

Bölüm 1

ALZHEİMER HASTALIĞININ PATOFİZYOLOJİSİ VE TEDAVİ YAKLAŞIMLARI

Leyli Can AYNAL ÖLÇÜCÜOĞLU¹

GİRİŞ

Gelişmiş ülkelerde en sık görülen nörodejeneratif hastalık olan Alzheimer hastalığı (AH), aynı zamanda demansın en önde gelen nedenidir(1). Anatomik olarak hipokampus ve entorinal korteksin etkilenmesiyle birlikte ilerleyici hafıza kaybı ve günlük aktivitelerin bağımsız gerçekleştirilmesine engel olan serebral atrofi ile karakterize ilerleyici bir hastalıktır (2). Hastalığın evresine bağlı olarak, apati, depresyon, iletişim bozukluğu, oryantasyon bozukluğu, zayıf muhakeme, yutma ve yürüme güçlüğü ve davranış değişiklikleri gibi günlük yaşam aktivitelerini engelleyici özellikler ortaya çıkmaktadır (3). Semptomların ortaya çıkması ve sürekliliği için gereken süre yaş, genetik ve cinsiyet gibi faktörlerden etkilenir (4).

1901-1906 yılları arasında hafıza kaybı, düzgün konuşamama, oryantasyon bozukluğu ve halüsinasyonlar yaşayan Auguste Deter vakasını takip eden psikiyatrist ve nörolog Alois Alzheimer'ın yaptığı beyin otopsisinde ciddi beyin atrofisine eşlik eden ekstranöronal senil plakların (SP) ve intranöronal nörofibriller yumakların (NFT'ler) varlığını gözlemlediği ve hastalığı tanımladığı 1906 yılından sadece bir yüzyıl sonrasında AH demans vakalarının yaklaşık %75 'ini oluşturur hale gelmiştir (5, 6). Günümüzde dünya çapında AH demansından etkilenen 50 milyondan fazla insan vardır. Bu verilerin AH gelişimi için ana risk faktörünün yaş olmasından ve yaşam beklentisinin son yüzyılda büyük ölçüde artmasından kaynaklandığı düşünüldüğünde 2050 yılına kadar 106,8 milyondan fazla vaka artışı olması beklenmektedir (7-9).

¹ Uzm. Dr., Gazi Mustafa Kemal Mesleki ve Çevresel Hastalıklar Hastanesi, Nöroloji Kliniği, leylicanaynal@gmail.com

davranışsal egzersizler yoluyla günlük yaşam aktivitelerinin geliştirilmesine ve dolayısıyla bu hastaların otonomisine sağlamak için önemlidir (102). Psikolojik terapi, Alzheimer hastalarında hem bilişsel hem de işlevsel düzeylerde önemli yansımaları olan depresyon veya anksiyete gibi süreçlerle başa çıkmak için gereklidir (103). Bilişsel stimülasyon ve eğitim egzersizlerini içeren bilişsel terapi, en iyi sonuçları olan farmakolojik olmayan tedavi olarak da konumlandırılmıştır. En iyi tedavi hastalığın korunmaktır ilkesi göz önüne alındığında bilişsel gerileme ve AH geliştirme riskinde azalma ile ilişkilendirildiği belirlenen fiziksel egzersiz(102) , akdeniz diyeti ve iyi bir uyku alışkanlığını içeren sağlıklı bir yaşam tarzını benimsemenin AH' den korunmak için etkili stratejilerden biri olduğu söylenebilir (104).

AH'ye terapötik yaklaşım konusunda kaydedilen ilerlemelere rağmen hastalığın ilerlemesini durdurabilecek bir tedavi henüz bulunmamaktadır. Hem patofizyolojik düzeyde hem de teşhis ve tedavi ile ilgili olarak hala açığa çıkarılması gereken konular olduğu düşünüldüğünde özellikle başlangıç evrelerinde hastalığın tanınmasına katkıda bulunabilecek potansiyel biyo-belirteçler, farmakolojik ve non-farmakolojik tedavilerin araştırılmasına ihtiyaç vardır. AH' nin ilerlemesini kontrol edebilecek bir terapötik bir yaklaşım hastaların yaşam kalitesinde artış ve bakım veren yükünde azalma sağlayacaktır.

KAYNAKLAR

1. Lleó A. Alzheimer's disease: An ignored condition. *Medicina clinica*. 2018;150(11):432-433.
2. Wanleenuwat P, Iwanowski P, Kozubski W. Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. *Postgraduate Medicine*. 2019;131(7):415-422.
3. 2021 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2021;17(3):327-406.
4. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2019;15(7):888-898.
5. Tiwari S, Atluri V, Kaushik A, et al. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *International journal of nanomedicine*. 2019;14:5541-5554.
6. Takizawa C, Thompson PL, van Walssem A, et al. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. *Journal of Alzheimer's disease : JAD*. 2015;43(4):1271-1284.

7. Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2013;9(1):63-75.e62.
8. Niu H, Álvarez-Álvarez I, Guillén-Grima F, et al. Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurologia (Barcelona, Spain)*. 2017;32(8):523-532.
9. Jordan B. [Life expectancy curves reveal major demographic events]. *Medecine sciences : M/S*. 2017;33(3):355-362.
10. 2016 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2016;12(4):459-509.
11. Garre-Olmo J. [Epidemiology of Alzheimer's disease and other dementias]. *Revista de neurologia*. 2018;66(11):377-386.
12. García-Morales V, González-Acedo A, Melguizo-Rodríguez L, et al. Current Understanding of the Physiopathology, Diagnosis and Therapeutic Approach to Alzheimer's Disease. *Biomedicines*. 2021;9(12).
13. Shieh JC, Huang PT, Lin YF. Alzheimer's Disease and Diabetes: Insulin Signaling as the Bridge Linking Two Pathologies. *Molecular neurobiology*. 2020;57(4):1966-1977.
14. St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science (New York, NY)*. 1987;235(4791):885-890.
15. Ikeda T, Yamada M. [Risk factors for Alzheimer's disease]. *Brain and nerve = Shinkei kenkyu no shinpo*. 2010;62(7):679-690.
16. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002;125(4):765-772.
17. Reitz C, Tang M-X, Manly J, et al. Hypertension and the Risk of Mild Cognitive Impairment. *Archives of Neurology*. 2007;64(12):1734-1740.
18. Pappolla MA. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. *Neurology*. 2008;71(24):2020; author reply 2020-2021.
19. Pappolla MA, Bryant-Thomas TK, Herbert D, et al. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. 2003;61(2):199-205.
20. Sensi SLJA. Alzheimer's Disease, time to turn the tide. 2018;10(10):2537.
21. Infante-Garcia C, Ramos-Rodriguez JJ, Galindo-Gonzalez L, et al. Long-term central pathology and cognitive impairment are exacerbated in a mixed model of Alzheimer's disease and type 2 diabetes. *Psychoneuroendocrinology*. 2016;65:15-25.
22. Ramos-Rodriguez JJ, Infante-Garcia C, Galindo-Gonzalez L, et al. Increased Spontaneous Central Bleeding and Cognition Impairment in APP/PS1 Mice with Poorly Controlled Diabetes Mellitus. *Molecular neurobiology*. 2016;53(4):2685-2697.
23. Ramos-Rodriguez JJ, Jimenez-Palomares M, Murillo-Carretero MI, et al. Central vascular disease and exacerbated pathology in a mixed model of type 2 diabetes and Alzheimer's disease. *Psychoneuroendocrinology*. 2015;62:69-79.

24. Thakur AK, Kamboj P, Goswami K, et al., editors. Pathophysiology and management of alzheimer's disease: an overview 2018.
25. Abubakar MB, Sanusi KO, Uguşman A, et al. Alzheimer's Disease: An Update and Insights Into Pathophysiology. *Frontiers in aging neuroscience*. 2022;14:742408.
26. Adams JN, Maass A, Harrison TM, et al. Cortical tau deposition follows patterns of entorhinal functional connectivity in aging. *eLife*. 2019;8.
27. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. *Nature reviews Neuroscience*. 2018;19(11):687-700.
28. Chen XQ, Mobley WC. Alzheimer Disease Pathogenesis: Insights From Molecular and Cellular Biology Studies of Oligomeric A β and Tau Species. *Frontiers in neuroscience*. 2019;13:659.
29. Shah S, Lee SF, Tabuchi K, et al. Nicastrin functions as a gamma-secretase-substrate receptor. *Cell*. 2005;122(3):435-447.
30. De-Paula VJ, Radanovic M, Diniz BS, et al. Alzheimer's Disease. In: Harris JR, editor. Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease. Dordrecht: Springer Netherlands; 2012. p. 329-352.
31. Staderini M, Martín MA, Bolognesi ML, et al. Imaging of β -amyloid plaques by near infrared fluorescent tracers: a new frontier for chemical neuroscience. 2015;44(7):1807-1819.
32. Serrano-Pozo A, Frosch MP, Masliah E, et al. Neuropathological alterations in Alzheimer disease. 2011;1(1):a006189.
33. Takahashi RH, Nagao T, Gouras GK. Plaque formation and the intraneuronal accumulation of β -amyloid in Alzheimer's disease. *Pathology international*. 2017;67(4):185-193.
34. Ding Y, Zhao J, Zhang X, et al. Amyloid Beta Oligomers Target to Extracellular and Intracellular Neuronal Synaptic Proteins in Alzheimer's Disease. *Frontiers in neurology*. 2019;10:1140.
35. Cheng X, Wu J, Geng M, et al. Role of synaptic activity in the regulation of amyloid beta levels in Alzheimer's disease. *Neurobiology of aging*. 2014;35(6):1217-1232.
36. Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron*. 2014;82(4):756-771.
37. de Wilde MC, Overk CR, Sijben JW, et al. Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2016;12(6):633-644.
38. Urbanc B, Cruz L, Le R, et al. Neurotoxic effects of thioflavin S-positive amyloid deposits in transgenic mice and Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(22):13990-13995.
39. Iaccarino L, Tammewar G, Ayakta N, et al. Local and distant relationships between amyloid, tau and neurodegeneration in Alzheimer's Disease. *NeuroImage Clinical*. 2018;17:452-464.
40. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, et al. Cerebral amyloid angiop-

- athy and Alzheimer disease - one peptide, two pathways. *Nature reviews Neurology*. 2020;16(1):30-42.
41. Chantran Y, Capron J, Alamowitch S, et al. Anti-A β Antibodies and Cerebral Amyloid Angiopathy Complications. *Frontiers in immunology*. 2019;10:1534.
 42. Vázquez-Costa JF, Baquero-Toledo M, Sastre-Bataller I, et al. Angiopatia amiloide inflamatoria. *Neurologia (Barcelona, Spain)*. 2014;29(4):254-256.
 43. van Veluw SJ, Reijmer YD, van der Kouwe AJ, et al. Histopathology of diffusion imaging abnormalities in cerebral amyloid angiopathy. *Neurology*. 2019;92(9):e933-e943.
 44. Nalivaeva NN, Belyaev ND, Zhuravin IA, et al. The Alzheimer's amyloid-degrading peptidase, neprilysin: can we control it? *International journal of Alzheimer's disease*. 2012;2012:383796.
 45. Klein C, Patte-Mensah C, Taleb O, et al. The neuroprotector kynurenic acid increases neuronal cell survival through neprilysin induction. *Neuropharmacology*. 2013;70:254-260.
 46. Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: review and hypothesis. *Neurobiology of aging*. 2006;27(2):190-198.
 47. Pivovarova O, Höhn A, Grune T, et al. Insulin-degrading enzyme: new therapeutic target for diabetes and Alzheimer's disease? *Annals of Medicine*. 2016;48(8):614-624.
 48. Pérez A, Morelli L, Cresto JC, et al. Degradation of soluble amyloid β -peptides 1-40, 1-42, and the Dutch variant 1-40Q by insulin degrading enzyme from Alzheimer disease and control brains. *Neurochemical Research*. 2000;25(2):247-255.
 49. Cook DG, Leverenz JB, McMillan PJ, et al. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E- ϵ 4 allele. 2003;162(1):313-319.
 50. Farris W, Mansourian S, Chang Y, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid β -protein, and the β -amyloid precursor protein intracellular domain in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100(7):4162-4167.
 51. Miller BC, Eckman EA, Sambamurti K, et al. Amyloid- β peptide levels in brain are inversely correlated with insulysin activity levels in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100(10):6221-6226.
 52. Hayrabydyan S, Todorova K, Spinelli M, et al. The core sequence of PIF competes for insulin/amyloid β in insulin degrading enzyme: potential treatment for Alzheimer's disease. 2018;9(74):33884.
 53. Toombs J, Zetterberg H. Untangling the tau microtubule-binding region. *Brain*. 2021;144(2):359-362.
 54. Avila JF. Tau phosphorylation and aggregation in Alzheimer's disease pathology. 2006;580(12):2922-2927.
 55. Matej R, Tesar A, Rusina R. Alzheimer's disease and other neurodegenerative dementias in comorbidity: A clinical and neuropathological overview. *Clinical Biochemistry*. 2019;73:26-31.

56. Gong CX, Grundke-Iqbal I, Iqbal K. Targeting tau protein in Alzheimer's disease. *Drugs & aging*. 2010;27(5):351-365.
57. Woodhouse A, West AK, Chuckowree JA, et al. Does beta-amyloid plaque formation cause structural injury to neuronal processes? *Neurotoxicity research*. 2005;7(1-2):5-15.
58. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2016;12(6):719-732.
59. Lyman M, Lloyd DG, Ji X, et al. Neuroinflammation: the role and consequences. *Neuroscience research*. 2014;79:1-12.
60. Wes PD, Sayed FA, Bard F, et al. Targeting microglia for the treatment of Alzheimer's Disease. 2016;64(10):1710-1732.
61. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, et al. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Frontiers in cellular neuroscience*. 2014;8:112.
62. Hierro-Bujalance C, Bacskai BJ, Garcia-Alloza MJFian. In vivo imaging of microglia with multiphoton microscopy. 2018;10:218.
63. Sankar SB, Infante-Garcia C, Weinstock LD, et al. Amyloid beta and diabetic pathology cooperatively stimulate cytokine expression in an Alzheimer's mouse model. *Journal of Neuroinflammation*. 2020;17(1):38.
64. Hickman SE, Allison EK, El Khoury JJJON. Microglial dysfunction and defective β -amyloid clearance pathways in aging Alzheimer's disease mice. 2008;28(33):8354-8360.
65. Lucin KM, Wyss-Coray TJN. Immune activation in brain aging and neurodegeneration: too much or too little? 2009;64(1):110-122.
66. Ionescu-Tucker A, Cotman CW. Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiology of aging*. 2021;107:86-95.
67. Kim TS, Pae CU, Yoon SJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. 2006;21(4):344-348.
68. Pardo-Moreno T, González-Acedo A, Rivas-Domínguez A, et al. Therapeutic Approach to Alzheimer's Disease: Current Treatments and New Perspectives. *Pharmaceutics*. 2022;14(6).
69. Pardo-Moreno T, González-Acedo A, Rivas-Domínguez A, et al. Therapeutic Approach to Alzheimer's Disease: Current Treatments and New Perspectives. 2022;14(6):1117.
70. Biogen. Highlights of Prescribing Information: Aduhelmmtm (Aducanumab-Avwa) Injection, for Intravenous Use Initial U.S. Approval: 2021; Biogen: Cambridge, MA, USA, 2021.
71. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature*. 2016;537(7618):50-56.
72. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. *JAMA Neurology*. 2022;79(1):13-21.

73. EMA. Aduhelm: Withdrawal of the marketing authorisation application 2022 [Available from: <https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/aduhelm>].
74. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. 2020;25(24):5789.
75. Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). *Molecular medicine reports*. 2019;20(2):1479-1487.
76. Jacobson SA, Sabbagh MN. Donepezil: potential neuroprotective and disease-modifying effects. *Expert Opinion on Drug Metabolism & Toxicology*. 2008;4(10):1363-1369.
77. Homma A, Atarashi H, Kubota N, et al. Efficacy and safety of sustained release donepezil high dose versus immediate release donepezil standard dose in Japanese patients with severe Alzheimer's disease: a randomized, double-blind trial. 2016;52(1):345-357.
78. Hong YJ, Han HJ, Youn YC, et al. Safety and tolerability of donepezil 23 mg with or without intermediate dose titration in patients with Alzheimer's disease taking donepezil 10 mg: a multicenter, randomized, open-label, parallel-design, three-arm, prospective trial. *Alzheimer's Research & Therapy*. 2019;11(1):37.
79. Cacabelos R. Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics. *Neuropsychiatric disease and treatment*. 2007;3(3):303-333.
80. Cacabelos RJNd, treatment. Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics. 2007.
81. Kandiah N, Pai M-C, Senanarong V, et al. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. 2017;12:697.
82. Liu Y, Zhang Y, Zheng X, et al. Galantamine improves cognition, hippocampal inflammation, and synaptic plasticity impairments induced by lipopolysaccharide in mice. *Journal of Neuroinflammation*. 2018;15(1):112.
83. Haake A, Nguyen K, Friedman L, et al. An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer's disease. 2020;19(2):147-157.
84. Atri A, Sheard S, Goldfarb DJTJoCP. A Multidisciplinary Approach for Addressing Challenges in Alzheimer's Disease. 2019;80(5):27537.
85. Tanović A, Alfaro V. [Glutamate-related excitotoxicity neuroprotection with memantine, an uncompetitive antagonist of NMDA-glutamate receptor, in Alzheimer's disease and vascular dementia]. *Revista de neurologia*. 2006;42(10):607-616.
86. Lo D, Grossberg GT. Use of memantine for the treatment of dementia. *Expert Review of Neurotherapeutics*. 2011;11(10):1359-1370.
87. Wong KH, Riaz MK, Xie Y, et al. Review of Current Strategies for Delivering Alzheimer's Disease Drugs across the Blood-Brain Barrier. 2019;20(2):381.
88. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. *Cochrane Database of Systematic Reviews*. 2019(3).
89. Li D-D, Zhang Y-H, Zhang W, et al. Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. 2019;13:472.

90. Rossom R, Adityanjee, Dysken M. Efficacy and tolerability of memantine in the treatment of dementia. *The American journal of geriatric pharmacotherapy*. 2004;2(4):303-312.
91. Guo J, Wang Z, Liu R, et al. Memantine, Donepezil, or Combination Therapy-What is the best therapy for Alzheimer's Disease? A Network Meta-Analysis. *Brain and behavior*. 2020;10(11):e01831.
92. Cappell J, Herrmann N, Cornish S, et al. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. *CNS drugs*. 2010;24(11):909-927.
93. Knapp M, King D, Romeo R, et al. Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer's disease (the DOMINO-AD trial). *International journal of geriatric psychiatry*. 2017;32(12):1205-1216.
94. Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. *Current Medical Research and Opinion*. 2007;23(5):1187-1197.
95. Hane FT, Robinson M, Lee BY, et al. Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *Journal of Alzheimer's disease : JAD*. 2017;57(3):645-665.
96. Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *Journal of central nervous system disease*. 2020;12:1179573520907397.
97. Bittar A, Sengupta U, Kaye R. Prospects for strain-specific immunotherapy in Alzheimer's disease and tauopathies. *npj Vaccines*. 2018;3(1):9.
98. Chang CW, Shao E, Mucke L. Tau: Enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. *Science (New York, NY)*. 2021;371(6532).
99. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nature reviews Neurology*. 2018;14(7):399-415.
100. Soeda Y, Takashima A. New Insights Into Drug Discovery Targeting Tau Protein. *Frontiers in molecular neuroscience*. 2020;13:590896.
101. Atri A, Sheard S, Goldfarb D. A Multidisciplinary Approach for Addressing Challenges in Alzheimer's Disease. *The Journal of clinical psychiatry*. 2019;80(5).
102. Matilla-Mora R, Martínez-Piédrola RM, Fernández Huete J. [Effectiveness of occupational therapy and other non-pharmacological therapies in cognitive impairment and Alzheimer's disease]. *Revista española de geriatría y gerontología*. 2016;51(6):349-356.
103. Zucchella C, Sinforiani E, Tamburin S, et al. The Multidisciplinary Approach to Alzheimer's Disease and Dementia. A Narrative Review of Non-Pharmacological Treatment. *Frontiers in neurology*. 2018;9:1058.
104. Preventive and Therapeutic Strategies in Alzheimer's Disease: Focus on Oxidative Stress, Redox Metals, and Ferroptosis. 2021;34(8):591-610.