedan od mogućih razloga je da više od četvrtine navedene populacije ima hiperglikemiju koja se pogoršava visokim unosom fruktoze.[42]

Zaključak

Polifenoli mogu smanjiti oksidativni stres, upalu zida krvnog suda, proliferaciju vaskularnih glatkih mišićnih ćelija i endotelnu disfunkciju. Značajan broj istraživanja ukazuje na sposobnost određenih polifenola da odgode razvoj ateroskleroze. Samim tim, suplementacija polifenolima predstavlja potencijalnu alternativu tradicionalnim farmakološkim sredstvima s relativno ograničenim nuspojavama. Široka upotreba polifenola zahtijeva dalja istraživanja biodostupnosti, apsorpcije i transformacije. Neophodno je utvrđivanje učinka pojedinačnih polifenola, kao i interakcije s drugim bioaktivnim jedinjenjima, definisanje dijetalnog referentnog unosa i sigurnost upotrebe u određenim subpopulacijama.

Literatura

1. Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients. 2010; 2(12): 1231–46. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257627/
2. Balta V. Bioraspoloživost, metabolizam i antioksidacijska sposobnost polifenola u organima miša C57BL/6, doktorska disertacija. Prirodoslovno-matematički fakultet, biološki odsjek Sveučilišta u Zagrebu. 2018. Dostupno na: https://core.ac.uk/download/pdf/185641849.pdf.
3. Truzzi F, Tibaldi C, Zhang Y, Dinelli G, D Amen E. An Overview on Dietary Polyphenols and Their Biopharmaceutical Classification System (BCS). Int J Mol Sci. 2021; 22(11): 5514. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8197262/
4. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2(5): 270–8. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835915/
5. Kamenjašević M, Oršolić N, Matković A, Matković BR. Učinkovitost polifenolne prehrane na zdravlje i funkcionalnu sposobnost sportaša i rekreativaca. Hrvat. Športskomed. Vjesn. 2017; 32: 5–21. Dostupno na: https://hrcak.srce.hr/197945
6. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016; 5: e47. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465813/.
7. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. The American Journal of Clinical Nutrition. 2004; 79 (5): 727–747. Available at: https://academic.oup.com/ajcn/article/79/5/727/4690182

8. Abdulsalam H, Alfarisi H, Hamad Mohamed ZB, Bin Ibrahim M. Basic pathogenic mechanisms of atherosclerosis. Egyptian Journal of Basic and Applied Sciences. 2022; 9: 1: 359–371. Available at: https://www.tandfonline.com/doi/full/10.1080/2314808X.2020.1769913
9. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol. 2002; 7(1): 40–53. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2716189/
10. Leiva E, Wehinger S, Guzmán L, Orrego R. Role of Oxidized LDL in Atherosclerosis. In (Ed.). Hypercholesterolemia. IntechOpen. 2015. Available at: https://www.intechopen.com/chapters/47808
11. Crowther MA. Pathogenesis of Atherosclerosis. Hematology Am Soc Hematol Educ Program 2005; 2005(1): 436–441. Available at: https://ashpublications.org/hematology/article/2005/1/436/19259/Pathogenesis-of-Atherosclerosis
12. Fruchart JC, Nierman MC, Stroes ESG, Kastelein JJP, Duriez P. New Risk Factors for Atherosclerosis and Patient Risk Assessment. Circulation. 2004; 109(23supl 1): 15–19. Available at: https://www.ahajournals.org/doi/10.1161/01.CIR.0000131513.33892.5b
13. Chen Y, She Y , Shi X , Zhang X , Wang R, Men1 K. Green tea catechin: does it lower blood cholesterol? IOP Conf. Series: Earth and Environmental Science. 2020; 559: 012027. Available at: https://iopscience.iop.org/article/10.1088/1755-1315/559/1/012027/pdf
14. Zheng XX, Xu YL, Li SH, Liu XX, Hui R, Huang XH. Green tea intake lowers fasting serum total and LDL cholesterol in adults: a meta-analysis of 14 randomized controlled trials. The American Journal of Clinical Nutrition. 2011; 94(2): 601–610. Available at: https://academic.oup.com/ajcn/article/94/2/601/4597944v
15. Zern TL, Fernandez ML. Cardioprotective Effects of Dietary Polyphenols. The Journal of Nutrition. 2005; 135(10): 2291–2294. Available at: https://academic.oup.com/jn/article/135/10/2291/4669864
16. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? Oxid Med Cell Longev. 2016; 2016: 7432797. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5055983/
17. Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients. 2018; 10(11): 1618. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6266803/
18. Andriantsitohaina R, Auger C, Chataigneau T, Étienne-Selloum N, Li H, Martínez M et al. Molecular mechanisms of the cardiovascular protective effects of polyphenols. British Journal of Nutrition. 2012; 108(9): 1532–1549. Available at: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/molecular-mechanisms-of-the-cardiovascular-protective-effects-of-polyphenols/19A4A5654AD711DAA76CAE61C5957B69
19. Araim O, Ballantyne J, Waterhouse AL, Sumpio BE. Inhibition of vascular smooth muscle cell proliferation with red wine and red wine polyphenols. Journal of Vascular Surgery. 2002; 35(6): 1226–1232. Available at: https://www.sciencedirect.com/science/article/pii/S0741521402396848

20. Stoclet JC, Chataigneau T, Ndiaye M, Oak MH, El Bedoui J, Chataigneau M et al. Vascular protection by dietary polyphenols. Eur J Pharmacol. 2004; 500(1–3): 299–313. Available at: https://pubmed.ncbi.nlm.nih.gov/15464042/
21. Cheng YC, Sheen JM, Hu WL, Hung YC. Polyphenols and Oxidative Stress in Atherosclerosis-Related Ischemic Heart Disease and Stroke. Oxidative Medicine and Cellular Longevity. 2017. Available at: https://www.hindawi.com/journals/omcl/2017/8526438/
22. Storniolo CE, Rosello-Catafau J, Pinto X, Mitjavila MT, Moreno JJ. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. Redox Biology. 2014; 2: 971–977. Available at: https://www.hindawi.com/journals/omcl/2017/8526438/
23. Mathur S, Devaraj S, Grundy SM, Jialal I. Cocoa Products Decrease Low Density Lipoprotein Oxidative Susceptibility but Do Not Affect Biomarkers of Inflammation in Humans. The Journal of Nutrition. 2002; 132(12): 3663–3667. Available at: https://academic.oup.com/jn/article/132/12/3663/4712128
24. Suzuki-Sugihara N, Kishimoto Y, Saita E et al. Green tea catechins prevent low-density lipoprotein oxidation via their accumulation in low-density lipoprotein particles in humans, Nutrition Research. 2016; 36(1): 16–23. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0271531715002699
25. Chen JH, Lee MS, Wang CP, Hsu CC, Lin HH. Autophagic effects of Hibiscus sabdariffa leaf polyphenols and epicatechin gallate (ECG) against oxidized LDL-induced injury of human endothelial cells. European Journal of Nutrition. 2017; 56(5): 1963–1981. Available at: https://link.springer.com/article/10.1007%2Fs00394-016-1239-4
26. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JP. Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients. 2010; 2(11): 1106–31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257622/
27. Loke WM, Proudfoot JM, Hodgson JM, McKinley AJ, Hime N, Magat M et al. Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and endothelial dysfunction. Arterioscler Thromb Vasc Biol. 2010; 30(4): 749–57. Available at: https://www.ahajournals.org/doi/10.1161/atvbaha.109.199687
28. Guo W, Kim SH, Wu D, Li L, Ortega EF, Thomas M. et al. Dietary Fruit and Vegetable Supplementation Suppresses Diet-Induced Atherosclerosis in LDL Receptor Knockout Mice, The Journal of Nutrition. 2021; 151(4): 902–910. Available at: https://academic.oup.com/jn/article/151/4/902/6131865
29. Fuhrman B, Volkova N, Coleman R, Aviram M. Grape Powder Polyphenols Attenuate Atherosclerosis Development in Apolipoprotein E Deficient (E0) Mice and Reduce Macrophage Atherogenicity. The Journal of Nutrition. 2005; 135(4): 722–728. Available at: https://academic.oup.com/jn/article/135/4/722/4663757
30. Bullon P, Quiles JL, Morillo JM, Rubini C, Goteri G, Granados-Principal S. Gingival vascular damage in atherosclerotic rabbits: Hydroxytyrosol and squalene benefits. Food

and Chemical Toxicology. 2009; 47(9): 2327–2331. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0278691509002968?via%3Dihub

31. Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, Corella D, Fito M, Ros E. Benefits of the Mediterranean diet: insights from the PREDIMED study. Progress in Cardiovascular Diseases. 2015; 58(1): 50–60. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0033062015000286?via%3Dihub
32. Medina-Remón A, Casas R, Tressserra-Rimbau A, Ros E, Martínez-González MA, Fitó M et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: a substudy of the PREDIMED trial. Br J Clin Pharmacol. 2017; 83: 114–128. Available at: https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.12986
33. Moreno-Luna, Rocio Muñoz-Hernandez, Maria L. Miranda, Alzenira F. Costa, Luis Jimenez-31. Jimenez R, Vallejo-Vaz AJ, Muriana FJG, Villar J, Stiefel P. Olive Oil Polyphenols Decrease Blood Pressure and Improve Endothelial Function in Young Women with Mild Hypertension. American Journal of Hypertension. 2012; 25(12): 1299–1304. Available at: https://academic.oup.com/ajh/article/25/12/1299/231681
34. Dalgaard F, Bondonno NP, Murray K, Bondonno CP, Lewis JR, Croft KD et al. Associations between habitual flavonoid intake and hospital admissions for atherosclerotic cardiovascular disease: a prospective cohort study. Lancet Planet Health. 2019; 3: 450–59. Available at: https://www.thelancet.com/action/showPdf?pii=S2542-5196%2819%2930212-8
35. Cassidy A, Minihane AM. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. Am J Clin Nutr. 2017; 105(1): 10–22. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5183723/
36. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A et al. Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. Clin Hemorheol Microcirc. 2012; 50(3): 179–87. Available at: https://www.researchgate.net/publication/221743193_Cardioprotection_by_resveratrol_A_human_clinical_trial_in_patients_with_stable_coronary_artery_disease
37. Ellingsen I, Hjerkinn E, Seljeflot I, Arnesen H, Tonstad S. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men. British Journal of Nutrition. 2008; 99(3): 674–681. Available at: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/consumption-of-fruit-and-berries-is-inversely-associated-with-carotid-atherosclerosis-in-elderly-men/FAC71CD83395EA2436A0191BED21C442
38. Speer H, D'Cunha NM, Botek M, McKune AJ, Sergi D, Georgousopoulou D et al. The Effects of Dietary Polyphenols on Circulating Cardiovascular Disease Biomarkers and Iron Status: A Systematic Review. Nutrition and Metabolic Insights. 2019; 12. Available at: https://journals.sagepub.com/doi/10.1177/1178638819882739
39. Bentzon JF, Skovenborg E, Hansen C, Møller J, Saint-Cricq de Gaulejac N, Proch J. Red Wine Does Not Reduce Mature Atherosclerosis in Apolipoprotein E–Deficient Mice. Circulation. 2001; 103(12): 1681–1687. Available at: https://www.ahajournals.org/doi/10.1161/01.CIR.103.12.1681

40. Gendron ME, Théorêt JF, Mamarbachi AM, Drouin A, Nguyen A, Bolduc W. Late chronic catechin antioxidant treatment is deleterious to the endothelial function in aging mice with established atherosclerosis. American Journal of Physiology-Heart and Circulatory Physiology 2010; 298: 6, H2062–H2070. Available at: https://journals.physiology.org/doi/full/10.1152/ajpheart.00532.2009
41. Yang X, Dai H, Deng R, Zhang Z, Quan Y, Giri M, Shen J. Association between tea consumption and prevention of coronary artery disease: A systematic review and dose-response meta-analysis. Front Nutr. 2022; 9: 1021405. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9729734/?fbclid=IwAR24VI7k7PsCKfDNULjkmZtZBJ-4D7Eza-oTgxDVV-UpHqtzE1TFh5I_lzY8
42. Zhu F, Qin Y, Bi Y, Su J, Cui L, Luo P et al. Fresh vegetable and fruit consumption and carotid atherosclerosis in high-cardiovascular-risk population: a cross-sectional study in Jiangsu, China. Cad Saude Publica. 2021; 37(5): e00033020. Available at: https://www.scielosp.org/article/csp/2021.v37n5/e00033020/

Marijana C. Jandrić-Kočič[1]

THE INFLUENCE OF POLYPHENOLS ON ATHEROSCLEROSIS DEVELOPMENT

Summary: Polyphenols represent one of the biggest and most widespread groups of secondary plant metabolites with more than 8000 polyphenolic compounds. Fruits, vegetables and beverages such as tea and red wine are the main sources of polyphenols. A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis. According to the same polyphenols reduce lipid deposition, oxidative stress, inflammation of the blood vessel wall, proliferation of vascular smooth muscle cells and endothelial dysfunction. The widespread use of polyphenols requires further research on bioavailability, absorption and transformation. It is necessary to determine the effect of individual polyphenols as well as the interaction with other bioactive compounds, define the dietary reference intake and the safety of use in certain subpopulations.

Key words: polyphenols, atherosclerosis, cardiovascular diseases

Introduction

Polyphenols are compounds that in their structure contain 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 compounds[2,3]. According to the structure, biological activity and biosynthetic pathway, we distinguish between flavonoids and non-flavonoids[4]. Flavonoids are divided into six main subclasses: flavonols, flavanones, flavanols, flavones, anthocyanins and isoflavones[4-6]. Other groups of flavonoids include less abundant chalcones, dihydrochalcones, dihydroflavonols, flavan-3,4-diols, coumarins and aurones[2]. Non-flavonoids include phenolic acids (benzoic acid and cinnamic acid), stilbenes, lignans, tannins and other polyphenols (curcumin, gingerol)[2]. The main sources of polyphenols are fruits, vegetables and drinks such as tea and red wine[7,8,9].

[1] Marijana Jandrić-Kočić, Dom zdravlja Krupa na Uni, Banjaluka, Republika Srpska, e-mail: marijanajandrickocic@gmail.com

Their content in plant products is determined by pedoclimatic and agronomic conditions, as well as the degree of maturity[7]. Absorption of polyphenols is conditioned by phytochemical properties (molecular structure, lipophilicity, dissociation constant and solubility), direct interaction with food components and host factors (intestinal and systemic)[7,9]. The estimated daily intake of polyphenols is 1g[7].

Atherosclerosis is the leading cause of morbidity and mortality in Europe and the United States of America[8-11]. It is defined as a chronic inflammatory disease of the walls of large and medium arteries (predominantly the aorta, carotid arteries, coronary arteries and arteries of the lower extremities)[8]. Risk factors for atherosclerosis are hypercholesterolemia, hypertension, cigarette smoking, obesity, physical inactivity, age, family history, diabetes mellitus, male sex, but also hypertriglyceridemia, hyperhomocysteinemia and hyperfibrinogenemia[9,11,12]. Atherosclerosis is caused by chronic inflammation in the blood vessel wall induced by unbalanced lipid metabolism and impaired immune response[8,9]. Oxidative modification of LDL cholesterol (low-density lipoprotein, LDL) (mediated by reactive oxygen species, myeloperoxidase, lipoperoxidase, nicotinamide adenine dinucleotide phosphate) into oxidized low-density lipoprotein (Ox-LDL) within the extracellular matrix of the subendothelial space induces endothelial dysfunction, formation of foam cells, migration and subsequent proliferation of blood vessel smooth muscle cells (SMC), adhesion and aggregation of platelets[8,10]. Clinical manifestations of atherosclerosis are conditioned by the place of plaque development and the presence of thromboembolic changes (myocardial infarction, transient ischemic attack and stroke, intermittent claudication, intestinal infarction)[9].

A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis[13-20]. According to the same polyphenols reduce lipid deposition, oxidative stress, inflammation of the blood vessel walls, proliferation of vascular smooth muscle cells and endothelial dysfunction[13-20].

The influence of polyphenols on atherosclerosis development

Polyphenols modify the processes involved in the formation, progression and eventual rupture of atherosclerotic plaque[13-20]. Polyphenols can significantly reduce lipid absorption by inhibiting emulsification in the small intestine, inhibiting pancreatic lipase activity, reducing micellar solubility and precipitation of micellar cholesterol[13-16]. Reduced cholesterol absorption causes increased production of mitochondrial ribonucleic acid for the LDL receptor in the liver[16]. They reduce the production of apolipoprotein B100 in the liver by reducing the formation of cholesterol esters, reducing the activity of Acyl-CoA cholesterol acyltransferase and reducing the activity of microsomal protein for the transfer of triglycerides[15]. Therefore, polyphenols reduce the concentration of LDL in the extracellular matrix of the subendothelial

space[8,23]. They reduce the concentration of triglycerides by reducing the activity of the microsomal protein for the transfer of triglycerides and possibly increasing the activity of lipoprotein lipase[15]. A reduced concentration of triglycerides modifies the delipidation cascade and reduces the concentration of LDL in plasma[15]. Polyphenols exert antioxidant activity in several ways[2]. The most effective involves the neutralization of free radicals (transfer of hydrogen atoms from active hydroxyl groups of polyphenols to free radicals)[2]. The ability to neutralize free radicals is conditioned by the arrangement and total number of hydroxyl groups, the degree of polymerization, glycosidation, O-methylation and 2-3 double bonds in conjugation with the 4-keto group[2]. The anti-inflammatory effect of polyphenols involves the inhibition of pro-inflammatory enzymes (lipoxygenase a, cyclooxygenase-2, inducible nitric oxide synthase, nuclear factor-κB, activating protein-1) and activation of mitogen-activated protein kinase, protein kinase-C, nuclear factor erythroid 2-related factor 2 and phase-II enzymes of antioxidant detoxification[16- 18]. Polyphenols can inhibit the proliferation of vascular smooth muscle cells by arresting the cell cycle in the S phase of mitosis (deoxyribonucleic acid chain breaking in the presence of copper ions) and apoptosis[19]. Independently of their antioxidant effects, polyphenols achieve vasoprotective, antiaggregative, antiatherogenic, vasorelaxant and antihypertensive effects by activating the production of vasodilating factors (nitric oxide, hyperpolarizing factor derived from the endothelium, prostacyclin), by inhibiting the synthesis of vasoconstrictor endothelin-1 in endothelial cells, and by inhibiting the expression of two main proangiogenic factor, vascular endothelial growth factor and matrix metalloproteinase-2 in smooth muscle cells[20]. In endothelial cells, polyphenols increase the level of calcium, induce redox-sensitive activation of the phosphatidylinositol 3 kinase/Akt protein kinase B pathway and increase the expression of nitric oxide synthase[20]. In smooth muscle cells, there is a redox-sensitive inhibition of the activation of the p38 mitogen-activated protein kinase pathway (inhibition platelet-derived growth factor-activated vascular endothelial growth factor gene expression) and redox-independent inhibition of thrombin-induced matrix metalloproteinase-2 formation[20].

Red wine phenols inhibit LDL oxidation, vascular smooth muscle cell proliferation and activate endothelial nitric oxide synthase[21]. Pomegranate polyphenols reduce platelet aggregation[21]. Dark chocolate flavonoids increase plasma antioxidant capacity and cause endothelium-dependent vasodilation[22,23]. Green tea catechins are incorporated into LDL particles and reduce their oxidation[24]. Flavonoids in hibiscus sabdarife leaves inhibit LDL oxidation[25]. Blueberry phenolics reduce the activity of the proliferation signaling pathway[21]. Polyphenols from extra virgin olive oil suppress the formation of reactive oxygen species, promote the formation of nitric oxide, inhibit angiogenesis, migration and proliferation of vascular cells and prevent vascular injuries caused by advanced glycation end products[26]. Resveratrol, isorhamnetin, curcumin and vanillic acid reduce the release of pro-inflammatory cytokines[21]. Resveratrol reduces

platelet activation and aggregation[21]. Curcumin reduces the proliferation of vascular smooth muscle cells and reduces oxidative stress[21].

Method

The literature was searched using the keywords: polyphenols, atherosclerosis and cardiovascular diseases. The search was conducted for the period from 2001. until 2022 within the following databases: PubMed, Emabase, Scopus, SCin-dex and Hrcak. Due to the limited number of available studies, no available filters were used in the database search. After the summaries were read, the papers were studied in more detail and those that did not correspond to the research objective were excluded.

Atheroroprotective effect of polyphenol

A significant number of animal studies confirmed the integral association of polyphenols with the development of atherosclerosis[27-30]. Research in Australia found that specific dietary polyphenols, predominantly quercetin and theaflavin, could slow atherosclerosis in mice with the apolipoprotein E27 gene removed. According to the same, the atheroprotective effect of a diet rich in fruits and vegetables can partly be the result of the effect of flavonoids[27]. Research on mice with the LDL receptor gene removed determined that the consumption of fruits and vegetables equivalent to 8-9 servings of fruits and vegetables in humans slows down the development of atherosclerotic plaque caused by an atherogenic diet[28]. Similar research in Israel confirmed the atheroprotective effect of grape polyphenols[29]. Research with New Zealand rabbits on an atherosclerotic diet in Spain observed the atheroprotective effect of components of extra virgin olive oil[30]. Hydroxytyrosol improved endothelial function, while squalene reduced plaque fibrosis[30].

The atheroprotective effect of polyphenols has been the subject of numerous studies with humans[31-38]. The multicenter, randomized, controlled study PREDI-MED in Spain lasting 8 years in which 7447 people at high risk for developing cardiovascular disease participated found that a Mediterranean diet based on vegetables rich in unsaturated fatty acids enriched with olive oil slows the progression of subclinical atherosclerosis (measured by ultrasound of the carotid arteries)[31]. A substudy of the PREDIMED study in which 1139 individuals at high risk for cardiovascular disease participated observed a significant inverse correlation between one-year intake of polyphenols and circulating inflammatory molecules associated with atherosclerosis[32]. A double-blind randomized crossover

controlled study with 24 female adults with an average age of 26 years confirmed the atheroprotective role of polyphenols[33]. According to the same, a diet rich in polyphenols improves the function of the endothelium, which stimulates the nitric oxide synthase system and reduces the oxidation of LDL (predominantly hydroxytyrosol and its derivatives)[33]. A 23-year prospective cohort study in Denmark involving 53,552 individuals found that polyphenol intake (1000 mg/day) was associated with a 14% lower risk of atherosclerotic cardiovascular disease (9% ischemic heart disease, 9% ischemic stroke and 32 % peripheral artery disease)[34]. The strongest association is the confirmed disease in peripheral artery disease and atherosclerotic cardiovascular disease in smokers and people with alcohol abuse disease[34]. Obese people had a low association, which could be explained by a change in the intestinal microbiota and impaired bioconversion of flavonoids in the large intestine[34,35]. A double-blind randomized controlled study in Hungary among people with myocardial infarction found that resveratrol intake (without alcohol consumption) slows down the development of atherosclerosis in people with coronary artery disease[36]. A study among 558 men aged 40-49 years with elevated serum total cholesterol and/or high coronary risk determined that the consumption of fruits and berries rich in polyphenols can slow down the progression of atherosclerosis of the carotid arteries[37]. A meta-analysis of 7 studies involving 133 participants who used a variety of foods and supplements rich in hydroxytyrosol, quercetin and resveratrol (45-1015 mg/100 g) for up to 145 days found a reduction in lipids and inflammatory markers[38].

On the other hand, a study of mice with the Apolipoprotein E gene removed in the United States of America determined that the polyphenols of red wine do not reduce the size of the formed atherosclerotic plaque, nor the content of collagen in the same[39]. A similar study in Canada observed that catechin in young mice protects against the development of atherosclerosis40. In older mice with developed atherosclerotic plaque, catechin favors further endothelial dysfunction and leukocyte adhesion[40]. A systematic review and meta-analysis of 35 prospective cohort studies in the Czech Republic observed that moderate drinking of black tea, less than 4 cups per day, has an atheroprotective effect, while consumption of 4 to 6 cups per day predisposes to atherosclerosis[40]. This effect is conditioned by the caffeine content in black tea[41]. In the same study, there was a significant inverse correlation between drinking green tea and the development of atherosclerosis in the Asian but not in the Western population4[1]. Research in China found that consumption of fruit rich in polyphenols does not have an atheroprotective effect in people with a high risk of cardiovascular diseases42. One of the possible reasons is that more than a quarter of the mentioned population has hyperglycemia, which is aggravated by high fructose intake[42].

Conclusion

Polyphenols can reduce oxidative stress, inflammation of the blood vessel wall, proliferation of vascular smooth muscle cells and endothelial dysfunction. A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis. Therefore, supplementation with polyphenols represents a potential alternative to traditional pharmacological agents with relatively limited side effects. The widespread use of polyphenols requires further research on bioavailability, absorption and transformation. It is necessary to determine the effect of individual polyphenols as well as the interaction with other bioactive compounds, define the dietary reference intake and the safety of use in certain subpopulations.

Literature

1. Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients. 2010; 2(12): 1231–46. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257627/
2. Balta V. Bioraspoloživost, metabolizam i antioksidacijska sposobnost polifenola u organima miša C57BL/6, doktorska disertacija. Prirodoslovno-matematički fakultet, biološki odsjek Sveučilišta u Zagrebu. 2018. Dostupno na: https://core.ac.uk/download/pdf/185641849.pdf.
3. Truzzi F, Tibaldi C, Zhang Y, Dinelli G, D Amen E. An Overview on Dietary Polyphenols and Their Biopharmaceutical Classification System (BCS). Int J Mol Sci. 2021; 22(11): 5514. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8197262/
4. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2(5): 270–8. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835915/
5. Kamenjašević M, Oršolić N, Matković A, Matković BR. Učinkovitost polifenolne prehrane na zdravlje i funkcionalnu sposobnost sportaša i rekreativaca. Hrvat. Športskomed. Vjesn. 2017; 32: 5–21. Dostupno na: https://hrcak.srce.hr/197945
6. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016; 5: e47. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465813/.
7. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. The American Journal of Clinical Nutrition. 2004; 79 (5): 727–747. Available at: https://academic.oup.com/ajcn/article/79/5/727/4690182
8. Abdulsalam H, Alfarisi H, Hamad Mohamed ZB, Bin Ibrahim M. Basic pathogenic mechanisms of atherosclerosis. Egyptian Journal of Basic and Applied Sciences. 2022; 9: 1: 359–371. Available at: https://www.tandfonline.com/doi/full/10.1080/2314808X.2020.1769913
9. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol. 2002; 7(1): 40–53. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2716189/

10. Leiva E, Wehinger S, Guzmán L, Orrego R. Role of Oxidized LDL in Atherosclerosis. In (Ed.). Hypercholesterolemia. IntechOpen. 2015. Available at: https://www.intechopen.com/chapters/47808
11. Crowther MA. Pathogenesis of Atherosclerosis. Hematology Am Soc Hematol Educ Program 2005; 2005(1): 436–441. Available at: https://ashpublications.org/hematology/article/2005/1/436/19259/Pathogenesis-of-Atherosclerosis
12. Fruchart JC, Nierman MC, Stroes ESG, Kastelein JJP, Duriez P. New Risk Factors for Atherosclerosis and Patient Risk Assessment. Circulation. 2004; 109(23supl 1): 15–19. Available at: https://www.ahajournals.org/doi/10.1161/01.CIR.0000131513.33892.5b
13. Chen Y, She Y , Shi X , Zhang X , Wang R, Men1 K. Green tea catechin: does it lower blood cholesterol? IOP Conf. Series: Earth and Environmental Science. 2020; 559: 012027. Available at: https://iopscience.iop.org/article/10.1088/1755-1315/559/1/012027/pdf
14. Zheng XX, Xu YL, Li SH, Liu XX, Hui R, Huang XH. Green tea intake lowers fasting serum total and LDL cholesterol in adults: a meta-analysis of 14 randomized controlled trials. The American Journal of Clinical Nutrition. 2011; 94(2): 601–610. Available at: https://academic.oup.com/ajcn/article/94/2/601/4597944v
15. Zern TL, Fernandez ML. Cardioprotective Effects of Dietary Polyphenols. The Journal of Nutrition. 2005; 135(10): 2291–2294. Available at: https://academic.oup.com/jn/article/135/10/2291/4669864
16. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? Oxid Med Cell Longev. 2016; 2016: 7432797. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5055983/
17. Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients. 2018; 10(11): 1618. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6266803/
18. Andriantsitohaina R, Auger C, Chataigneau T, Étienne-Selloum N, Li H, Martínez M et al. Molecular mechanisms of the cardiovascular protective effects of polyphenols. British Journal of Nutrition. 2012; 108(9): 1532–1549. Available at: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/molecular-mechanisms-of-the-cardiovascular-protective-effects-of-polyphenols/19A4A5654AD711DAA76CAE61C5957B69
19. Araim O, Ballantyne J, Waterhouse AL, Sumpio BE. Inhibition of vascular smooth muscle cell proliferation with red wine and red wine polyphenols. Journal of Vascular Surgery. 2002; 35(6): 1226–1232. Available at: https://www.sciencedirect.com/science/article/pii/S0741521402396848
20. Stoclet JC, Chataigneau T, Ndiaye M, Oak MH, El Bedoui J, Chataigneau M et al. Vascular protection by dietary polyphenols. Eur J Pharmacol. 2004; 500(1–3): 299–313. Available at: https://pubmed.ncbi.nlm.nih.gov/15464042/
21. Cheng YC, Sheen JM, Hu WL, Hung YC. Polyphenols and Oxidative Stress in Atherosclerosis-Related Ischemic Heart Disease and Stroke. Oxidative Medicine and Cellular Longevity. 2017. Available at: https://www.hindawi.com/journals/omcl/2017/8526438/

22. Storniolo CE, Rosello-Catafau J, Pinto X, Mitjavila MT, Moreno JJ. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. Redox Biology. 2014; 2: 971–977. Available at: https://www.hindawi.com/journals/omcl/2017/8526438/
23. Mathur S, Devaraj S, Grundy SM, Jialal I. Cocoa Products Decrease Low Density Lipoprotein Oxidative Susceptibility but Do Not Affect Biomarkers of Inflammation in Humans. The Journal of Nutrition. 2002; 132(12): 3663–3667. Available at: https://academic.oup.com/jn/article/132/12/3663/4712128
24. Suzuki-Sugihara N, Kishimoto Y, Saita E et al. Green tea catechins prevent low-density lipoprotein oxidation via their accumulation in low-density lipoprotein particles in humans, Nutrition Research. 2016; 36(1): 16–23. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0271531715002699
25. Chen JH, Lee MS, Wang CP, Hsu CC, Lin HH. Autophagic effects of Hibiscus sabdariffa leaf polyphenols and epicatechin gallate (ECG) against oxidized LDL-induced injury of human endothelial cells. European Journal of Nutrition. 2017; 56(5): 1963–1981. Available at: https://link.springer.com/article/10.1007%2Fs00394-016-1239-4
26. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JP. Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients. 2010; 2(11): 1106–31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257622/
27. Loke WM, Proudfoot JM, Hodgson JM, McKinley AJ, Hime N, Magat M et al. Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and endothelial dysfunction. Arterioscler Thromb Vasc Biol. 2010; 30(4): 749–57. Available at: https://www.ahajournals.org/doi/10.1161/atvbaha.109.199687
28. Guo W, Kim SH, Wu D, Li L, Ortega EF, Thomas M. et al. Dietary Fruit and Vegetable Supplementation Suppresses Diet-Induced Atherosclerosis in LDL Receptor Knockout Mice, The Journal of Nutrition. 2021; 151(4): 902–910. Available at: https://academic.oup.com/jn/article/151/4/902/6131865
29. Fuhrman B, Volkova N, Coleman R, Aviram M. Grape Powder Polyphenols Attenuate Atherosclerosis Development in Apolipoprotein E Deficient (E0) Mice and Reduce Macrophage Atherogenicity. The Journal of Nutrition. 2005; 135(4): 722–728. Available at: https://academic.oup.com/jn/article/135/4/722/4663757
30. Bullon P, Quiles JL, Morillo JM, Rubini C, Goteri G, Granados-Principal S. Gingival vascular damage in atherosclerotic rabbits: Hydroxytyrosol and squalene benefits. Food and Chemical Toxicology. 2009; 47(9): 2327–2331. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0278691509002968?via%3Dihub
31. Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, Corella D, Fito M, Ros E. Benefits of the Mediterranean diet: insights from the PREDIMED study. Progress in Cardiovascular Diseases. 2015; 58(1): 50–60. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0033062015000286?via%3Dihub
32. Medina-Remón A, Casas R, Tressserra-Rimbau A, Ros E, Martínez-González MA, Fitó M et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers

related to atherosclerosis: a substudy of the PREDIMED trial. Br J Clin Pharmacol. 2017; 83: 114–128. Available at: https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.12986

33. Moreno-Luna, Rocio Muñoz-Hernandez, Maria L. Miranda, Alzenira F. Costa, Luis Jimenez-31. Jimenez R, Vallejo-Vaz AJ, Muriana FJG, Villar J, Stiefel P. Olive Oil Polyphenols Decrease Blood Pressure and Improve Endothelial Function in Young Women with Mild Hypertension. American Journal of Hypertension. 2012; 25(12): 1299–1304. Available at: https://academic.oup.com/ajh/article/25/12/1299/231681
34. Dalgaard F, Bondonno NP, Murray K, Bondonno CP, Lewis JR, Croft KD et al. Associations between habitual flavonoid intake and hospital admissions for atherosclerotic cardiovascular disease: a prospective cohort study. Lancet Planet Health. 2019; 3: 450–59. Available at: https://www.thelancet.com/action/showPdf?pii=S2542-5196%2819%2930212-8
35. Cassidy A, Minihane AM. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. Am J Clin Nutr. 2017; 105(1): 10–22. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5183723/
36. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A et al. Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. Clin Hemorheol Microcirc. 2012; 50(3): 179–87. Available at: https://www.researchgate.net/publication/221743193_Cardioprotection_by_resveratrol_A_human_clinical_trial_in_patients_with_stable_coronary_artery_disease
37. Ellingsen I, Hjerkinn E, Seljeflot I, Arnesen H, Tonstad S. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men. British Journal of Nutrition. 2008; 99(3): 674–681. Available at: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/consumption-of-fruit-and-berries-is-inversely-associated-with-carotid-atherosclerosis-in-elderly-men/FAC71CD83395EA2436A0191BED21C442
38. Speer H, D'Cunha NM, Botek M, McKune AJ, Sergi D, Georgousopoulou D et al. The Effects of Dietary Polyphenols on Circulating Cardiovascular Disease Biomarkers and Iron Status: A Systematic Review. Nutrition and Metabolic Insights. 2019; 12. Available at: https://journals.sagepub.com/doi/10.1177/1178638819882739
39. Bentzon JF, Skovenborg E, Hansen C, Møller J, Saint-Cricq de Gaulejac N, Proch J. Red Wine Does Not Reduce Mature Atherosclerosis in Apolipoprotein E–Deficient Mice. Circulation. 2001; 103(12): 1681–1687. Available at: https://www.ahajournals.org/doi/10.1161/01.CIR.103.12.1681
40. Gendron ME, Théorêt JF, Mamarbachi AM, Drouin A, Nguyen A, Bolduc W. Late chronic catechin antioxidant treatment is deleterious to the endothelial function in aging mice with established atherosclerosis. American Journal of Physiology-Heart and Circulatory Physiology 2010; 298: 6, H2062–H2070. Available at: https://journals.physiology.org/doi/full/10.1152/ajpheart.00532.2009
41. Yang X, Dai H, Deng R, Zhang Z, Quan Y, Giri M, Shen J. Association between tea consumption and prevention of coronary artery disease: A systematic review and dose-response meta-analysis. Front Nutr. 2022; 9: 1021405. Available at: https://www.ncbi.

nlm.nih.gov/pmc/articles/PMC9729734/?fbclid=IwAR24VI7k7PsCKfDNULjkmZtZBJ-4D7Eza-oTgxDVV-UpHqtzE1TFh5I_lzY8

42. Zhu F, Qin Y, Bi Y, Su J, Cui L, Luo P et al. Fresh vegetable and fruit consumption and carotid atherosclerosis in high-cardiovascular-risk population: a cross-sectional study in Jiangsu, China. Cad Saude Publica. 2021; 37(5): e00033020. Available at: https://www.scielosp.org/article/csp/2021.v37n5/e00033020/