BÖLÜM 17

İSKEMİ-REPERFÜZYON HASARINDA VİTAMİNLERİN KORUYUCU ROLÜ

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GİRİŞ

İskemi, trombolitik ve tromboembolik arter tıkanıklığı sonucu organlara giden kan akımında geçici veya kalıcı azalma sonucu oluşur. Organlara giden kan akımını tekrar sağlamak için trombolitik tedavi uygulanmaktadır. İskemik organlara tekrar kan akımını sağlayan reperfüzyon, doku ölümünü önlemek için hayati öneme sahiptir. Ancak reperfüzyonun kendisi, nötrofillerin ve trombositlerin aktivasyonu dahil olmak üzere, doku hasarı ile sonuçlanan bir dizi inflamatuar yanıta sebep olur (1). Özellikle nötrofil kaynaklı reaktif oksijen türlerinin oluşumu iskemi-reperfüzyon hasarını tetikler (2-3).

Hem hücresel hem de moleküler düzeyde gerçekleşen iskemi-reperfüzyon hasarının patogenezine katkıda bulunan çoklu ve etkileşimli mekanizmalar sonucunda, hücre ve dokudaki proteinler, lipidler, karbonhidratlar ve DNA zarar görür. Bu hasar yeterince şiddetliyse nekroz yolu ile hücre ölümü veya apoptoz gerçekleşir (4) (Şekil 1).

İSKEMİ-REPERFÜZYON HASARININ MEKANİZMALARI

Enerji Tükenmesi

Doku iskemisi sırasında ilk metabolik değişiklik ATP'nin (adenozin trifosfat), oksijen yokluğu nedeniyle sentezlenememesi sonucu enerjinin tükenmesidir. ATP, ADP (adenozin difosfat) ve AMP (adenozin monofosfat) yoluyla adenosine ve son olarak da hipoksantine parçalanır. Fizyolojik koşullar altında hipoksantin, NAD (nikotinamid adenin dinükleotit) tüketimi ile ksantin dehidrogenaz enzimi tarafından ksantine dönüştürülür. Fakat iskemik koşullar altında ksantin dehidrojenaz, reaktif oksijen türleri üretebilen ksantin oksidaza konformasyonel bir değişime uğrar (5). Ksantin oksidaz ksantini parçalar ve birçok reaktif oksijen türü üretilir. Bu konformasyonel değişiklik hücre içi Ca^{+2} artışı ile de desteklenir. Kalsiyum artışına bağlı olarak proteaz aktivitesi artar. Bu da ksantin dehidrogenazın ksantin oksidaza ve reaktif oksijen türlerine dönüşümünü teşvik eder (6).

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ğü tespit edilmiştir (87-89). MDA, lipid peroksidasyonunun en hassas göstergelerinden biridir. Yağ asitleri, O_2 ve metalkatalizörler (Fe^{+2}, Cu^{+}) var olduğu sürece lipid peroksidasyonu yeni serbest radikallerin oluşumuna yol açar. Bu nedenle reperfüzyon periyodu lipid peroksidasyonu için oldukça uygundur (90). lipid peroksidasyonu nedeniyle membran geçirgenliğinde bozulma, membrana bağlı Na^{+}-K^{+}-ATPaz enzim aktivitelerinde azalmaya neden olur. Sonuçta protein sentezi için hayati öneme sahip K^{+} ve Mg^{+} konsantrasyonları değişir ve protein sentezi engellenir. Artmış lipid peroksidasyonu ayrıca proteolitik lizozomal enzimlerin ve mitokondriyal matriks enzimlerinin sitoplazmaya salınmasıyla da sonuçlanabilir. Bu da hücre içi proteoliz ve hücresel yıkıma yol açar. Bu koşullar altında SOD gibi antioksidan enzimleri içeren antioksidan savunma sistemi, nöronal hücrelerin reaktif oksijen türleri kaynaklı ölümüne karşı direncinde çok önemli bir role sahiptir. E vitamini, lipid peroksidasyon zincir reaksiyonuna müdahale ederek reaktif oksijen türlerini süpürücü olarak iş görür (91).

Kan beyin bariyerinin yıkılmasının iskemik inmede hasara katkıda bulunan önemli bir faktör olduğu bilinmektedir. İskemik inme koşulları altında bu bariyerin bozulması, serebral damarlar arasında artan paraselüler geçirgenliğe ve beyin ödemine yol açar (92). Ayrıca iskemi-reperfüzyondaki lökosit infiltrasyonu daha sonra inflamatuar faktörlerin üretimine sebep olur, kan-beyin bariyerinin geçirgenliğini arttırır ve daha yoğun hasara neden olur (93). E vitamini ön tedavisi ile beyin dokusunda lökosit infiltrasyonu azalır, lokomotif ve bilişsel kabiliyet korunur ve uzamsal bellek gelişir (88). Buna bağlı olarak E vitamininin iskemik dokuda nötrofil infiltrasyonunu engelleyerek kan-beyin bariyerini serebral iskemi-reperfüzyonun neden olduğu aşırı geçirgenlikten koruduğu, beyin antioksidan kapasitesini güçlendirerek iskemik ödem oluşumunu azalttığı söylenebilir.

E vitamininin reaktif oksijen türelerinin ve ardından gelen inflamatuar kaskadın ve zararlı inflamatuar gen ürünlerinin ekspresyonunu inaktive etme yeteneği ile iskemi-reperfüzyon hasarının önlenmesinde potansiyel bir ajan olduğu söylenebilir.

SONUÇ

Dokuda meydana gelen iskemi-reperfüzyon sonucu oluşan reaktif oksijen türlerinin verdiği hasara karşı genel olarak 3 kademeli bir antioksidan savunma sistemi vardır;

1. Albumin, heptaglobulin, ferritin ve seruloplazmin gibi antioksidan proteinlerin plazma miktarları artar (94).
2. Hücre içinde bulunan antioksidan enzim (SOD, GPx, katalax) aktiviteleri artar (94).
3. Suda çözünen askorbik asit, ürik asit, bilirubin, glutatyon, ç,nko, selenyum gibi küçük moleküllü antioksidanlar ile yağda çözünen β-karoten, ubiquinol-10 (koenzinQ10), likopen, E vitamini gibi küçük moleküllü antioksidanlar bulunur.

Genel olarak baktığımızda vitaminler, antioksidan kapasiteleri sayesinde iskemi-reperfüzyon hasarına karşı önemli bir endojen mekanizma olarak görünmektedir.

KAYNAKLAR

1. Lefer AM, Lefer DJ. The role of nitric oxide and cell adhesion molecules on the microcirculation in ischaemia-reperfusion. *Cardiovascular Research*. 1996;32(4):743–751. doi:10.1016/S0008-6363(96)00073-9
2. Droge W. Free radicals in the physiological control of cell function. *Physiological Reviews*. 2002;82:47–95. doi: 10.1152/physrev.00018.2001
3. Kadambi A, Skalak TC. Role of leukocytes and tissue-derived oxidants in short-term skeletal muscle ischemia-reperfusion injury. *American Journal of Physiology Heart Circulation Physiology*. 2000;278(2):H435–H43. doi: 10.1152/ajpheart.2000.278.2.H435
4. Kalogeris T, Baines CP, Krenz M, et al. Ischemia/Reperfusion. *Comprehensive Physiology*. 2017;7(1):113–170. doi:10.1002/cphy.c160006.
5. Chambers DE, Parks DA, Petterson G, et al. Xantine oxidase as a source of free radical damage in myocardial ischemia. Journal of Molecular and Cellular Cardiology. 1985;17(2):145-152. Doi: 10.1016/S0022-2828(85)80017-1
6. Vanden Hoek TL, Becker LB. Shao Z, et al. *Journal of Biological Chemistry. 1998;*273(29):18092–18098. doi:10.1074/ibc.273.29.18092
7. McCully JD, Wakiyama H, Hsieh YJ, et al. Differential contribution of necrosis and apoptosis in myocardial ischemia-reperfusion injury. *Heart and Circulatory Physiology*. 2004;286(5):1923-1935. doi:10.1152/ajpheart.00935.2003

8. Szabo G, Liaudet L, Hagl S, et al. Poly(ADP-ribose) polymerase activation in the reperfused myocardium. *Cardiovascular research*. 2004;61(3):471-480. doi:10.1016/j.cardiores.2003.09.029
9. Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. *Cardiovascular Research*. 2004;61(3):461-470. doi:10.1016/j.cardiores.2003.10.025
10. Granger DN. The role of xantine oxidase and granulocytes in ischemia-reperfusion injury. *American Journal of Physiology Heart and Circulatory Physiology*. 1988;255(6):1269-1275. doi:10.1152/ajpheart.1988.255.6.H1269
11. **Hensley K, Robinson KA, Gabbita SP, et al. Reactive oxygen species, cellsignaling and cell injury.** *Free Radical Biology and Medicine*. **2000;28:1456-1462.** doi:10.1016/S0891-5849(00)00252-5
12. He Q, Zhou W, Xiong C, et al. Lycopene attenuates inflammation and apoptosis in post.myocardial infarction remodeling by inhibiting the nuclear factor-κB signaling pathway. *Molecular Medicine Reports*. 2015;11(1):374–378. doi:10.3892/mmr.2014.2676.
13. Rex J, Lutz A, Faletti LE, et al. IL-1β and TNFα differentially influence NF-κB activity and FasL-induced apoptosis in primary murine hepatocytes during LPS-induced inflammation. *Frontiers in Physiology*. 2019;10:1–15. doi:10.3389/ fphys.2019.00117
14. Mentzer RM, Lasley RD, Jessel A, et al. Intracellular sodium hydrogen exchange inhibition and clinical myocardial protection, *The Annals of Thoracic Surgery*. 2003;75(2):700-708. doi:10.1016/S0003-4975(02)04700-8
15. Seal JB, Gewetz BL. Vascular disfunction in ischemia-reperfusion injury. *Annals of Vascular Surgery*. 2005;19(4):572-584. doi:10.1007/s10016-005-4616-7
16. Ferran C, Millan MT, Csizmadia V, et al. Inhibition of NF-kappa B by pyrrolidine dithiocarbamate blocks endothelial cell activation. *Biochemical and Biophysical Research Communication*. 1995;214(1):212–223. doi:10.1006/bbrc.1995.2277
17. De Caterina R, Libby P, Peng HB, et al. Nitric oxide decreases cytokineinduced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. *The Journal of Clinical Investigation*. 1995;96(1):60–88. doi:10.1172/JCI118074
18. Menger MD, Rucker M, Vollmar B. Capillary dysfunction in striated muscle ischemia/reperfusion: on the mechanisms of capillary "no-reflow". *Shock*.1997;8(1):2-7.
19. Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modülatör of leukocyte adhesion. *Proceedings of The National Academy of Sciences of The United States of America*. 1991;88(11):4651–4655. doi:10.1073/pnas.88.11.46
20. Vinten-Johansen J, Zhao ZQ, Nakamura M, et al. Nitric oxide and the vascular endothelium in myocardial ischemia-reperfusion injury. *Annals of New York Academy of Sciences*. 1999;874(1):354–370. doi:10.1111/j.1749-6632.1999.tb09251.x
21. Roumen RMH, Hendriks T, Ven-Jongekrijg J, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Annals of Surgery*. 1993;218(6):769-776. doi:10.1097/00000658-199312000-00011
22. Matsumoto T, Ikeda K, Mukaida N, et al. Prevention of cerebral edema and infarct in cerebral reperfusion injury by an antibody to interleukin-8. *Laboratory Investigation*. 1997;77(2):119-125.
23. Arumugam TV, Shiels IA, Woodruff TM, et al. The role of the complement system in ischemia-reperfusion injury. *Shock*. 2004;21(5):401-409. doi:10.1097/01.shk.0000121227.73012.86
24. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology*. 2001;94:1133-1138. doi:10.1097/00000542-200106000-00030
25. Cuzzocrea S, Riley DP, Caputi AP, et al. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. *Pharmacological Reviews*. 2001;53(1):135–159.
26. Ikeda K, Negishi H, Yamori Y. Antioxidant nutrients and hypoxia/ischemia brain injury in rodents. *Toxicology*. 2003;189(1-2):55–61. doi:10.1016/S0300-483X(03)00152-5
27. Maulik N, Engelman RM, Rousou JA, et al. Ischemic preconditioning reduces apoptosis by upregulating anti-death gene Bcl-2. *Circulation* 1999;100:369-375. doi:10.1161/circ.100.suppl_2.Ii-369
28. Bailey DM, Raman S, McEneny J, et al. Lewis Vitamin C prophylaxis promotes oxidative lipid damage during surgical ischemia–reperfusion. *Free Radical Biology and Medicine*. 2006;40(4):591-600. doi:10.1016/j.freeradbiomed.2005.09.024
29. Lassnigg A, Punz A, Barker R, et al. Influence of intravenous vitamin E supplementation in cardiac surgery on oxidative stress: a double-blinded, randomized, controlled study. *British Journal of Anaesthesia*. 2003;90(2):148–154. doi:10.1093/bja/aeg042
30. Hao j, Li WW, Du H, et al. Role of vitamin C in cardioprotection of ischemia/reperfusion injury by activation of mitochondrial KATP channel. *Chemical and Pharmaceutical Bulletin*. 2006;64:548–557. doi:10.1248/cpb.c15-00693
31. De Sales KPF, Pinto BAS, Ribeiro NLX, et al. Effects of vitamin C on the prevention of ischemia-reperfusion brain injury: Experimental study in rats. *International Journal of Vascular Medicine*. 2019;article ID 4090549,7 pages. doi:10.1155/2019/4090549
32. Baltalarli A, Ozcan V, Ferda B, et al. Ascorbic acid (vitamin C) and iloprost attenuate the lung injury caused by ischemia/reperfusion of the lower extremities of rats. *Annals of Vascular Surgery*. 2006;20(1):49-55. doi:10.1007/s10016-005-9284-0
33. Pleiner J, Schaller G, Mittermayer F, et al. Intra-arterial vitamin C prevents endothelial dysfunction caused by ischemia-reperfusion. *Atherosclerosis*. 2008;197(12):383–391. doi:10.1016/j.atherosclerosis.2007.06.011
34. Lehr HA, Frei B, Olofsson M. Protection from oxidised LDL induced leukocyte adhesion to microvascular

and macrovascular endothelium in vivo by vitamin C but not by vitamin E. *Circulation*. 1995;91:1525-1532. doi:10.1161/01.CIR.91.5.1525
35. Song J, Park J, Kim JH, et al. Dehydroascorbic acid attenuates ischemic brain edema and neurotoxicity in cerebral ischemia: an in vivo study. *Experimental Neurobiology*, 2015;24(1):41–54. doi:10.5607/en.2015.24.1.41
36. Chen X, Touyz RM, Park JB, et al. Antioxidant effects of vitamins C and E are associated with altered activation of vascular NADPH oxidase and superoxide dismutase in stroke-prone SHR. *Hypertension*, 2001;38(3):606–611. doi:10.1161/hy09t1.094005
37. Zamani M, Soleimani M, Golab F, et al. NeuroProtective effects of adenosine receptor agonist coadministration with ascorbic acid on CA1 hippocampus in a mouse model of ischemia reperfusion injury. *Metabolic Brain Disease*, 2013;28(3):367–374. doi:10.1007/s11011-013-9408-0
38. Iwata N, Okazaki M, Xuan M, et al. Orally administrated ascorbic acid suppresses neuronal damage and modifies expression of SVCT2 and GLUT1 in the brain of diabetic rats with cerebral ischemiareperfusion. *Nutrients*. 2014;6(4):1554–1577. doi:10.3390/nu6041554
39. Miura S, Ishida-Nakajima W, Ishida A, et al. Ascorbic acid protects the newborn rat brain from hypoxic-ischemia. *Brain and Development*. 2009;31(4):307–317. doi:10.1016/j.braindev.2008.06.010
40. Huang A, Vita JA, Venema RC, et al. Ascorbic acid enhances endothelial nitric-oxide synthase activity by increasing intracellular tetrahydrobiopterin. *Journal of Biological Chemistry*. 2000;275(23):17399–17406. doi:10.1074/jbc.M002248200
41. Choi BK, Kim JH, Jung JS, et al. Reduction of ischemia-induced cerebral injury by all-trans-retinoic acid. *Experimental Brain Research*. 2009;193:581-589. doi:10.1007/s00221-008-1660-x
42. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *The New England Journal of Medicine*. 2007;357:1121-1135.
43. Tao L, Huang K, Wang J, et al. Retinol palmitate protects against myocardial ischemia/reperfusion injury via reducing oxidative stress and inhibiting apoptosis. *American Journal of Translational Research*. 2019;11(3):1510-1520.
44. Jiang W, Guo M, Gong M, et al. Vitamin A bio-modulates apoptosis via the mitochondrial pathway after hypoxic-ischemic brain damage. *Molecular Brain*. 2018;11:14. doi:10.1186/s13041-018-0360-0
45. Palgi A. Association between dietary changes and mortality rates: Israel 1949 to 1977; a trend-free regression model. *The American Journal of Clinical Nutrition*. 1981;34(8):1569-1583. doi:10.1093/ajcn/34.8.1569
46. Jiang W, Yu Q, Gong M, et al. Vitamin A deficiency impairs postnatal cognitive function via inhibition of neuronal calcium excitability in hippocampus. *Journal of Neurochemistry*. 2012;121(6):932–943. doi:10.1111/j.1471-4159.2012.07697.x
47. Kaplan S, Türk A. Effects of vitamin B12 on rat ovary with ischemia- reperfusion injury. *Biotechnic and Histochemistry*. doi:10.1080/10520295.2021.1961863
48. Deniz E, Topcu A, Ozturk A, et al. The effects of vitamin B12 on the TLR-4/NF-κB signaling pathway in ovarian ischemia-reperfusion injury-related inflammation. *International Immunopharmacology*. 2022;107:108676. doi:10.1016/j.intimp.2022.108676
49. Lia F, Bahnsonb EM, Wildera J, et al. Oral high dose vitamin B12 decreases renal superoxide and post-ischemia/reperfusion injury in mice. *Redox Biology*. 2020;32:101504, https://doi.org/10.1016/j.redox.2020.101504
50. Moreira ES, Brasch NE, Yun J. Vitamin B12 protects against superoxide-induced cell injury in human aortic endothelial cells, *Free Radical Biology and Medicine*. 2011;51(4):876–883. doi:10.1016/j.freeradbiomed.2011.05.034
51. Caylak E, Aytekin M, Halifeoglu I. Antioxidant effects of methionine, a-lipoic acid, N-acetylcysteine and homocysteine on lead-induced oxidative stress to erythrocytes in rats. Experimental and *Toxicologic Pathology*. 2008;60(4-5):289–294. doi:10.1016/j.etp.2007.11.004.
52. Green R, Allen LH, Bjørke-Monsen AL, et al. Vitamin B12 deficiency. *Nature Reviews Disease Primers*. 2017;3:17040. doi:10.1038/nrdp.2017.40.
53. Rzepka Z, Respondek M, Rok J, et al. Vitamin B12 deficiency ınduces ımbalance in melanocytes homeostasis-a cellular basis of hypocobalaminemia pigmentary manifestations. *International Journal of Molecular Sciences*. 2018;19(9):1-13. doi:10.3390/ijms19092845.
54. Abdulkhaleq FM, Alhussainy TM, Badr MM, et al. Antioxidative stress effects of vitamins C, E, and B12, and their combination can protect the liver against acetaminophen-induced hepatotoxicity in rats. *Drug Design, Development and Therapy*. 2018;12:3525–3533. doi:10.2147/DDDT.S172487.
55. Veber D, Mutti E, Tacchini L, et al. Indirect down-regulation of nuclear NF-kappa B levels by cobalamin in the spinal cord and liver of the rat. *Journal of Neuroscience Research*. 2008;86(6):1380-1387. doi:10.1002/jnr.21599.
56. Ichimura T, Bonventre JV, Bailly V, et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *Journal of Biological Chemistry*. 1998;273:4135–4142. doi:10.1074/jbc.273.7.4135
57. Oh E, Humphreys BD. Fibrotic changes mediating acute kidney injury to chronic kidney disease transition. *Nephron*. 2017;137:264–267. doi:10.1159/000474960
58. Assalin HB, Rafacho BP, Dos Santos PP, et al. Impact of the length of vitamin D deficiency on cardiac remodeling. *Circulation Heart Failure*. 2013;6(4):809-816. doi:10.1161/CIRCHEARTFAILURE.112.000298
59. Bae S, Singh SS, Yu H, et al. Vitamin D signaling pathway plays an important role in the development of heart failure after myocardial infarction. *Journal of Applied Physiology*. 2013;114(8):979-987. doi:10.1152/japplphysiol.01506.2012
60. Azak A, Huddam B, Haberal N, et al. Effect of novel vitamin D receptor activator paricalcitol on renal ischaemia/reperfusion injury in rats. *Annals of The Royal Collage of Surgeon of England*. 2013;95(7):489-494. doi:10.1308/003588413X13629960049117

61. Shih PK, Chen YC, Huang YC, et al. Pretreatment of vitamin D3 ameliorates lung and muscle injury induced by reperfusion of bilateral femoral vessels in a rat model. Journal of Surgical Research. 2011;171(1):323–328. doi:10.1016/j.jss.2010.03.008
62. Wang Y, Chiang YH, Su TP, et al. Vitamin D(3) attenuates cortical infarction induced by middle cerebral arterial ligation in rats. *Neuropharmacology*. 2000; 39(5):873–880. doi:10.1016/S0028-3908(99)00255-5
63. Tokgoz VY, Sipahi M, Keskin O, et al. Protective effects of vitamin D on ischemia-reperfusion injury of the ovary in a rat model. *Iranian Journal of Basic Medical Sciences*. 2018;21(6):593-599. doi:10.22038/IJBMS.2018.26914.6581
64. Seif AA, Abdelwahed DM. Vitamin D ameliorates hepatic ischemic/reperfusion injury in rats. *Journal of Physiology and Biochemistry*. 2014;70:659–666. doi:10.1007/s13105-014-0335-2
65. Qian X, Zhu M, Qian W, et al. Vitamin D attenuates myocardial ischemia–reperfusion injury by inhibiting inflammation via suppressing the RhoA/ROCK/NF-κB pathway. *Biotechnology and Applied Biochemistry*. 2019;66(5):850-857. doi:10.1002/bab.1797
66. Lee TI, Lee MH, Chen YC, et al. Vitamin D attenuates ischemia/reperfusion-induced cardiac injury by reducing mitochondrial fission and mitophagy. *Frontiers in Pharmacology*. 2020;11:604700. doi:10.3389/fphar.2020.604700
67. Nunes KP, Rigsby CS, Webb RC. RhoA/Rho-kinase and vascular diseases: what is the link? *Cellular and Molecular Life Sciences*. 2010;67,3823–3836. doi:10.1007/s00018-010-0460-1
68. Chen W, Chen S, Chen W, et al. Screening RhoA/ROCK inhibitors for the ability to prevent chronic rejection of mouse cardiac allografts. *Transplant Immunology*. 2018;50,15–25. doi:10.1016/j.trim.2018.06.002
69. Zeitelhofer M, Adzemovic MZ, Gomez-Cabrero D, et al. Functional genomics analysis of vitamin D effects on CD4+ T cells in vivo in experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;14(9):1678-1687. doi:10.1073/pnas.16157 83114
70. Hart PH, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? *Nature Reviews Immunology*. 2011;11(9):584–596. doi:10.1038/nri30 45.
71. Gu L, Xiong X, Zhang H, et al. Distinctive effects of T cell subsets in neuronal injury induced by cocultured splenocytes in vitro and by in vivo stroke in mice. *Stroke*. 2012;43(7),1941-1946. doi:10.1161/STROKEAHA.112.656611
72. Jain SK, Micinski D. Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes. *Biochemical and Biophysical Research Communications*, 2013;437(1),7–11. Doi:10.1016/j.bbrc.2013.06.004.
73. Dong J, Wong SL, Lau CW, et al. Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. *European Heart Journal*, 2012;33(23),2980–2990. doi:10.1093/eurhe artj/ehr45 9.
74. Bulger EM, Helton S, Clinton CM, et al. Enteral vitamin E supplementation inhibits the cytokine response to endotoxin. Archives of Surgery 1997;132(12):1337–1341. doi:10.1001/archsurg.1997.01430360083015
75. Nakamura YK, Omaye ST. Alpha-tocopherol modulates human umbilical vein endothelial cell expression of Cu/Zn superoxide dismutase and catalase and lipid peroxidation. *Nutrition Research*. 2008;28(10):671–680. doi:10.1016/j. nutres.2008.07.002.
76. Uemura M, Manabe H, Yoshida N, et al. Alpha-tocopherol prevents apoptosis of vascular endothelial cells via a mechanism exceeding that of mere antioxidation. *European Journal of Pharmacology*. 2002;456(1-3):29–37. doi:10.1016/S0014-2999(02)02639-0
77. Khastar H. Protective effects of vitamin E against liver damage caused by renal ischemia reperfusion. *Renal Failure*. 2015;37(3):494–496. doi:10.3109/0886022X.2015.1006084
78. Aktoz T, Aydogdu N, Alagol B, et al. Protective Effects of melatonin and vitamin E against renal ischemia-reperfusion injury in rats. *Renal Failure*. 2007;29:535–542. doi:10.1080/08860220701391738
79. Medling BD, Bueno R, Chambers C, et al. The effect of vitamin E succinate on ischemia reperfusion injury. *HAND*. 2010;5:60-64. doi:10.1007/s11552-009-9196-5
80. Brennan P, O'Neill LA. Inhibition of nuclear factor kappaB by direct modification in whole cells–mechanism of action of nordihydroguaiaritic acid, curcumin and thiol modifiers. *Biochemical Pharmacology*. 1998;55(7):965–73. doi:10.1016/S0006-2952(97)00535-2.
81. Suzuki YJ, Packer L. Inhibition of NF-κB DNA binding activity by α-tocopheryl succinate. *Biochemistry and Molecular Biology International*. 1993;31(4):693-700.
82. Nakamura T, Goto M, Matsumoto A, et al. Inhibition of NF-κB transcriptional activity by α-tocopheryl succinate. *Biofactors*. 1998;7:21-30. doi:10.1002/biof.5520070104
83. Wallerta M, Zieglera M, Wanga X, et al. α-Tocopherol preserves cardiac function by reducing oxidative stress and inflammation in ischemia/reperfusion injury. *Redox Biology*. 2019;26:101292. doi:10.1016/j.redox.2019.101292
84. Dianat M, Esmaeilizadeh M, Badavi M, et al. Protective Effects of Crocin on Ischemia-reperfusion Induced Oxidative Stress in Comparison With Vitamin E in Isolated Rat Hearts. *Jundishapur Journal of Nature Pharmaceutical Products*. 2014;9(2):e17187. doi:10.17795/jjnpp-17187
85. Naegelen I, Beaume N, Plançon S, et al. Regulation of neutrophil degranulation and cytokine secretion: a novel model approach based on linear fitting. *Journal of Immunology Research*. 2015;817038. doi:10.1155/2015/817038
86. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease, *Arteriosclerosis, Thrombosis,and Vascular Biology*. 2005;25(6):1102–1111. doi:10.1161/01.ATV.0000163262.83456.6d.

87. Onem G, Aral E, Enli Y, et al. neuroprotective effects of L-carnitine and vitamin E alone or in combination against ischemia-reperfusion injury in rats. *Journal of Surgical Research*. 2006;131:124–130. doi:10.1016/j.jss.2005.12.017
88. Salehi C, Seiiedy M, Soraya H, et al. Pretreatment with bisoprolol and vitamin E alone or in combination provides neuroprotection against cerebral ischemia/reperfusion injury in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2021;394:685–695. doi:10.1007/s00210-020-02007-9
89. Owoeye O, Mpetcha A, Malomo AO. The protective effect of *Carica papaya* and vitamin E on ischaemic-reperfusion insult of rat brain following bilateral occlusion of common carotid artery. *African Journal of Medicine and Medical Sciences*. 2019;48(2):139-140.
90. White BC, Grossman LI, Krause GS. Brain injury by global ischemia and reperfusion: A theoretical perspective on membrane damage and repair. *Neurology*. 1993;43(9):1656. doi:10.1212/WNL.43.9.1656
91. Islekel H, Islekel S, Guner G, et al. Evaluation of lipid peroxidation, cathepsin L and acid phosphatase activities in experimental brain ischemia-reperfusion. *Brain Research*. 1999;843(1-2):18-24. doi:10.1016/S0006-8993(99)01845-4
92. Petty M, Wettstein J. Elements of cerebral microvascular ischaemia. *Brain Research Reviews*. 2001;36(1):23–34. doi:10.1016/S0165-0173(01)00062-5
93. Wang S, Guo H, Wang X, et al. Pretreatment with Danhong injection protects the brain against ischemia-reperfusion injury. *Neural Regeneration Research*. 2014;9(15):1453-1459. doi:10.4103/1673-5374.139462
94. Halliwell B. Antioxidant defence mechanisms: from the beginning to the end (of the beginning). *Free Radical Reserach*. 1999;31(4):261-272. doi:10.1080/10715769900300841