Journal of Experimental and Basic Medical Sciences 2021;2(1):1-6

Review

Effects of Green Tea Polyphenols and Oxidative Stress on Alzheimer's and Parkinson's Diseases

Aylin Doğanoğlu[1], Oytun Erbaş[1,2]

ABSTRACT

Alzheimer's disease is a progressive brain disorder that starts with mild memory loss and aggravates the loss of speech, facial expressions, and many everyday activities. Similarly, Parkinson's disease is a brain disorder that causes various movement disorders by tightening muscles and making them rigid. Alzheimer's and Parkinson's diseases are the most common neurodegenerative diseases among older adults and the number of cases is rapidly increasing. Although many factors leading to these diseases are not discovered, many studies found ROS production-induced oxidative stress leads to oxidation and modification of various cellular structures and subsequently cell death and neuronal degeneration. Polyphenol compounds are micronutrients that are featured by many plant-based foods and renowned for their antioxidant capacities, which play an impactful role in the inhibition of arachidonic acid metabolizing enzymes and regulation of mitochondrial dysfunction. Especially green tea polyphenols, which are rich in (-)-epigallocatechin-3-gallate (EGCG), scavenge radicals, chelate metal ions, inhibit the nuclear translocation of NF-κB, and thus reduce oxidative stress and prevent many factors that lie behind Alzheimer's and Parkinson's diseases.

Keywords: Alzheimer's disease, green tea, oxidative stress, Parkinson's disease, polyphenols, ROS.

Polyphenols are natural substances that are present in many plants, fruits, and vegetables, such as tea, cloves, and other seasonings, red wine, and berries. Flavonoids, which is the largest group of polyphenols, are split into aurones, dihydrochalcones, flavanonols, isoflavones, flavones, flavonols, leucoanthocyanidins, anthocyanins, and proanthocyanidins.[1] All polyphenols feature at least one phenolic ring connected to hydroxyl groups in either ortho or para positions, which satisfy the need for redox reactions to take place.[2] Hydroxyl groups and phenolic rings provide antioxidant capacities.[3] Their strong antioxidant capacities complement and supplement the functions of antioxidant vitamins and enzymes as a defence against oxidative stress induced by excess reactive oxygen species (ROS). In recent years, more connections between oxidative stress and neurodegenerative diseases have been revealed and these diseases have been related to oxidative stress generated by reactive oxygen and nitrogen species.[4] Experimental studies have shown that polyphenols play a part in the prevention of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

OXIDATIVE STRESS AND ROS

An antioxidant system is responsible for neutralizing reactive oxygen species (ROS), and when it cannot, oxidative stress takes place in cells and tissues.[5] Oxygen presence in higher than normal ratios in biological systems intermediates potential damage to cells that might cause cell death. "Free radical" refers to any molecular species that contains one or more unpaired electrons in its outermost shell and can exist independently.[6] Many phenomena in the cell, such as respiratory chain in mitochondria, in

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey

Correspondence: Aylin Doğanoğlu. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

E-mail: aylindoganoglu@gmail.com

Cite this article as: Doğanoğlu A, Erbaş O. Effects of Green Tea Polyphenols and Oxidative Stress on Alzheimer's and Parkinson's Diseases. JEB Med Sci 2021;2(1):1-6.

doi: 10.5606/jebms.2021.75632

Received : March 21, 2021
Accepted : March 29, 2021
Published online : May 31, 2021

photochemical and enzymatic reactions, as a result of the exposure to UV light, ionizing radiation, or heavy metal ions, can give rise to ROS production, which can be hydroxyl radical ($OH^{\cdot}$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and superoxide anion (O_2^{-}).[7]

The reduction of oxygen results in superoxide generation that, afterwards the dismutase to hydrogen peroxide. Although hydrogen peroxide has low reactivity, it can easily penetrate the cell's membranes and produce the most reactive form of oxygen, the hydroxyl radical, by Fenton's reaction ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^{-} + OH^{\cdot}$).[7] Multitude enzymes in the antioxidant system including superoxide dismutase (SOD), catalase, and peroxidases control big amounts of ROS produced by the strong metabolism of the brain.[8,9] Nevertheless, when ROS gets overly generated, it overpowers intrinsic antioxidant capacity. This leads to oxidative stress and ultimately damage to the biomolecules of tissues and cells.[10]

OXIDATIVE STRESS AND NEURODEGENERATIVE DISEASES

In neurodegenerative diseases, oxidative stress and mitochondrial dysfunction both contribute to cell death. In the ETC (electron transport chain), complex I (NADH dehydrogenase-ubiquinone oxidoreductase) and III (ubiquinone-cytochrome c oxidoreductase) give electrons to oxygen to generate superoxide, which is then transformed into hydrogen peroxide via superoxide dismutase (SOD) and peroxynitrite by reacting with nitric oxide. voltage-dependent anion channel (VDAC) discharges ROS and RNS (reactive nitrogen species), generated in mitochondria, into the cytoplasm, and thus, they modify and oxidize DNA, protein, and lipid.[11]

OXIDATIVE STRESS AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) and other dementias are one of the main reasons for mortality in the elderly worldwide, with a rate increasing rapidly that will double in 20 years.[12] As oxidative stress has begun to be seen as an important pathogenic factor in AD, many theorized that oxidative stress is involved in the induction of the disease. Indeed, among all AD hallmarks, oxidative damage was discovered to be the first observable phenomenon in the progression of AD.[13] Peroxidation of lipids jeopardizes the collectivity of cellular membranes and produces diffusible aldehydic by-products, including the α, β-unsaturated aldehydes acrolein, 4-hydroxyhexenal (HHE), and 4-hydroxynonenal (HNE).[14]

Acrolein, a derivative arachidonate and linoleate, has toxic effects on neurons and, in Alzheimer's disease, levels of acrolein are increased.[15] High levels of the GSH-HNE Michael adduct (HNE-GSH) were encountered in the AD hippocampus, and substantia innominata, frontal and temporal cortex, entorhinal cortex, and cerebellum.[16] Multidrug-resistant protein 1 (MRP-1) expels the HNE-GSH adducts in normal cells, but in AD brain, gl333utathione S-transferase (GST) and MRP-1 get modified by HNE, which may explain the loss of GST activity in AD.[17,18] Also, it has been supposed that vascular Aβ deposits bring on the degeneration of arterial vessels and cerebral capillaries, assumedly mediated by reactive oxygen species (ROS) initiation caused by activation of NADPH oxidase. Followingly, the vascular Aβ(β-amyloid) deposition can damage the blood-brain barrier and harm the regulation of brain perfusion and cerebral blood vessels.[19-21]

OXIDATIVE STRESS AND PARKINSON'S DISEASE

Being the second most common neurodegenerative disorder, Parkinson's disease is qualified by severe movement disturbances such as rigidity, tremor, and bradykinesia.[22] Some particular PD phenotypes such as mitochondria depolarization, ER stress, α-synuclein accumulation and altered level of cytosolic DA can give rise to cellular oxidative stress, by itself or interacting with one another.[22] With a number decline of 5% to 10% per decade by aging, Dopamine neurons, located in the substantia nigra in the human brain, are potentially susceptible to harm. Enzymatic and non-enzymatic oxidation of dopamine produces reactive oxygen species, and thus, begets apoptotic cell death in dopamine neurons.[23]

In support, similar to Alzheimer's, studies in postmortem brains of PD patients pointed out elevated levels of 4-hydroxy-2-nonenal (HNE), a lipid peroxidation by-product, and the DNA and RNA oxidation products 8-hydroxy-deoxyguanosine and 8-hydroxyguanosine, and carbonyl modifications of soluble proteins in the SN.[24-28] Modeling the motor aspects of PD in animals with toxins that cause oxidative stress including 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), rotenone, 1,1'-dimethyl-4,4'-bipyridinium dichloride (paraquat),

and 6-hydroxydopamine (6-OHDA) helped indicate the connection between dopaminergic neuronal degeneration and oxidative stress.[29-33]

OXIDATIVE STRESS AND POLYPHENOLS

Antioxidant properties of polyphenols

An antioxidant molecule is responsible for avoiding or postponing the oxidation of other molecules, such as lipids, proteins, or nucleic acids.[34] Polyphenols were discovered as powerful antioxidants able to neutralize free radicals by giving a hydrogen atom or an electron. In the antioxidant activities, the greatly conjugated system and particular hydroxylation patterns like the 3-hydroxyl group in flavonols play a significant role.[35] Indeed, effective mechanisms on the antioxidant capacity of polyphenols include suppression of the production of ROS by either inhibiting the enzymes that are contributed to their generation, scavenging of ROS, or conservation or upregulation of antioxidant defences.[36] Antioxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase can be stimulated by polyphenols, and thus, they can break down hydroperoxides, hydrogen peroxide and superoxide anions, respectively, and inhibit the expression of enzymes such as xanthine oxidase.[37] Polyphenols also work as metal chelators. Because of their lower redox potentials, polyphenols thermodynamically can decrease greatly oxidizing free radicals as a result of their capacity to chelate metal ions (irons, copper, etc.) and free radicals.[38]

Inhibition of enzymes caused by oxidation

Several studies have revealed the activity of arachidonic acid metabolizing enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), and NOS can be regulated by different polyphenols.[39] Some of the key mediators of oxidative stress and inflammation including the generation of AA, prostaglandins, leukotrienes, and NO can be inhibited by these enzymes.[40] COX and LOX control the production of metabolites with the potential to expand the oxidative lesion in tissues.[41] Reduced XO activity and less oxidative injury have been reported with polyphenol intake.[42]

Regulation of mitochondrial dysfunction

Polyphenols have many functions within mitochondria such as ameliorating mitochondrial functions, particularly the ETC activity, regulating the redox state, as well as inhibiting the apoptosis system. The selective accumulation of bioactive compounds in mitochondria are elevated by arranged mitochondria-targeting polyphenols.[43-45]

Green tea polyphenols

Green tea, also called unoxidized tea, is produced purely from the leaves of the Camellia sinensis plant. The leaves are culled, shrivelled to a small extent, and afterwards immediately cooked to conserve the green quality and avoid oxidation. Due to this process, green teas have significantly higher levels of chlorophyll, polyphenols, and antioxidants than other tea types.[46] In thoroughly directed epidemiological studies, green tea polyphenols are now being thought to be therapeutic agents, aiming at regulation of brain aging processes and serve as potential neuroprotective elements in progressive neurodegenerative diseases such as Parkinson's and Alzheimer's.[47] Green tea features distinguishable polyphenolic compounds including, (-)-epigallocatechin-3-gallate (EGCG)-which is the most abundant catechin- (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC). Moreover, various flavonols as well as their glycosides are present in tea.[48]

Tea polyphenols scavenge ROS and generate more stable phenolic radicals in vivo and in vitro to relieve oxidative stress.[49] EGCG scavenging radicals mainly derive their ability from the D ring in the galloyl group of its structure.[50] Electron paramagnetic resonance spectroscopy is analyzed, then oxidizing the D ring of galloyl group used to scavenge OH and O_2.[51,52]

Reduction in EGCG attenuated 3-HK–induced cell viability and an increase in the levels of ROS and caspase-3 activity in neuronal culture is assumedly a result of its antioxidant activity.[53] As shown in rat brain tissue, green tea extracts hinder lipid peroxidation brought about by iron ascorbate in brain mitochondrial membrane homogenates (IC50: 2.44 and 1.40 mol/L, respectively).[54]

The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can lead to symptoms akin to PD by ruining the structure of neurons that generate dopamine in the substantia nigra. MPTP-induced oxidative stress damage can be decreased by EGCG in PD mice, whose mechanism is relatable to inhibiting inducible nitric oxide synthase (iNOS) expression level.[55]

EGCG can augment cellular antioxidant defence capacity and attenuate Aβ-mediated oxidative and/or nitrosative cell death, creating protective

and/or therapeutic effects on AD patients. Oxidative stress and nitrosative might mediate Aβ-induced damage of neurons as well as glia. When BV2 cells were exposed to Aβ, they underwent nitrosative stress, which was pointed out by the augmented expression of inducible nitric oxide synthase (iNOS) and followingly, the production of nitric oxide (NO) and peroxynitrite, which were highly repressed via EGCG pretreatment. Fortification of the cellular GSH pool through increased mRNA expression of γ-glutamylcysteine ligase, a rate-limiting enzyme in glutathione biosynthesis, by EGCG treatment is considered to be the operative mechanism.[56]

In in vitro systems, EGCG was discovered to inhibit the nuclear translocation of NF-κB: initiation of green tea extract before 6-OHDA-induced oxidative stress inhibited both NF-κB nuclear translocation and binding activity in neuroblastoma SH-SY5Y cells, as indicated by immunofluorescence and electromobility shift analyses.[54]

It is agreed that, in the brain, the fibrillation of AS might be caused by iron accumulation. Nevertheless, EGCG can force its way into the blood-brain barrier, chelate metal ions, and in this way, inhibit the fibrillation of amyloid proteins. EGCG's chelating Fe(III) defends AS-PC12 cells against the toxicity that arose from ROS and β-sheet-enriched AS fibrils.[57]

"In another study based on the generation of transgenic mouse models of AD, Li et al.,[58] investigated on EGCG (orally 20 mg/kg/day, for 3 months) capacity to interfere with Aβ deposits in different brain areas.[58] "The data concluded by immunohistochemistry pointed out that Aβ deposits decreased up to 52% in the hippocampus and 60% in the frontal cortex.[59]

Miscellaneous experiments based on population showed that drinking tea can lower the risk of cognitive impairment among the elderly. A follow-up study experiment conducted over 65 years old and older 13,645 Japanese proved that the risk of dementia could be notably reduced by green tea consumption.[60] Also, a study conducted with 278 PD patients disclosed that the progression of PD could be postponed by 7.7 years when green tea consumption was more than 3 cups a day.[61]

In conclusion, this research has demonstrated the beneficial effects of polyphenolic compounds and especially green tea polyphenols on preventing two major neurodegenerative disorders, Alzheimer's and Parkinson's diseases. Miscellaneous protective features of polyphenols regulate and mitigate ROS production-based oxidative stress generation and oxidative stress-induced complexities, such as mitochondrial dysfunction and arachidonic acid caused enzyme secretion. Thus, the oxidation of several cellular systems in Alzheimer's and Parkinson's patients might be prevented, and the advancement of these diseases decelerated. Given the importance of reducing the onset and progression of Alzheimer's and Parkinson's, additional research should be performed to establish whether there are direct relationships between diets high in various polyphenols and reduced oxidative stress.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Butterfield D, Castegna A, Pocernich C, Drake J, Scapagnini G, Calabrese V. Nutritional approaches to combat oxidative stress in Alzheimer's disease. J Nutr Biochem 2002;13:444.
2. Ignat I, Volf I, Popa VI. A critical review of methods for characterisation of polyphenolic compounds in fruits and vegetables. Food Chem 2011;126:1821-35.
3. Minatel I, Borges C, Ferreira, MI, Gomez Gomez H, Chen O, Pace G, et al. Functional Properties, Impact of Processing, and Bioavailability. In: Palma-Tenango M, Garcia-Mateos R, editors. Phenolic compounds: Biological activity. London: IntechOpen; 2017. p. 1-24.
4. Wikipedia Contributors. Polyphenol. En.wikipedia.org. 2020.
5. Ďuračková Z. Some current insights into oxidative stress. Physiol Res 2010;59:459-69.
6. Halliwell B. Oxidative stress and neurodegeneration: Where are we now? J Neurochem 2006;97:1634-58.
7. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J 2009;417:1-13.
8. Brigelius-Flohé R. Tissue-specific functions of individual glutathione peroxidases. Free Radic Biol Med 1999;27:951-65.
9. Halliwell B. Drug antioxidant effects. A basis for drug selection? Drugs 1991;42:569-605.
10. Dröge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82:47-95.
11. Lustgarten MS, Bhattacharya A, Muller FL, Jang YC, Shimizu T, Shirasawa T, et al. Complex I generated, mitochondrial matrix-directed superoxide is released from the mitochondria through voltage dependent anion channels. Biochem Biophys Res Commun 2012;422:515-21.

12. Macreadie IG, Arvanitis C, Bharadwaj P. Finding chemopreventatives to reduce amyloid beta in yeast. Neural Regen Res 2016;11:244-5.
13. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol 2001;60:759-67.
14. Bradley MA, Xiong-Fister S, Markesbery WR, Lovell MA. Elevated 4-hydroxyhexenal in Alzheimer's disease (AD) progression. Neurobiol Aging 2012;33:1034-44.
15. Lovell MA, Xie C, Markesbery WR. Acrolein is increased in Alzheimer's disease brain and is toxic to primary hippocampal cultures. Neurobiol Aging 2001;22:187-94.
16. Völkel W, Sicilia T, Pähler A, Gsell W, Tatschner T, Jellinger K, et al. Increased brain levels of 4-hydroxy-2-nonenal glutathione conjugates in severe Alzheimer's disease. Neurochem Int 2006;48:679-86.
17. Lovell MA, Xie C, Markesbery WR. Decreased glutathione transferase activity in brain and ventricular fluid in Alzheimer's disease. Neurology 1998;51:1562-6.
18. Sultana R, Butterfield DA. Oxidatively modified GST and MRP1 in Alzheimer's disease brain: Implications for accumulation of reactive lipid peroxidation products. Neurochem Res 2004;29:2215-20.
19. Cole SL, Vassar R. Linking vascular disorders and Alzheimer's disease: Potential involvement of BACE1. Neurobiol Aging 2009;30:1535-44.
20. Iadecola C. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Acta Neuropathol 2010;120:287-96.
21. Smith EE, Greenberg SM. Beta-amyloid, blood vessels, and brain function. Stroke 2009;40:2601-6.
22. Puspita L, Chung SY, Shim JW. Oxidative stress and cellular pathologies in Parkinson's disease. Mol Brain 2017;10:53.
23. Naoi M, Maruyama W. Cell death of dopamine neurons in aging and Parkinson's disease. Mech Ageing Dev 1999;111:175-88.
24. Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003;53 Suppl 3:S26-36.
25. Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER, Mizuno Y. Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease. Proc Natl Acad Sci U S A 1996;93:2696-701.
26. Floor E, Wetzel MG. Increased protein oxidation in human substantia nigra pars compacta in comparison with basal ganglia and prefrontal cortex measured with an improved dinitrophenylhydrazine assay. J Neurochem 1998;70:268-75.
27. Alam ZI, Jenner A, Daniel SE, Lees AJ, Cairns N, Marsden CD, et al. Oxidative DNA damage in the parkinsonian brain: An apparent selective increase in 8-hydroxyguanine levels in substantia nigra. J Neurochem 1997;69:1196-203.
28. Isobe C, Abe T, Terayama Y. Levels of reduced and oxidized coenzyme Q-10 and 8-hydroxy-2'-deoxyguanosine in the cerebrospinal fluid of patients with living Parkinson's disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. Neurosci Lett 2010;469:159-63.
29. Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW. Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci 2005;88:193-201.
30. Callio J, Oury TD, Chu CT. Manganese superoxide dismutase protects against 6-hydroxydopamine injury in mouse brains. J Biol Chem 2005;280:18536-42.
31. Vila M, Przedborski S. Targeting programmed cell death in neurodegenerative diseases. Nat Rev Neurosci 2003;4:365-75.
32. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 1996;20:933-56.
33. Fukushima T, Gao T, Tawara T, Hojo N, Isobe A, Yamane Y. Inhibitory effect of nicotinamide to paraquat toxicity and the reaction site on complex I. Arch Toxicol 1997;71:633-7.
34. López-Alarcón C, Denicola A. Evaluating the antioxidant capacity of natural products: A review on chemical and cellular-based assays. Anal Chim Acta 2013;763:1-10.
35. Mishra A, Kumar S, Pandey AK. Scientific validation of the medicinal efficacy of Tinospora cordifolia. ScientificWorldJournal 2013;2013:292934.
36. Mishra A, Sharma AK, Kumar S, Saxena AK, Pandey AK. Bauhinia variegata leaf extracts exhibit considerable antibacterial, antioxidant, and anticancer activities. Biomed Res Int 2013;2013:915436.
37. Du Y, Guo H, Lou H. Grape seed polyphenols protect cardiac cells from apoptosis via induction of endogenous antioxidant enzymes. J Agric Food Chem 2007;55:1695-701.
38. Perier C, Bové J, Vila M, Przedborski S. The rotenone model of Parkinson's disease. Trends Neurosci 2003;26:345-6.
39. Nagao A, Seki M, Kobayashi H. Inhibition of xanthine oxidase by flavonoids. Biosci Biotechnol Biochem 1999;63:1787-90.
40. Sarkar A, Bhaduri A. Black tea is a powerful chemopreventor of reactive oxygen and nitrogen species: Comparison with its individual catechin constituents and green tea. Biochem Biophys Res Commun 2001;284:173-8.
41. Hong J, Smith TJ, Ho CT, August DA, Yang CS. Effects of purified green and black tea polyphenols on cyclooxygenase- and lipoxygenase-dependent metabolism of arachidonic acid in human colon mucosa and colon tumor tissues. Biochem Pharmacol 2001;62:1175-83.
42. Cheon BS, Kim YH, Son KS, Chang HW, Kang SS, Kim HP. Effects of prenylated flavonoids and biflavonoids on lipopolysaccharide-induced nitric oxide production from the mouse macrophage cell line RAW 264.7. Planta Med 2000;66:596-600.
43. Gibellini L, Bianchini E, De Biasi S, Nasi M, Cossarizza A, Pinti M. Natural compounds modulating mitochondrial functions. Evid Based Complement Alternat Med 2015;2015:527209.
44. Solanki I, Parihar P, Mansuri ML, Parihar MS. Flavonoid-based therapies in the early management of neurodegenerative diseases. Adv Nutr 2015;6:64-72.

45. de Oliveira MR, Nabavi SF, Manayi A, Daglia M, Hajheydari Z, Nabavi SM. Resveratrol and the mitochondria: From triggering the intrinsic apoptotic pathway to inducing mitochondrial biogenesis, a mechanistic view. Biochim Biophys Acta 2016;1860:727-45.
46. What is Green Tea?. Art of Tea. 2020.
47. Weinreb O, Mandel S, Amit T, Youdim MB. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. J Nutr Biochem 2004;15:506-16.
48. Severino JF, Goodman BA, Kay CW, Stolze K, Tunega D, Reichenauer TG, et al. Free radicals generated during oxidation of green tea polyphenols: Electron paramagnetic resonance spectroscopy combined with density functional theory calculations. Free Radic Biol Med 2009;46:1076-88.
49. Mao X, Gu C, Chen D, Yu B, He J. Oxidative stress-induced diseases and tea polyphenols. Oncotarget 2017;8:81649-61.
50. Khan N, Mukhtar H. Tea and health: Studies in humans. Curr Pharm Des 2013;19:6141-7.
51. Ikeda M, Kodama H, Fukuda J, Shimizu Y, Murata M, Kumagai J, et al. Role of radical oxygen species in rat testicular germ cell apoptosis induced by heat stress. Biol Reprod 1999;61:393-9.
52. Shi X, Ye J, Leonard SS, Ding M, Vallyathan V, Castranova V, Rojanasakul Y, et al. Antioxidant properties of (-)-epicatechin-3-gallate and its inhibition of Cr(VI)-induced DNA damage and Cr(IV)- or TPA-stimulated NF-kappaB activation. Mol Cell Biochem 2000;206:125-32.
53. Jeong JH, Kim HJ, Lee TJ, Kim MK, Park ES, Choi BS. Epigallocatechin 3-gallate attenuates neuronal damage induced by 3-hydroxykynurenine. Toxicology 2004;195:53-60.
54. Levites Y, Youdim MB, Maor G, Mandel S. Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures. Biochem Pharmacol 2002;63:21-9.
55. Kim JS, Kim JM, O JJ, Jeon BS. Inhibition of inducible nitric oxide synthase expression and cell death by (-)-epigallocatechin-3-gallate, a green tea catechin, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. J Clin Neurosci 2010;17:1165-8.
56. Kim CY, Lee C, Park GH, Jang JH. Neuroprotective effect of epigallocatechin-3-gallate against beta-amyloid-induced oxidative and nitrosative cell death via augmentation of antioxidant defense capacity. Arch Pharm Res 2009;32:869-81.
57. Zhao J, Xu L, Liang Q, Sun Q, Chen C, Zhang Y, et al. Metal chelator EGCG attenuates Fe(III)-induced conformational transition of α-synuclein and protects AS-PC12 cells against Fe(III)-induced death. J Neurochem 2017;143:136-46.
58. Li Q, Gordon M, Tan J, Morgan D. Oral administration of green tea epigallocatechin-3-gallate (EGCG) reduces amyloid beta deposition in transgenic mouse model of Alzheimer's disease. Exp Neurol 2006;198:576.
59. Cascella M, Bimonte S, Muzio MR, Schiavone V, Cuomo A. The efficacy of Epigallocatechin-3-gallate (green tea) in the treatment of Alzheimer's disease: An overview of pre-clinical studies and translational perspectives in clinical practice. Infect Agent Cancer 2017;12:36.
60. Tomata Y, Kakizaki M, Nakaya N, Tsuboya T, Sone T, Kuriyama S, et al. Green tea consumption and the risk of incident functional disability in elderly Japanese: The Ohsaki Cohort 2006 Study. Am J Clin Nutr 2012;95:732-9.
61. Kandinov B, Giladi N, Korczyn AD. Smoking and tea consumption delay onset of Parkinson's disease. Parkinsonism Relat Disord 2009;15:41-6.