International Research Journal of Natural and Applied Sciences
ISSN: (2349-4077)
Impact Factor 7.032 Volume 11, Issue 01,Jan 2024
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Oxidative stress a causal factor for neurodegeneration: A review

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Abstract:

In present time an individual's life is not only going through social competence but working stress is also prevalent. A compromised and processed diet and mental stress is responsible of changes at biological and cellular levels. Free radicals are generated which because of their unstable nature can react unpredictably. Reactive oxygen species are free radical of oxygen and bring about a stressful condition at cellular and organ level termed as oxidative stress. Almost all prevalent diseases have been associated with oxidative stress like obesity, cancer, metabolic disorders, diabetes etc. When oxidative stress approaches the central nervous system, it causes neurodegenerative disorder. Here in this review article, we have discussed basal cause of oxidative stress, its relation to mitochondrial dysfunction, its transmission via blood brain barrier and causal factor of neurodegeneration. At last various therapeutic preventive mechanisms have also been discussed and concluded that antioxidant both in natural forms and supplementary medicine can be helpful to prevent neurodegenerative problems.

Keywords: Neurodegeneration, Oxidative Stress, Mitochondrial Dysfunction, Blood Brain Barrier

Introduction to oxidative stress

Life has changed vastly for people in current era as they are more inclined towards a faster and stress full life. Great economic changes, sociocultural status management and lifestyle comparisons have led to compromise the nutritional quality of the food and consumption of high ultra-processed products[1]. We live in an uncertain society with continual change with excessive stress and these characteristics are reflected in the approaches to health

systems, leading to challenging consequences in the form of development of Oxidative stress, associated with the current prevalence of chronic metabolic diseases[2].

Oxidative stress was initially reported in 1956 by Dr. Harman, who firstly describe ageing as a process characterised by the progressive decline of cellular function and oxidative stress theory for the conditions under which cells age and die[3]. In recent decades, research about oxidative stress and its association with various metabolic disorders is proliferating such as Neurodegenerative diseases[4], obesity[5], diabetes[6], cardiovascular diseases[7], and cancer[8]. This may be considered an indicative pattern of the change in intake guidelines, regarding foods such as those high in simple carbohydrates and in saturated fatty acids[1]. Food consumption guidelines play very significant role in improving levels of systemic pro-oxidants and inflammatory mediators, which result in neuroinflammatory reactions in the central nervous system[9].

Neurodegenerative disease

Neurodegenerative diseases are basically progressive brain conditions that are caused by nerve cell damage leading to memory loss, movement problems, and other symptoms. It forms a diverse group that generally have any point of damage in the nervous[10]. Research shows that, in 2021, more than 3 billion people worldwide were living with a neurological condition and The World Health Organization (WHO) contributed to the analysis of the Global Burden of Disease, Injuries, and Risk Factor Study (GBD) 2021 data[11]. Neurological disorders are concern for all people from globally and irrespective of sex, scholastic level and financial status. The WHO encourages that neurological treatment be combined into basic health procedure[12, 13].

Neurodegenerative diseases share a common ground with other health problems such as diabetes, cardiovascular disease and obesity etc. Oxidative Stress is an important causative factor in the development of several metabolic disease[14] and various research are being performed for a clear picture of the connection between redox potential of the cell and nervous system injury[15]. Answer to question are being searched like what impact oxidative stress holds on nervous system? If neurogenerative diseases can be triggered by systemic oxidative stress. In this review article we tend to discuss effects and mechanisms of systemic oxidative stress derived neurodegeneration, its role a potential inducer of neurogenerative diseases with the help of available literature.

Role of mitochondrial dysfunction in systemic oxidative stress

Oxygen inhaled for respiration is used by cell in oxidative-reductive reactions to obtain energy and metabolites essential for cell's growth and development[16]. These oxidative-

reductive reactions are part of cellular respiration and take place in mitochondrion where nutrients are metabolized for energy production[17]. Mitochondria usually utilizes 95 to 98% of O_2 for oxidative processes. Remaining O_2 gets reactive with water molecules to produce hydrogen peroxide (H_2O_2) and free radicals called reactive oxygen species[18]. There several factors affecting production of reactive oxygen species like diet, lifestyle etc. Carbohydrate and saturated fatty acids concentration correlates increase pro-oxidant elements. Increased intracellular glucose concentration leads to a high substrate conc. for oxidative metabolic enzymes and ultimately initial enzymes velocity increases maximum[19]. This causes decline in physiological utilization of oxygen and availability of free oxygen for reactive oxygen species production increases with decrease in oxidative phosphorylation[16, 18]. These disruption in mitochondrial function is termed as mitochondrial dysfunction[20].

Mitochondrial dysfunction is considered main triggering factor to oxidative stress. Reactive oxygen species and free radicals are unstable atoms with an unpaired electron, characterised by gaining electrons from stable molecules, such as proteins, lipids and nucleic acids[21]. Reactive atomic species are produced as part of routine physiological processes and have vital roles in cell signalling, gene transcription and immune response[22] but still free radical overproduction, is associated with oxidative damage of cellular structures[23]. Reactive oxygen species aggregation in matrix induces oxidation of membrane lipids and proteins, which further contributes to mitochondrial dysfunction[18].

Oxidative stress prevalence may lead to a chronic state and may spread to other body parts. Reactive oxygen species and reactive nitrogen species in blood are proficient of triggering proinflammatory and oxidative processes in organs such as liver[24], kidney[25], enterocyte[26], endocrine glands[14], encephalon[27].

Impact of Oxidative stress Blood-Brain barrier

Blood Brain Barrier is a physical obstacle located between blood vessels and brain tissues, which selectively permits the passage of molecules, and its permeability can be modified by different stimuli[28]. Nervous system protects itself from the pro-oxidants in blood via the Blood Brain Barrier[29]. Distribution of pro-oxidant composites in the blood and inflammatory processes initiation compromises CNS functions via distinct communication channels, such as the vagus nerve, the choroid plexus and the Blood Brain Barrier[30]. Oxidative stress causes a chronic oxidative background leading to epigenetic changes of the neurovascular unit that result in alteration of the Blood brain barrier function[29].

Blood brain barrier possess significant ion channels and transporters, tight junction proteins and cell adhesion molecules, which restrain paracellular permeability and

pinocytosis[28]. As additional protection, endothelial cells of the Blood brain barrier display a high antioxidant activity with reduced glutathione, glutathione peroxidase, glutathione reductase and catalase, compared to rest of the brain for the reduction in damage caused by Reactive oxygen species and free radical[29]. But antioxidant activity is not as efficient in chronic oxidation environment[31], sugar and saturated fatty acids being most widely noticed factors[32, 33]. Reactive oxygen species overrun impacts the Blood brain barrier penetrability by a variety of processes which includes the alteration of junction proteins[34] for example Occludin oligomers, bound together by covalent disulfide bonds, are sensitive to reactive oxygen species oxidation[35] and any changes in their structure leads to reduction in binding capacity, which affects the paracellular diffusion of molecule to the brain[36].

Cells display a resistance mechanism against the oxidative stress called adaptive response[37]. Cells initiate expression of genes for antioxidant enzymes in oxidative stressed condition and activates the transcription factor Nrf2, which inhibits genes of enzymes involved in the reactive oxygen species production, such as NADPH oxidase, anti-inflammatory mediators etc[38]. Though the CNS itself has additional protective mechanism against the Oxidative stress[29], but the widespread and persistent oxidative environment may lead to the decline in adaptive response[21]. Lower genes expression involved in the NVU integrity, causes a hypometabolic state that influences the oxidative processes of the cells that make Blood brain barrier The triggered mitochondrial dysfunction accounts for cellular injury that results in endothelial cell necrosis and loss of Blood brain barrier integrity[33].

Oxidative stress and Neurodegeneration

Nervous system comprises of an intricate, particularly organised network of neurons and glial cells. The brain makes its principal constituent, whose cognitive process involves the involvement of neurons, main functional units of the CNS that have the capacity to transfer information quickly and efficiently via electrical or chemical signals known as action potentials[39]. Anatomically, they are composed of a cell body, its known as dendrites and a longer extension known as axon[40]. Neurons have high mitochondrial activity and high oxygen consumption and thus a crucial point for increased reactive oxygen species production, its accumulation and induced damage[41]. Glial cells do not have synaptic contacts but function for Maintaining the ionic medium, Modulation of the nerve signals propagation, Modulation of the synaptic action by neurotransmitters and maintenance of neural development in case of neuronal lesion[42]. These with NVU are responsible for the Blood brain barrier integrity and metabolism, by reacting to nerve tissue injury[43].

Normally these are in resting stage but in response to nervous system injury, the microglia becomes polarised and trigger mechanisms that promote neurotoxic activities, including the reactive oxygen species overproduction, RNS, chemokines and proinflammatory cytokines and the process is called microgliosis, which include not only an increase in number but also a complex cascade of physiological acute inflammation responses[44].

A hyper state of oxidative stress, systemic reactive oxygen species propagation and Blood brain barrier interference, causes a enduring microgliosis that promotes a chronic state of inflammation and activation of the microglia lasts until it leads to an imbalance in the inflammatory response, ultimately generating a neuroinflammation cycle and tissue damage[42]. Neuroinflammation is a reactive state of the immunological component of the central nervous system[45]. The reason for triggering neuroinflammation can be Physical injury such as trauma, Biological such as infections and Chemical, which induces reactive oxygen species production, free radical, and RNS, present in the Oxidative stress[17].

In response to microglial activation, proinflammatory molecules facilitate the reaction at the injured site like IL1β induces the expression of the inducible nitric oxide synthase gene (iNOS), accountable for triggering the nitric oxide discharge on glial cells and cause nitrosative stress and an exacerbated reactive nitrogen species production in the chronic neuroinflammatory response upsurges the oxidation of membrane lipids[44].

Astrogliosis also increases the number and size of the fibrillary acid protein of the glia, protein cytoskeleton that causes to hypertrophy and hyperplasia of astrocytes. Active astrocytes produce pro and anti-inflammatory cytokines for expression of the gene cyclooxygenase–2 (COX-2) enzymes e iNOS, as well as higher reactive nitrogen species production. Thus, neuroinflammatory reaction, triggered by reactive oxygen species and free radical, contributes to oxidative stress in the central nervous system and help generation of a continuous state between neuroinflammation and chronic oxidative stress[42].

Oxidative stress performs a significant role in the neuronal activation death mechanisms, associated in the several studies of neurodegenerative diseases[47]. Continuous oxidative stress activates the genes involved in the recovery and cell death for example one of the most reviewed is the FOXO transcription factors which has a prominent role in oxidative stress-induced neuronal cell death and promotes neuronal apoptosis in response to oxidative stress via inducing the expression of pro-apoptotic downstream genes including Bim and FasL [48].

Similarly, aggravated intracellular reactive oxygen species production and DNA damage activates the expression of the p53 gene, activating the Bcl2 pro-apoptotic protein

family ultimately leading to release of cytochrome C that forms a complex with apoptotic protease activating factor 1 (Apaf-1) that result is the 9 caspase activation, execution of the cell death process, as well as changes in the plasma membrane like blistering and phosphatidyl-serine exposure on the cell that culminates in the condensation and nuclear chromatin fragmentation[49, 50]. Additionally increase in reactive oxygen species concentrations in the neuron, induces a quick upsurge in intracellular Ca+2, from extracellular spaces, after the rupture of the membrane and from endoplasmic reticulum, because of cytochrome C translocation from the mitochondrial outer membrane to the cytosol, triggering cell death signals[50].

Disruption of Blood brain barrier is another process responsible for cell death, which dispels the reactive oxygen species transit and proinflammatory cytokines to nervous system. Disruption and microgliosis increases the inflammation moderator's production i. e. reactive oxygen species and reactive nitrogen species causing cell death signs, by recognising the FAS receptor or cell death receptor and TNF receptor 1, activating the necroptotic pathway which are also connected to the neurodegenerative diseases pathogenesis[51].

Neurons have almost negligible regeneration capacity compared to other cells and apoptotic pathway is strictly constrained, to let neurons to persist during the life of the individual[52]. For the particular reason its protection from any damaging force is necessary to protect from any degeneration.

Preventive approach

In recent decades there has been advances in the field of medical and biotechnology sciences and our nutrition challenges have readdressed following the new pattern. At present the implementation of a food habit is being done with the bioactive compounds in them and whose biological reactions have shown beneficial effects on the Oxidative stress biochemical-metabolic alterations[53]. Compounds that can manifest reactive oxygen species are termed as antioxidants and These use to mitigate the Oxidative stress and is complementary in the modulation of the oxidative environment. An antioxidant is any component present at low concentrations with respect to those of an oxidisable substrate, retards or inhibits the oxidation of the substrate[54]. Currently, very impactful role of antioxidants is anticipated as neuroprotective agents in neurodegenerative diseases. Various Polyphenols such as quercetin, catechin and resveratrol have shown neuroprotective role in several animal models with neurological disorder[55] and epidemiological research sustain the probable polyphenols' use in the diet, for better neuronal health[56]. The anticipated mechanisms include the blocking of

enzymes that produce free radical, metals chelation and neutralising reactive oxygen species, anti-inflammatory effects and microglia inhibition recruitment[57].

Various fruits, vegetable and beverages such as tea, red wine, cocoa and coffee are the most prevalent sources of polyphenols[56]. Their neuroprotective functions are concurrent across the potential to guard neurons against lesions induced by neurotoxins and the ability to restrain neuroinflammation and the capacity to promote memory, learning and cognitive function[58]. Contemporary evidence suggest that food polyphenols favourable impact involves their ability to decrease Oxidative stress signalling and modulation of gene expression of antioxidant enzymes, neurotrophic factors and cytoprotective protein[59]. Caffeine[60], Ginkgo biloba[61], α-tocoferol[62] and curcumin[63] have also been displayed for important and protective activities and suggest their potential use in the neurodegenerative diseases' treatment. The medicinal approaches based on the potential antioxidant and anti-inflammatory effect of food are beneficial for modulating the oxidative conditions and mitigating Oxidative stress alterations and inflammation[64].

Conclusion

Oxidative stress is a condition induced by lifestyle disturbance and some medicinal impacts and is revocable mechanism. its complexity and severeness can lead to further systemic disturbances of various organs such as neurodegeneration. for the neurodegenerative diseases prevention early detection of oxidative stress is best to dealt with. Dietary antioxidants are important to comprehend the biochemical and metabolic modifications generated by the Oxidative stress. Thus, healthy diet with lots of polyphenols is key point in fighting oxidative stress. In more thar moderate cases antioxidants can be taken as medicinal supplements. Further mechanisms are being searched not only for handling of oxidative stress but also neurodegeneration caused.

References:

1. Monteiro C, Moubarac J, Cannon G, Ng S, Popkin B. Ultra-processed products are becoming dominant in the global food system. 2014; Obesity rev. 2:21-28
2. Jovell AJ. The XXI century patient. Anales del Sistema Sanitario de Navarra. 2006; 29(3): 85-90.
3. HARMAN D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956 Jul;11(3):298-300.
4. Roy-Sarkar S, Banerjee S. Gut microbiota in neurodegenerative disorders. J Neuroimmunol. 2019; 328 (15): 98-104

5. Mechanick J, Hurley D, Garvey W. Adiposity-based chronic disease as a new diagnostic term: The American Association of Clinical Endocrinologists and American College of Endocrinology position statement. Endocrine Practice. 2017; 23(3): 372-378
6. Oliveira C, Villar-Delfino P, Dos Anjos P, Nogueira A. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death Dis. 2018; 9 (119) https://doi.org/10.1038/ s41419-017-0135-z.
7. Vaziri N, Rodríguez- Iturbide B. Mechanisms of Disease: oxidative stress and inflammation in the pathogenesis of hypertension. Nat Clin Prac Nephrol. 2006; 2: 582–593
8. Paschos A, Pandya R, Duivenvoorden WCM, Pinthus JH. Oxidative stress in prostate cancer: changing research concepts towards a novel paradigm for prevention and therapeutics. Prostate Cancer Prostatic Dis. 2013; 16: 217–225
9. Parimisetty A. Dorsemans AC, Awada R, Ravanan P, Diotel N, Lefebvre d'Hellencourt C. Secret talk between adipose tissueand central nervous system via secreted factors – an emerging frontier in the neurodegenerative research. J. Neuroinflammation. 2016; 13: 67
10. Torrell G. Enfermedades neurodegenerativas. Actualización en Medicina de Familia. 2015; 11(7): 374- 383.
11. Steinmetz, Jaimie D et al. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021 The Lancet Neurology, Volume 23, Issue 4, 344 – 381
12. National Institute of Neurological Disorders and Stroke. Neurodegenerative diseases. 2017.
13. Noncommunicable Diseases Progress Monitor, 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream /handle/10665 /258940/9789241513029-eng.pdf?sequence=1
14. Vitale G, Salvioli S, Franceschi C. Oxidative stress and the ageing endocrine system. Nat Rev Endocrinol. 2013; 9: 228–240
15. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. Nat Rev Neurol. 2017; 13: 477–491
16. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. 2015; 4: 180-183
17. Orrenius S, Gogvadze V, Zhivotovsky B. Mitochondrial oxidative stress: implications for cell death. Annu Rev Pharmacol Toxicol. 2007; 47:143-183
18. Schieber M, Chandel N. ROS Function in Redox Signaling and Oxidative Stress. Current Biol. 2014; 24(10): R453- R462
19. Davis RE, Williams M. Mitochondrial function and dysfunction: an update. J Pharmacol Exp Ther. 2012; 342: 598–607
20. Area-Gomez E, De Groof A, Bonilla E, Montesinos J, Tanji K, et al. A key role for MAM in mediating mitochondrial dysfunction in Alzheimer disease. Cell Death Dis. 2018; 9(335):1-10

21. Martínez-Leo E, Acevedo J, Segura M. Biopeptides with antioxidant and anti-inflammatory potential in the prevention and treatment of diabesity disease. Biomed Pharmacother. 2016; 83: 816–826
22. Sies H, Berndt C, Jones D. Oxidative stress. Annu. Rev. Biochem. 2017; 86: 25.1–25.34
23. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. Eur J Med Chem. 2015; 97(5): 55- 74
24. Kim SY, Jeong JM, Kim S, Seo W, Kim MH, Choi WM, et al. Pro-inflammatory hepatic macrophages generate ROS through NADPH oxidase 2 via endocytosis of monomeric TLR4–MD2 complex. Nat Commun. 2017; 8 (2247)
25. Kong MJ, Han SJ, Kim JI, Park JW, Park KM. Mitochondrial NADP+-dependent isocitrate dehydrogenase deficiency increases cisplatin-induced oxidative damage in the kidney tubule cells. Cell Death Dis. 2018; 9(488)
26. Hu Q, Ren J, Li G, Wu J, Wu X, Wang G, Gu G, et al. The mitochondrially targeted antioxidant MitoQ protects the intestinal barrier by ameliorating mitochondrial DNA damage via the Nrf2/ARE signaling pathway. Cell Death Dis. 2018; 9(403)
27. Mattson M, Magnus T. Ageing and neuronal vulnerability. Nat Rev Neurosci. 2006; 7: 278–294.
28. Nzou G, Wicks RT, Wicks EE, Seale SA, Sane CH, Chen A, Murphy SV, et al. Human Cortex Spheroid with a Functional Blood Brain Barrier for High-Throughput Neurotoxicity Screening and Disease Modeling. Sci Rep. 2018; 8 (7413)
29. Obermeier O, Daneman R, Ransohoff R. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013; 19: 1584–1596
30. Guillemot-Legris O, Muccioli G. Obesity- induced neuroinflammation: Beyond the hypothalamus. Trends Neurosci. 2017; 40(4): 237- 253..
31. Forsberg SL, Ilieva M, Michel T. Epigenetics and cerebral organoids: promising directions in autism spectrum disorders. Transl Psychiatry. 2018; 8(14)
32. Baufeld C, Osterloh A, Prokop S, Miller K, Heppner F. High-fat diet-induced brain region specific phenotypic spectrum of CNS resident microglia. Acta Neuropathol. 2016; 132: 361–375 https://doi.org/10.1007/s00401-016-1595-4
33. Rhea E, Salameh T, Logsdon A, Hanson A, Erickson M, Banks W. Blood-Brain Barriers in Obesity. The AAPS Journal. 2017; 19(4): 921- 930 https://doi.org/10.1208/s12248-017-0079-3.
34. Lochhead J, McCaffrey G, Quigley C, Finch J, De Marco K. et al. Oxidative stress increases blood–brain barrier permeability and induces alterations in occluding during hypoxia–reoxygenation. J Cereb Blood Flow Metab. 2010; 30: 1625–1636

35. McCaffrey G, Staatz WD, Quigley CA, Nametz N, Seelbach MJ, Campos CR, et al. Tight junctions contain oligomeric protein assembly critical for maintaining bloodbrain barrier integrity in vivo. J Neurochem. 2007; 103(6): 2540-55
36. Walter JK, Rueckert C, Voss M, Mueller SL, Piontek J, Gast K, Blasig IE. The oligomerization of the coiled coil-domain of occludin is redox sensitive. Ann NY Acad Sci. 2009; 1165:19–27
37. Morel Y, Barouki R. Repression of gene expression by oxidative stress. Biochem J.1999; 342: 481-496.
38. Tufekci K.U, Civi Bayin E, Genc S, Genc K. The Nrf2/ARE Pathway: A Promising Target to Counteract Mitochondrial Dysfunction in Parkinson's Disease, Parkinsons Dis. 2011; 314082
39. Shrestha R, Millington O, Brewer J, Bushell T. Is Central Nervous System an Immune-Privileged site? Kathmandu University Med J. 2013; 41(1): 102-107.
40. Avena-Koenigsberger A, Misic B, Sporns O. Communication dynamics in complex brain networks. Nat Rev Neurosci. 2018; 19: 17–33
41. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther. 2012; 342(3): 619-30
42. Mizuno T. Neuron–microglia interactions in neuroinflammation. Clin Exp Neuroimmunol. 2015; 6: 225–231.
43. Moraes JC, Coope A, Morari J, Cintra DE, Roman EA, Pauli JR, et al. High-fat diet induces apoptosis of hypothalamic neurons. PLoS One. 2009; 4(4): e5045.
44. Chen W, Zhang X, Huang W. Role of neuroinflammation in neurodegenerative diseases. Mol Med Rep. 2016; 13: 3391-3396
45. Becher B, Spath S, Goverman J. Cytokine networks in neuroinflammation. Nat Rev Immunol. 2016; https://doi.org/10.1038/nri.2016.123
46. Zhang D, Hu X, Qian L, O'Callaghan J, Hong J. Astrogliosis in CNS pathologies: Is there a role for microglia?. Mol neurobiol. 2010; 41: 232- 241
47. Zhu W. Methylation of FOXO3 regulates neuronal cell death. Acta Pharmacol Sinica. 2012; 33: 577
48. Xie Q, Hao Y, Tao L, Peng S, Rao C, Chen H, You H, et al. Lysine methylation of FOXO3 regulates oxidative stress-induced neuronal cell death. EMBO Rep. 2012; 13: 371- 377
49. Xin YJ, Yuan B, Yu B, Wang YQ, Wu JJ, Zhou WH, Qiu Z. Tet1-mediated DNA demethylation regulates neuronal cell death induced by oxidative stress. Sci Rep. 2015; 5 (7645): 1-9
50. Mattson M. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol. 2000; 1: 120–130
51. Zhang S, Tang M, Luo H, Shi C, Xu Y. Necroptosis in neurodegenerative diseases: a potential therapeutic target. Cell Death Dis. 2017; 8: e2905.
52. Cusack C, Swahari V, Henley W, Ramsey M, Deshmukh M. Distinct pathways mediate axon degeneration during apoptosis and axon-specific pruning. Nat Commun. 2013; 4(1876): 1-11

53. Pelcastre D, Martínez-Leo E, Segura-Campos M. Functional and Biological Potential of Bioactive Compounds in Foods for the Dietary Treatment of Type 2 Diabetes Mellitus. In: Functional Food - Improve Health through Adequate Food, 1st edition. Ed. InTech; 2017.
54. Halliwell B. Free radicals and antioxidants - quo vadis?. Trends Pharmacol Sci. 2011; 32. 125-130
55. Potter A, Buck AC, Self WK, Callanan ME, Sunil S, Capadona JR. The effect of resveratrol on neurodegeneration and blood brain barrier stability surrounding intracortical microelectrodes. Biomaterials. 2013; 34:7001–7015
56. Rodríguez C, Segura A, Del Mar M. Phenolic compounds as natural and multifunctional anti-obesity agents: A review. Crit Rev Food Sci Nutr. 2017; 20:1-18
57. Dong W, Gao D, Lin H, Zhang X, Li N, Li F. New insights into mechanism for the effect of resveratrol preconditioning against cerebral ischemic stroke: possible role of matrix metalloprotease-9. Med Hypotheses. Medical Hypotheses. 2008; 70:52–55
58. Shukitt-Hale B, Lau FC, Carey AN, Galli RL, Spangler EL, Ingram DK, Joseph JA. Blueberry polyphenols attenuate kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. Nutr Neurosci. 2008; 11: 172–182
59. Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. Oxid Med Cell Longev. 2012; 914273
60. Góngora JL. Caffeine as a preventive drug for Parkinson's disease: epidemiologic evidence and experimental support. Rev Neurol. 2010; 50(4), 221-9.
61. Fehske CJ, Leuner K, Müller WE. Ginkgo biloba extract (EGb761®) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment. Pharmacol Res. 2009; 60: 68–77
62. Grimm MO, Stahlmann CP, Mett J, Haupenthal VJ, Zimmer VC, et al. Vitamin E: Curse or benefit in Alzheimer's disease? A systematic investigation of the impact of α-, γ- and δ-tocopherol on Aβ generation and degradation in neuroblastoma cells. J Nutr Health Aging. 2015; 19:646–654
63. Zbarsky V, Datla K, Parkar S, Rai D, Aruoma O, Dexter D. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radical Res. 2005; 39: 1119– 25
64. Wu P, Zhang Z, Wang F, Che J. Natural compounds from traditional medicinal herbs in the treatment of cerebral ischemia/reperfusion injury. Acta Pharmacologica Sinica. 2010; 31: 1523–1531