

BÖLÜM 41

ANTIÖKSİDAN VİTAMİNLER

Said ALTİKAT¹

OKSİDATİF STRES VE OKSİDANLAR

Şu anda "oksidanlar ile antioksidanlar arasında, oksidanların tarafına kayan bir dengesizlik ve ayrıca redoks sinyal mekanizmalarında bir bozukluk ve kontrol kaybına yol açan bir dengesizlik ile moleküler hasar" olarak tanımlanan Oksidatif stres; önceleri "prooksidan/antioksidan oranında pay oranında artışla ilgili bir metabolik araz olarak yani, prooksidanların artışıyla karakterize bir bozukluk" olarak ifade edilmişti. (1,2)

Oksidatif stres; biyolojik sistemlerdeki iç mekanizmalarda etkenlere karşı koyma kapasitesinin azalmasıyla ilgili olarak bol miktarda reaktif oksijen türlerinin (ROS) üretiminden kaynaklanır. Yüksek miktarlarda biyolojik yapıları sistemleri ve molekülleri etkileyen tahrip gücü çok fazla olan ve bilindik birçok hastalığın kaynağı olarak tarif edilen Reaktif oksijen türleri, bir veya birden çok eşleşmeyen elektrona sahip serbest radikal moleküllerini ifade eder. Pek çok hastalık ve patolojik süreçlerde serbest radikallerin sebep olduğu Oksidatif stres etmen olarak gösterilmiştir. Süperoksit anyonu radikali ($O_2^{\bullet-}$), nitrik oksit radikali ($\bullet NO$),

hidrojen peroksittir (H_2O_2) ve hidroksil radikali ($\bullet OH$), üzerinde en fazla çalışılan ve olumsuz etkileri en çok bilinen esas reaktif oksijen türleridir. (3,4)

Oksidatif stres, birçok hastalık sürecinde ortak noktayı göstermesi bakımından önemlidir. ROS üretimi ile vücuttaki antioksidan savunma sistemleri arasında bir dengesizlik varsa bu durum bize, sisteme aşırı yüklenildiği gösterir.(5) ROS, biyolojik hücrelerde enzimatik ve nonenzimatik oluşturulan ve doğrudan veya çeşitli sinyal yollarında ara ürünler olarak çıkan ve hücresel hasarlanmalara neden olan oldukça reaktif türlerin bir bütünü olarak karşımıza çıkar. Metabolik yollarda, oksijen molekülü, önce süperoksit sonra hidrojen peroksit daha sonra ise ve hidroksil radikallerine dönüşerek ilerler. Oksijenden su üretimi ETZ de enzimatik bir işlemdir. ROS türlerinin üretimi sonucunda hücre zarı yapısında bazı enzim aktivasyonu sonucu lipidhidroperoksit molekülleri oluşur. Buradaki enzimler metaloenzimler olup bazı iyonları içerir.

Substrat konsantrasyonu arttığında ayrışır ve özellikle demir olmak üzere metal iyonları

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KAYNAKLAR

- Sies H. first ed. Academic Press; 1985. Oxidative Stress.
- Sies H. Biochemistry of oxidative stress. *Angew Chem. Int. Ed. Engl.* 1986;25:1058–1071.
- Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet.* 1994;344:721–724.
- Pisoschi A.M, Pop A., Iordache F. et al. Oxidative stress mitigation by antioxidants-an overview on their chemistry and influences on health status. *Eur. J. Med. Chem.* 2021;209:112891.
- Juránek I., Bezek Š. Controversy of free radical hypothesis: reactive oxygen species – cause or consequence of tissue injury? *Gen. Physiol. Biophys.* (2005) **24** 263– 278.
- Spiteller G. Are lipid peroxidation processes induced by changes in the cell wall structure and how are these processes connected with diseases? *Med. Hypotheses* (2003) **60** 69– 83.
- Webster N.R., Nunn J.F. Molecular structure of free radicals and their importance in biological reactions. *Br. J. Anaesth.* (1988) **60** 98– 108.
- Granger D.N. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *Am. J. Physiol.* (1988) **255** 1269– 1275.
- Kang S.M., Lim S., Song H. et al. Allopurinol modulates reactive oxygen species generation and Ca²⁺ overload in ischemia-reperfusion heart and hypoxia-reoxygenated cardiomyocytes. *Eur. J. Pharmacol.* (2006) **535** 212– 219.
- Tan S, Yokoyama Y, Dickens E, et al. Xanthine-oxidase activity in the circulation of rats following hemorrhagic shock. *Free Radic. Biol. Med.* (1993) **15** 407– 414.
- Terada L.S., Dormish J.J., Shanley P.F. et al. Circulating xanthine oxidase mediates lung neutrophil sequestration after intestinal ischemia-reperfusion. *Am. J. Physiol.* (1992) **263** L394 L401.
- Grisham M.B, Hernandez L.A, Granger D.N. Xanthine oxidase and neutrophil infiltration in intestinal ischemia. *Am. J. Physiol.* (1986) **251** G5 67 -G574.
- Nathan A.T, Singer M. The oxygen trail: tissue oxygenation. *Br. Med. Bull.* (1999) **55** 96– 108.
- Macdonald J., Galley H.F., Webster N.R. Oxidative stress and gene expression in sepsis. *Br. J. Anaesth.* (2003) **90** 221– 232.
- Pisoschi A.M., Pop A. The role of antioxidants in the chemistry of oxidative stress: a Review. *Eur. J. Med. Chem.* 2015;97:55–74.
- Cheeseman K.H., Slater T.F. An introduction to free radical biochemistry. *Br. Med. Bull.* 1993;49:481–493.
- Bouayed J, Bohn T. Exogenous antioxidants-double-edged swords in cellular redox state: health beneficial effects at physiologic doses versus deleterious effects at high doses. *Oxid. Med. Cell. Longev.* 2010;3:228-237. Article ID 267025.
- S.Altıkat, Çiftçi M, Büyükkuroğlu M.E., "In Vitro Effects of Some Anesthetic Drugs on Enzymatic Activity of Human Red Blood Cell Glucose 6-Phosphate Dehydrogenase", *Polish Journal of Pharmacology*, "54", 67-71 pp. 2001.
- Altıkat S, Çoban A, Çiftçi M, et al. "In Vitro Effects of Some Drugs on Catalase Purified From Human Skin", *Journal of Enzyme Inhibition and Medicinal Chemistry*, "21(2)", 231-234 pp. 2006, DOI: 10.1080/14756360 500483453.
- Büyükkuroğlu M. E, Altıkat S, Çiftçi M, "The Effects of Ethanol On Glucose 6-Phosphate Dehydrogenase Enzyme Activity from Human Erythrocytes In Vitro And Rat Erythrocytes in Vivo", *Alcohol and Alcoholism* , "37(4)", 327-329 pp. 2002, DOI: 10.1093/alcalc/37.4.327,
- Çiftçi M, Beydemir Ş, Altıkat S, et al. "Purification of Glucose 6-Phosphate Dehydrogenase from Buffalo (Bubalus Bubalis) Erythrocytes and Investigation of Some Kinetic Properties", *Protein Expression and Purification*, 29,304-310 pp.2003, DOI:10.1016/S1046-5928(03)00073 -1
- Jain S.K. Glutathione and glucose-6-phosphate dehydrogenase deficiency can increase protein glycosylation. *Free Radic. Biol. Med.* 1998;24:197–201.
- Ross C.A. In: *Encyclopedia of Dietary Supplements*. second ed. Coates P.M., Betz J.M., Blackman M.R., Cragg G.M., Levine M., Moss J., White J.D., editors. Informa Healthcare; London, New York: 2010. Vitamin A; pp. 778–791
- Lidén M, Eriksson U. Understanding retinol metabolism: Structure and function of retinol dehydrogenases. *J. Biol. Chem.* 2006;281:13001–13004. doi: 10.1074/jbc.R500027200
- Lefebvre P, Martin P.J, Flajollet S, et al. Transcriptional Activities of Retinoic Acid Receptors. *Vitam. Horm.* 2005;70:199–264. doi: 10.1016/ S0083-6729(05)70007-8.
- Tanumihardjo SA. Vitamin A: Biomarkers of nutrition for development *Am. J. Clin. Nutr.* 2011;94:658S–65S. doi: 10.3945/ajcn.110.005777.
- Tang G. Bioconversion of dietary provitamin A carotenoids to vitamin A in humans. *Am. J. Clin. Nutr.* 2010;91:1468S. doi: 10.3945/ajcn.2010.28674G.
- Dao D.Q, Ngo T.C, Thong N.M, et al. Is vitamin A an antioxidant or a pro oxidant? *J. Phys. Chem. B.* 2017;121:9348–9357. doi: 10.1021/acs.jpcc.7b07065
- Huang Z, Liu Y, Qi G, et al. Role of vitamin A in the immune system. *J. Clin. Med.* 2018;7:258. doi: 10.3390/jcm7090258. .
- Benn C.S. Combining vitamin A and vaccines: Convenience or conflict? *Dan. Med. J.* 2012;59:B4378.
- Palace V.P, Khaper N., Qin Q., et al. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radical Biol. Med.* 1999;26:746–761.
- Dao D.Q, Ngo T.C., Thong N.M., et al. Vitamin A an antioxidant or a pro-oxidant? *J. Phys. Chem. B.* 2017;121:9348–9357.
- Pravkin S.K., Yakusheva E.N., Uzbekova D.G. In vivo analysis of antioxidant and prooxidant, properties of retinol acetate. *Bull. Exp. Biol. Med.* 2013;156:220–223.
- Jovic T.H., Ali S.R., Ibrahim N., et al. Could vitamins help in the fight against COVID-19? *Nutrients.* 2020;12:2550.
- Caccialanza R, Laviano A, Lobascio F, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition.* 2020;74:110835. doi: 10.1016/j.nut.2020.110835.
- Hashimoto S, Hayashi S, Yoshida S, et al. Retinoic acid differentially regulates interleukin-1β and interleukin-1 receptor antagonist production by human alveolar macrophages. *Leuk. Res.* 1998;22:1057–1061. doi: 10.1016/S0145-2126(98)00119-

37. Yang C, Yang X, Du J, et al. Retinoic acid promotes the endogenous repair of lung stem/progenitor cells in combined with simvastatin after acute lung injury: A stereological analysis. *Respir. Res.* 2015;16:140. doi: 10.1186/s12931-015-0300
38. Trottier C, Colombo M, Mann K.K, et al. Retinoids inhibit measles virus through a type I IFN-dependent bystander effect. *FASEB J.* 2009;23:3203–3212. doi: 10.1096/fj.09-129288.
39. Raverdeau M, Mills KHG. Modulation of T cell and innate immune responses by retinoic acid. *J Immunol.* 2014;192(7):2953–2958. doi: 10.4049/jimmunol.1303245.
40. Matikainen S, Ronni T, Hurme M, et al. (1996) Retinoic acid activates interferon regulatory factor-1 gene expression in myeloid cells.
41. Angulo A, Chandraratna RA, LeBlanc JF, et al. Ligand induction of retinoic acid receptors alters an acute infection by murine cytomegalovirus. *J Virol.* 1998;72(6):4589–4600. doi: 10.1128/JVI.72.6.4589-4600.1998.
42. Li B, Wang Y, Shen F, et al. Identification of retinoic acid receptor agonists as potent hepatitis B virus inhibitors via a drug repurposing screen. *Antimicrob Agents Chemother.* 10.1016/j.antiviral.2019.04.009
43. Gudas LJ Emerging roles for retinoids in regeneration and differentiation in normal and disease states. *Biochim Biophys Acta (BBA)-Molecular Cell Biol Lipids.* 1821(11):213–21.10.1016/j.bbalip.2011.08.002
44. Palace V.P, Khaper N, Qin Q, et al. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radical Biol. Med.* 1999;26:746–761.
45. Dao D.Q, Ngo T.C, Thong N.M, et al. Is Vitamin A an antioxidant or a pro-oxidant? *J. Phys. Chem. B.* 2017;121:9348–9357.
46. Samad N, Dutta S, Sodunke T.E, et al. Fat-soluble vitamins and the current global pandemic of COVID-19: evidence-based efficacy from literature review. *J. Inflamm. Res.* 2021;14:2091–2110.
47. Jovic T.H, Ali S.R, Ibrahim N, et al. Could vitamins help in the fight against COVID-19? *Nutrients.* 2020;12:2550.
48. Al-Sumiadai M.M, Ghazzay H, Al-Dulaimy W.Z.S. Therapeutic effect of Vitamin A on severe COVID-19 patients. *EurAsia J. BioSci.* 2020;14: 7347-7350.
49. Higashi-Okai K, Nagino H, Yamada K., Okai Y. Antioxidant and prooxidant activities of B group vitamins in lipid peroxidation. *J. UOEH.* 2006; 28:359–368.
50. Spinas E., Saggini A., Kritas S.K., Cerulli G., Carafa A., Antinolf P., Pantalone A., Frydas A., Tei M., Speziali A., Saggini R., Pandolfi P., Conti P. Crosstalk between vitamin B and immunity. *J. Biol. Regul. Homeost. Agents.* 2015;29:283–288. [PubMed] [Google Scholar]
51. Yadav U.C., Kalariya N.M., Srivastava S.K., Ramana K.V. Protective role of benfotiamine, a fat-soluble vitamin B1 analogue, in lipopolysaccharide-induced cytotoxic signals in murine macrophage. *Free Radic. Biol. Med.* 2010;48:1423–1434.
52. Mikkelsen K, Apostolopoulos V. In: *Nutrition and Immunity.* Mahmoudi M, Rezaei N, editors. Springer; Cham: 2019. Vitamin B1, B2, B3, B5, and B6 and the immune system; pp. 115–125.
53. Hashida S, Yuzawa S., Suzuki N.N., et al. Binding of FAD to cytochrome b558 is facilitated during activation of the phagocyte NADPH oxidase, leading to superoxide production. *J. Biol. Chem.* 2004;279:26378–26386.
54. Pfeiffer C.M., Schleicher R.L., Caldwell K.L. In: *Encyclopedia of Human Nutrition.* third ed. Caballero B., editor. Elsevier, Academic Press; 2013. Biochemical indices; pp. 156–174.
55. Kumar P, Kumar M., Bedi O., et al. Role of vitamins and minerals as immunity boosters in COVID-19. *Infammopharmacology.* 2021;29:100110
56. Mikkelsen K., Apostolopoulos V. In: *Biochemistry and Cell Biology of Ageing: Part I Biomedical Science.* Harris J.R., Korolchuk V.I., editors. Springer Singapore; 2018. B vitamins and ageing, biochemistry and cell biology of ageing: part I biomedical science; pp. 451–470.
57. Ueland P.M., McCann A., Midttun Ø., Ulvik A. Inflammation, vitamin B6 and related pathways. *Mol. Aspect. Med.* 2017;53:10–27.
58. Kuroishi T. Regulation of immunological and inflammatory functions by biotin. *Can. J. Physiol. Pharmacol.* 2015;93:1091–1096.
59. Froese D.S., Fowler B., Baumgartner M.R. Vitamin B folate, and the methionine remethylation cycle-biochemistry, pathways, and regulation. *J. Inherit. Metab. Dis.* 2019;42:673–685.
60. Courtemanche C., Huang A.C., Elson-Schwab I., Kerry N., Ng B.Y., Ames B.N. Folate deficiency and ionizing radiation cause DNA breaks in primary human lymphocytes: a comparison. *Faseb. J.* 2004;18:209–211
61. Mikkelsen K., Stojanovska L., Prakash M., Apostolopoulos V. The effects of vitamin B on the immune/cytokine network and their involvement in depression. *Maturitas.* 2017;96:58–71.
62. Wolffenbuttel B.H.R., Wouters H.J.C.M., Heiner-Fokkema M.R., Van der Klauw M.M. The many faces of cobalamin (vitamin B12) deficiency. *Mayo Clin. Proc. Innov. Quality Outcomes.* 2019;3:200–214.
63. Manzanares W, Hardy G. Vitamin B12 pharmacotherapy for COVID-19. *Rev. Nutr. Clin. Metab.* 2021;4:65–69.
64. Vissers M.C.M., Wilkie R.P. Ascorbate deficiency results in impaired neutrophil apoptosis and clearance and is associated with up-regulation of hypoxia-inducible factor 1 α . *J. Leukoc. Biol.* 2007;81:1236–1244
65. Carr A.C, Maggini S. Vitamin C and immune function. *Nutrients.* 2017;9: 211.55
66. Tanaka M., Muto N., Gohda E., Yamamoto I. Enhancement by ascorbic acid 2-glucoside or repeated additions of ascorbate of mitogen-induced IgM and IgG productions by human peripheral blood lymphocytes. *Jpn. J. Pharmacol.* 1994;66:451–456.
67. Yaqinuddin A., Ambia A.R., Alaujan R.A. Immunomodulatory effects of Vitamin D and Vitamin C to improve immunity in COVID-19 patients. *J. Health Allied Sci. J. Health Allied Sci.* 2022;12:1–6.
68. Hoang B.X, Shaw G, Fang W, Han B. Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection. *J. Glob. Antimicrob. Resist.* 2020;23:256–262.
69. Shiozawa K, Shiozawa S, Shimizu S, et al. 1 α , 25-dihydroxyvitamin D3 inhibits pokeweed mitogen-stimulated human B-cell activation: an analysis using serum-free culture conditions. *Immunology.* 1985;56:161

70. Bruce D, Ooi J.H, Yu S, et al. Vitamin D and host resistance to infection? Putting the cart in front of the horse. *Exp. Biol. Med.* 2010;235:921–927.
71. Ntyonga P.M.P. COVID-19 infection and oxidative stress: an underexplored approach for prevention and treatment? *Pan Afr. Med. J.* 2020;35:12. doi: 10.11604/pamj.2020.35.2.2287.
72. Xu Y, Baylink D.J, Chen C.S, et al. The importance of vitamin D metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19. *J. Transl. Med.* 2020;18:322.
73. Xiao D, Li X, Su X, et al. Could SARS-CoV-2-induced lung injury be attenuated by vitamin D? *Int. J. Infect. Dis.* 2021;102:196–202.
74. Chen Y, Zhang J, Ge X, et al. Vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein. *J. Biol. Chem.* 2013;288:19450–19458.
75. Ulivieri F.M, Banfi G, Camozzi V, et al. Vitamin D in the Covid-19 era: a review with recommendations from a G.I.O.S.E.G. expert panel. *Endocrine.* 2021;72:597–603
76. Verdecchia P, Cavallini C, Spanevello A, et al. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur. J. Intern. Med.* 2020;76:14–20.
77. Smith L.L. Another cholesterol hypothesis: cholesterol as antioxidant. *Free Radic. Biol. Med.* 1991;11:47–61.
78. Sardar S, Chakraborty A, Chatterjee M. Comparative effectiveness of vitamin D3 and dietary vitamin E on peroxidation of lipids and enzymes of the hepatic antioxidant system in Sprague-Dawley rats. *Int. J. Vitam. Nutr. Res.* 1996;66:39–45.
79. Tagliaferri S, Porri D, De Giuseppe R. et al. The controversial role of vitamin D as an antioxidant: results from randomised controlled trials. *Nutr. Res. Rev.* 2019;32:99–105.
80. Mutlu M, Sariaydin M., Aslan Y. et al. Status of vitamin D, antioxidant enzymes, and antioxidant substances in neonates with neonatal hypoxic-ischemic encephalopathy. *J. Matern. Fetal Neonatal Med.* 2016;29:2259–2263.
81. Jeremy M., Gurusubramanian G., Roy V.K. Vitamin D3 regulates apoptosis and proliferation in the testis of D-galactose-induced aged rat model. *Sci. Rep.* 2019;9:14103.
82. Hekmatdoost Z. Mokhtari A., Nourian M. Antioxidant efficacy of vitamin D. *J. Parathy. Dis.* 2017;5:11–16.
83. Lee W.C., Mokhtar S.S., Munisamy S., Yahaya S., Rasool A. Vitamin D status and oxidative stress in diabetes mellitus. *Cell. Mol. Biol.* 2018;64:60–69.
84. Bruce D., Ooi J.H., Yu S., Cantorna M.T. Vitamin D and host resistance to infection? Putting the cart in front of the horse. *Exp. Biol. Med.* 2010;235:921–927.
85. Shiozawa K., Shiozawa S., Shimizu S., Fujita T. 1 alpha, 25-dihydroxyvitamin D3 inhibits pokeweed mitogen-stimulated human B-cell activation: an analysis using serum-free culture conditions. *Immunology.* 1985;56:161–167.
86. Bikle D.D. Extraskeletal actions of vitamin D. *Ann. N. Y. Acad. Sci.* 2016;1376:29–52.
87. Cantorna M.T., Snyder L., Lin Y.D., Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients.* 2015;7:3011–3021.
88. Sloka S., Silva C., Wang J., Yong V.W. Predominance of Th2 polarization by vitamin D through a STAT6-dependent mechanism. *J. Neuroinflammation.* 2011;8:56.
89. Jovic T.H, Stephen R.A, Nader I, et al. Could Vitamins Help in the Fight Against COVID-19? *Nutrients.* 2020 Sep; 12(9): 2550. Published online 2020 Aug 23. doi:10.3390/nu12092550
90. Meydani S.N, Leka L.S, Fine B.C, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: A randomized controlled trial. *J. Am. Med. Assoc.* 2004;292:828–836. doi:10.1001/jama.292.7.828
91. Tian S, Hu W, Niu L, et al. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J. Thorac. Oncol.* 2020;15:700–704. doi:10.1016/j.jtho.2020.02.0
92. Beck M.A, Handy J, Levander O.A. Host nutritional status: The neglected virulence factor. *Trends Microbiol.* 2004;12:417–423. doi: 10.1016/j.tim. 2004.07.007.
93. Richard C., Lemonnier F., Thibault M., Couturier M., Auzepy P. Vitamin E deficiency and lipoperoxidation during adult respiratory distress syndrome. *Crit. Care Med.* 1990;18:4–9. doi: 10.1097/000032 46-199001000-00002.
94. Lee G.Y., Han S.N. The role of vitamin E in immunity. *Nutrients.* 2018;10:1614. doi: 10.3390/nu10111614.
95. Traber M.G., Atkinson J. Vitamin E, antioxidant and nothing more. *Free Radic. Biol. Med.* 2007;43:4–15. doi: 10.1016/j.freeradbiomed.2007.
96. Lobo V., Patil A., Phatak A., Chandra N. Free radicals, antioxidants, and functional foods: impact on human health. *Phcog. Rev.* 2010;4:118.
97. Ramanathan N., Tan E., Loh L.J., Soh B.S., Yap W.N. Tocotrienol is a cardioprotective agent against ageing-associated cardiovascular disease and its associated morbidities. *Nutr. Metab.* 2018;15:6.
98. Miyazawa T., Burdeos G.C., Itaya M., Nakagawa K., Miyazawa T. Vitamin E: regulatory redox interactions. *IUBMB Life.* 2019;71:430–441.
99. Hinman A., Holst C.R., Latham L.C., Bruegger J.J., Ulas G., McCusker K.P., Amagata A., Davis D., Hoff K.G., Kahn-Kirby A.H., Kim V., Kosaka Y., Lee E., Malone S.A., Mei J.J., Richards S.J., Rivera V., Miller G., Trimmer J.K., Shrader W.D. Vitamin E hydroquinone is an endogenous regulator of ferroptosis via redox control of 15-lipoxygenase. *PLoS One.* 2018;13
100. Maggini S., Maldonado P., Cardim P., Newball C.F., Sota Latino E.R. Vitamins C, D and zinc: synergistic roles in immune function and infections. *Vitam. Miner.* 2017;6:3.
101. Hubicka U, Padiasek A, Żuromska W.B, et al. Determination of Vitamins K1, K2 MK-4, MK-7, MK-9 and D3 in pharmaceutical products and dietary supplements by TLC-Densitometry. *Processes.* 2020;8(7): 870. doi: 10.1021/jf204194z.
102. Janssen R, Walk J. Vitamin K epoxide reductase complex subunit 1 (VKORC1) gene polymorphism as determinant of differences in Covid-19-related disease severity. *Med Hypotheses.* 2020;144:110218. doi:10. 1016/j.mehy. 2020. 110218.
103. Hodges S.J, Pitsillides A.A, Ytrebø L.M, et al. In: *Vitamin K2: Vital for Health and Wellbeing.* Gordeladze J, editor. IntechOpen; 2017. Anti-inflammatory actions of vitamin K. Chap. 8.
104. Janssen R, Visser M.P.J, Dofferhoff A.S.M, et al. Vitamin K metabolism as the potential missing link between lung damage and thromboembolism in Coronavirus disease 2019. *Br. J. Nutr.* 2021;126:191–198