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A concise overview of the role played by Reactive Oxygen Species in Alzheimer's disease.

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Research Article

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ABSTRACT

Alzheimer's disease (AD) is a typical slow progressive neurodegenerative disease that causes dementia in the elderly. Alzheimer's pace of occurrence is rising in an alarming rate. This disease is categorized as irreversible, debilitating and is distinguishable by the gradual decline of the memory and other cognitive functions as it passes through various stages and ultimately resulting in complete incapacity. It poses a great burden on both the patient and their care takers. The two pathological trademarks of this neurodegenerative disease are aggregated beta-amyloid deposits and hyper phosphorylated neurofibrillary tangles. These lesions are capable of inducing the neuronal damage that eventually leads to cell death associated with a decline in cognitive impairments, through the evolution of reactive oxygen species (ROS). Evidences indicate that the most critical role is of Aβ metabolism in prompting the oxidative stress that has been observed in AD patients. The brain retains high levels of ascorbic acid (AA) despite a concentration gradient favouring diffusion from brain to plasma. Age-linked neurological disorders such as Alzheimer's have long been associated with free radical-induced oxidative stress and these are driven by the no homeostatic generation of reactive oxygen species (ROS). This review particularly examines the possibility of oxidative stress, defined as an imbalance between the formation and quenching of free radicals from oxygen species causing a deleterious condition as the brain cells create more ROS than they can cope up with and this is a major cause of brain cell death.

INTRODUCTION

Alzheimer's is a degenerative brain disease that generally has a later onset time, causing a person to forget recent events or familiar tasks in old age. Its rate of progression varies from individual to individual; eventually this disease leads to confusion, personality and behavioral changes and impaired judgment. Communicating with each other becomes more problematic as the disease progresses, leaving those affected struggling to search for words, accumulate thoughts or follow instructions. Eventually, most people with Alzheimer's disease become unable to care for themselves. Alzheimer's disease is characterized by blood-brain barrier disruption, oxidative stress, mitochondrial impairment, neuroinflammation, and hypometabolism; it is related to amyloid-β peptide accumulation and tau hyperphosphorylation as well as a decrease in acetylcholine levels and a reduction of cerebral blood flow. [1-13] Mutations of amyloid precursor protein or apolipoprotein E gene polymorphism appear to affect amyloid formation, which in turn causes neuronal death due to many processes including Ca2+ homeostasis disruption, oxidative stress, excitotoxicity, energy depletion, neuro- inflammation and apoptosis. [14-16]

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Oxidative stress

Oxidative stress - Oxidative stress, the immediate result of the imbalance between the production of reactive oxygen species (ROS) and intracellular antioxidant defences, is linked with the onset of neurological pathologies such as Alzheimer's disease (AD). This theory is supported by the following observations: (a) the mitochondrial dysfunction, which is likely to lead to the electron leakage in the respiratory chain resulting in accumulation of ROS; (b) the unbalanced high activity of superoxide dismutase and monoamine oxidase B which causes the production of more H2O2; (c) the alteration of iron homeostasis which, in combination with the superoxide and H2O2, gives rise to the most deleterious hydroxyl radicals; (d) the enhanced levels of lipid peroxidation and membrane alterations, that can weaken cell membranes causes ion imbalance and impair metabolism. (e) the pro-aggregating effect of ROS on beta/A4 protein and the C-terminal fragment of amyloid precursor (A4CT). [17-21] Primarily all of these changes are already present in the normal aging brain but are aggravated in AD presumably over a number of years. The process of aging is also associated with increased oxidative stress. Through pathological reactions ROS has the ability to denature biomolecules such as lipids, proteins and nucleic acids; they also are the causative agent behind tissue damage via apoptosis and necrosis. Oxidative stress plays a vital role in the pathogenesis of AD resulting in neuronal dysfunction that favours tau aggregation and cell death. Although it has been recommended that this cluster formation is a type of protection against oxidative damage, it also has been proposed that these aggregates encourages the generation of ROS. One revision suggested that the level of oxidative markers is directly linked to the severity of cognitive impairment. [22-38] Oxidative stress has the potential to influence DNA methylation which regulates gene expression. The triggering force for oxidative stress is an active area of current research. There are natural processes of aging that would likely contribute in making the brain more vulnerable to oxidative insults but other factors are necessary. [39-50]In the brain, free radicals primarily contribute to ageing and age-interlinked neurodegenerative disorders. The brain is commonly prone to oxidative damage as it utilises lots of oxygen to produce energy, contains high levels of unsaturated fatty acids, and relatively scarce amounts of antioxidants. [51]

Reactive Oxygen Species

Oxidative stress mediated by reactive oxygen species (ROS) is supposed to be one of the leading contributors to age-associated diseases, such as AD. Oxidative damage occurs early in the brain of AD patients before the commencement of plaque pathology and precedes Aβ deposition and formation of intracellular neurofibrillary tangles composed of abnormally hyper phosphorylated protein, tau.[52,53] Another degenerative process in AD involves the production of reactive oxygen species (ROS) that holds properties to damage neurons in the brain. A free radical can be termed as any species that consists of one or more unpaired electron occupying an atomic or molecular orbital by itself. The major function of these free radicals is to decrease the molecular oxygen in water that initially yields the superoxide radical, which produces hydrogen peroxide by the accumulation of an electron. [54-62] Hydrogen peroxide (H2O2) is not a free radical, but it may be considered as an oxidant. Hydrogen peroxide (H2O2) is little reactive. Its reactivity in biological systems depends on two properties one that it can diffuse long distances crossing membranes and other that it reacts with transition metals by a homolytic cleavage yielding the highly reactive hydroxyl radical (HO). Thus, tissues and organs, particularly the brain that is largely composed of easily oxidized lipids being a vulnerable organ, are affected by ROS. Because the brain, has a high oxygen consumption rate, and lacks strong antioxidant defenses, it is quite vulnerable to oxidative injury. Reactive oxygen species (ROS) can get produced either by normal and abnormal processes in humans, including atheroma, asthma, joint diseases, cancer, and aging. The most principal players specifically of this neurodegenerative disease is electron transport chain defects and reactive oxygen species (ROS) production. Appropriate management of ROS and disposal of damaged cellular components are vital for the survival and function of neurons. Certain proteins are involved in these pathways are frequently mutated in neurodegenerative diseases like Alzheimer's disease, Parkinson's disease and Huntington's disease. Many free radicals are likely involved in AD. The idea that free oxygen radicals might be involved in AD was originally based on general considerations focusing on free radical processes involved in aging and many medical conditions, particularly in cerebral pathologies. Although some antioxidants might be having properties to reduce the incidence of AD, but the magnitude of the effect may be dependent on individual factors such as genetic predisposition (e.g. apolipoprotein E genotype) and habitual behaviours. [63-65]

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Diet

The diet is another significant factor to be considered in the process of regulating this multiplex network. Diets containing high intakes of refined sugars, salt, animal-derived proteins and fats and minimal intakes of fruit and vegetables are associated with a greater risk of developing AD. Foodstuffs that definitely protect against AD include fruits, vegetables, grains, low-fat dairy products, legumes, and fish, whereas risk factors include meat, sweets, and high-fat dairy products. These evidences can be drawn from ecological and observational research as well as studies of the mechanisms whereby dietary factors affect risk. Various numbers of nutrients can serve as antioxidants. [66-69] Amongst them the most well-known include vitamin C, vitamin E, beta-carotene and other associated carotenoids, flavonoids, phenols. The mechanism that links dietary risk factors to AD are hardly known and includes increased oxidative stress from metal ions such as copper as well as from advanced glycation end products related with high-temperature cooking, increased homocysteine concentrations. Medical associated risk factors for AD include traumatic brain injury, stroke, acute hypertension, diabetes mellitus, hypercholesterolemia.[70-76] It is nowadays predicted that environmental and lifestyle-related risk factors that are also responsible for AD include aluminium exposure, smoking, high calorie intake, lack of exercise, and lack of intellectual activities.

CONCLUSION

Active involvement of reactive oxygen species (ROS) in a variety of pathological and physiological processes has fascinated the researchers and they are growing interest in studying the mechanisms. Actually, identification of this global signalling system has provided new understandings into underlying pathophysiological mechanism of Alzheimer's disease (AD). Specially, to counteract the effects of oxidative stress in Alzheimer's, therapeutic strategies involving AGE inhibitors and anti-inflammatory antioxidants looks like to be most promising therapy. It has been well established that oxidative damage of cellular molecules plays a vital role in neurodegenerative disorders. Oxidative damage is not just distinctly a by-product or end product of neuronal degenerative processes but can be assumed to be more likely the direct initiation factor in neurodegeneration.[77-88] Irrespective of the current scope of knowledge, there is much uncertainty regarding the probability of success with antioxidant therapy in AD. Attempts to fight oxidative stress have included the use of the well-known 'one shot' antioxidants (primarily vitamin C, cysteine derivatives) and anti-inflammatory inhibitors of ROS-forming enzymes that blocks the production of ROS (e.g. rofecoxib, and naproxen).[89-100]

REFERENCES

1. Mendiola-Precoma J, et al. therapies for prevention and treatment of Alzheimer's disease. biomed res int. 2016.
2. Cacabelos R. the complexity of Alzheimer's disease Pharmacogenomics and Metabolomics in Drug Development.Metabolomics. 2016;6:e145.
3. Melamed I. Alzheimer's disease of the Immune System: a new variant of immune deficiency. immunother open acc. 2016;2:115.
4. Wu Y, et al. observation study of the retina with the Alzheimer's disease or amnestic mild cognitive impairment patients. J Clin Exp Ophthalmol.2016;7:545.
5. Cacabelos R. Epigenetics of brain disorders: the paradigm of Alzheimer's disease. J Alzheimers Dis Parkinsonism. 2016;6:229.
6. Dessouky MM and Elrashidy MA. feature extraction of the Alzheimer's disease images using different optimization algorithms. J Alzheimers Dis Parkinsonism. 2016;6:230.
7. Cifuentes D, et.al. targeting hypertension to manage Alzheimer's disease: rational and promise. J Alzheimers Dis Parkinsonism. 2016;6:228.
8. Bambo MP, et al. retinal and optic disc alterations in Alzheimer's disease: the eye as a potential central nervous system window. J Alzheimers Dis Parkinsonism. 2016;6:223.
9. Sourdet S, et al. effectiveness of a specific care plan in Alzheimer's disease in the oldest old. J Alzheimers Dis Parkinsonism. 2015;5:194.
10. Kaliman P. the value of exercise training for prevention and complementary treatment of brain aging and neurodegeneration. J Yoga Phys Ther. 2014;4:152.
11. Carman A, et al. Chaperone-dependent Neurodegeneration: a molecular perspective on therapeutic intervention. J Alzheimers Dis Parkinsonism. 2013;S10:007.
12. Singh A. neurodegeneration - a means to an end. J Cell Sci Ther. 2012;3:e107.
13. Jhala DD, et al. optimization and validation of an in vitro blood brain barrier permeability assay using artificial lipid membrane. J Bioequiv Availab.2012;S14:009.

e-ISSN: 2319-9865
p-ISSN: 2322-0104

14. Iuliano L, et al. Antioxidants and cognitive function: misleading concepts and new strategies. J Alzheimers Dis Parkinsonism. 2012;2:e125.
15. Gu Z, et al. Apolipoprotein E mimetic promotes functional and histological recovery in Lysolecithin-Induced Spinal Cord Demyelination in mice. J Neurol Neurophysiol. 2014;S12:S12-010.
16. Kivipelto M, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002
17. Benzi G and Moretti A, are Reactive Oxygen Species involved in Alzheimer's disease? Neurobiol Aging. 1995;16(4):661-74.
18. Caldeira GL, et al. impaired transcription in Alzheimer's disease: key role in mitochondrial dysfunction and Oxidative Stress. J Alzheimers Dis. 2013;34:115-131.
19. Fleming JL, et al. the role for Oxidative Stress in aberrant DNA methylation in Alzheimer's disease. Curr Alzheimer Res. 2012;9:1077-1096.
20. Venkateshappa C, et al. elevated Oxidative Stress and decreased antioxidant function in the human hippocampus and frontal cortex with increasing age: implications for neurodegeneration in Alzheimer's disease. Neurochem Res. 2012;37:1601-1614.
21. Mohsenzadegan M and Mirshafiey A. the immunopathogenic role of Reactive Oxygen Species in Alzheimer disease. Iran J Allergy Asthma Immunol. 2012;(3):203-16.
22. Kim K, et al. a comparison of three types of trail making test in the korean elderly: higher completion rate of trail making test-black and white for mild cognitive impairment. J Alzheimers Dis Parkinsonism. 2016;6:239.
23. Wu Y, et al. observation study of the retina with the Alzheimer's Disease or amnestic mild cognitive impairment patients. J Clin Exp Ophthalmol. 2016;7:545.
24. Zhou B, et al. Shanghai Cohort Study on mild cognitive impairment: study design and baseline characteristics. J Alzheimers Dis Parkinsonism. 2016;6:224.
25. Shinno H, et al. alterations in Rapid Eye Movement Sleep parameters predict for subsequent progression from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis Parkinsonism. 2016;6:218.
26. Nakaya M. cognitive impairment in Bipolar Disorder: comparison with cognitive impairment in Schizophrenia. Bipolar Disord. 2016;2:106.
27. Rima R. A Cohort study of cognitive impairment in patients of Multiple Sclerosis. J Mult Scler. 2015;2:161.
28. Cintra MTG,et al. p300 evoked potential and risk of mild cognitive impairment progression to Alzheimer's Dementia: A Literature Review. J Neurol Neurophysiol. 2015;6:322.
29. Luo P and Guo L. HCN Channels: from the role in Chronic Cerebral Hypoperfusion-Induced Cognitive Impairments to a new therapeutic target for Vascular Dementia. J Neurol Neurophysiol. 2015;6:308.
30. Zirnheld AL, et al. target genes of circulating mir-34c as Plasma Protein Biomarkers of Alzheimer's Disease and mild cognitive impairment. Aging Sci. 2015;3:140.
31. Khan F. mild cognitive impairment (mci) or normal ageing!. J Gerontol Geriatr Res. 2015;4:235.
32. Kim H, et al. differences in C-reactive Protein Level in patients with Alzheimer's disease and mild cognitive impairment. J Psychiatry. 2015;18:194.
33. Shin HW, et al. differences in BDNF Serum Levels in patients with Alzheimer's Disease and mild cognitive impairment. J Psychiatry. 2015;18:245
34. Kim H, et al. a voxel-based Morphometry Study in Alzheimer's disease and mild cognitive impairment. J Psychiatry. 2015;18:237.
35. Neugroschl J, et al. why they stay: understanding research participant retention in studies of aging, cognitive impairment and Dementia. J Gerontol Geriat Res. 2014;3:170.
36. Grandy JK. Melatonin: therapeutic intervention in mild cognitive impairment and Alzheimer disease. J Neurol Neurophysiol. 2013;4:148.
37. Curiel RE, et al. a new scale for the evaluation of Proactive and Retroactive interference in mild cognitive impairment and early Alzheimer's disease. Aging Sci. 2013;1:102.
38. Daulatzai MA. Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications. J Mol Genet Med. 2014;S1:005.
39. Vadakedath S and Kandi V. DNA methylation and its effect on various Cancers: An Overview. J Mol Biomark Diagn. 2016;S2:017.
40. Zhang H, et al. the effects of DNA methylation on the expression of Non-imprinted Genes in rice. J Rice Res. 2016;4:168.
41. Kaut O, et al. DNA methylation of Imprinted Loci on Autosomal Chromosomes and IGF2 are not affected in Parkinson's Disease patients Peripheral Blood Monocytes. Brain Disord Ther. 2016;5:211.
42. Gu N, et al. the special DNA Methylation status in the promoter of IL-12B in Psoriatic Epidermis. J Clin Exp Dermatol Res. 2016;7:341.
43. Dawood M and Efferth T. Medicinal Plants and DNA Methylation of Cancer. Med Aromat Plants. 2015;4:e161.

e-ISSN: 2319-9865
p-ISSN: 2322-0104

44. Teschler S, et al. Aberrant DNA Methylation of Ribosomal RNA Genes in Human Cancer. Mol Biol. 2015;4:128.
45. Wang Y, et al. altered expression and DNA methylation profiles of ercc6 gene in Lens Tissue from Age-Related Cortical Cataract. J Clin Exp Ophthalmol.2015;6:392
46. Su J, et al. advances in Bioinformatics Tools for High-Throughput Sequencing Data of DNA Methylation. Hereditary Genet. 2012;1:107.
47. Szilagyi K, et al. exploring DNA methylation of MYLK as a contributor to Acute Respiratory Distress Syndrome Disparities. J Pulm Respir Med.2013;3:e127.
48. Liu J, et al. Liquid Chromatography Tandem Mass Spectrometry for the measurement of global DNA methylation and hydroxymethylation. J Proteomics Bioinform. 2013;S2:005.
49. Leo E and Martinelli G. DNA methylation in Chronic Myeloid Leukemia. J Mol Genet Med. 2014;08:118.
50. Gigek CO, et al. SIRT1, IGFBP-3 and CAV1 Promoter DNA methylation in aging . Transl Med (Sunnyvale). 2014;4:133.
51. Patten DA, et al. Reactive oxygen species: stuck in the middle of neurodegeneration. J Alzheimers Dis. 2010;20 Suppl 2:S357-67.
52. Smith MA, et al. iron accumulation in Alzheimer disease is a source of redox-generated free radicals. Proc Natl Acad Sci USA. 1997;94:9866–8.
53. Leibson CL, et al. risk of Dementia among persons with Diabetes Mellitus: A population-based cohort study. Am J Epidemiol 1997.
54. Sinha BK. roles of Free Radicals in the toxicity of Environmental Pollutants and Toxicants. J Clinic Toxicol. 2013;S13:e001.
55. Butnariu M and Samfira I. Free Radicals and Oxidative Stress. J Bioequiv Availab. 2012;4: iv-vi.
56. Butnariu M. action and protection mechanisms of Free Radicals. J Pharmacogenomics Pharmacoproteomics. 2012;3:e129.
57. Niknam M, et al. anti- inflammatory effects of Dietary Antioxidants in patients with Coronary Artery Disease. Endocrinol Metab Syndr. 2015;4:207.
58. Garcia-Sierra F. commentary on Ubiquitin is associated with early truncation of Tau Protein at Aspartic Acid 421 during the maturation of Neurofibrillary Tangles in Alzheimer Disease . J Med Surg Pathol. 2016;1:121.
59. Paris D, et al. Anatabine attenuates Tau Phosphorylation and Oligomerization in P301S Tau Transgenic mice. Brain Disord Ther. 2014;3:126.
60. Guo Z, et al. head injury and the risk of AD in the MIRAGE study. Neurology 2000.
61. Hartman D. Free radical theory of aging: Alzheimer's disease pathogenesis. Age 1995;18:97–119.
62. Halliwell B. Free radicals in biology and medicine. Oxford, United Kingdom: Oxford University Press, 1989.
63. Lee SJ. a different role of Metallothionein-3 (Mt3) in Oxidative Stress and Neurodegeneration of Brain. J Neuroinfect Dis. 2016;7:221.
64. Sahib AS, et al. effects of Oral Antioxidants on lesion counts associated with Oxidative Stress and inflammation in patients with Papulopustular Acne. J Clin Exp Dermatol Res. 2012;3:163.
65. Da Silva NMO, et al. Oxidative Stress: a comparison of different groups of patients with Hepatitis-C in Hemodialysis Units. Kidney Disord Clin Pract. 2015;1:104.
66. Seshadri S, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002.
67. Honig LS, et al. Stroke and the risk of Alzheimer disease. Arch Neurol 2003.
68. Ott A, et al. smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam Study. Lancet 1998.
69. Cemile MS and Çigdem E. the effects of Oxidative Stress and some of the popular antioxidants on reproductive system: a mini review. J Nutr Food Sci. 2016;6:464.
70. Eken ZE. Antioxidants. Pigmentary Disorders. 2015;2:163.
71. Neeti Sharma. Free Radicals, Antioxidants and Disease. Biol Med. 2014;6:214.
72. Rondeau V and Dartigues JF. relation between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study. Am J Epidemiol 2000.
73. Luchsinger JA, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002.
74. Singh S and Immanuel G. extraction of antioxidants from fruit peels and its utilization in paneer. J Food Process Technol. 2014;5:349.
75. Elansary HO. natural antioxidants and their role against human Cancer. J Plant Biochem Physiol. 2014;2:e125.
76. Aditi ,et al. an insight in to the pathogenesis of Diabetic Vascular Diseases: Role of Oxidative Stress and Antioxidants. Pharmaceut Anal Acta. 2013;4:273.
77. Friedland RP. patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci USA 2001.

e-ISSN: 2319-9865
p-ISSN: 2322-0104

78. Archer T. amelioration of symptoms and Biomarkers of Alzheimers disease by physical exercise. Open access. 2016;2:e105.
79. Woods JJ, et al. cigarette smoking: a causal factor for Alzheimers disease? JGerontol Geriatr Res. 2016; 5:286.
80. Zerovnik E, et al. recent developments in treating Alzheimer's disease. J Alzheimers Dis Parkinsonism. 2016;6:220.
81. Nunes-Silva A and Freitas-Lima LC. the association between physical exercise and Reactive Oxygen Species (ROS) Production. J Sports Med Doping Stud. 2015;5:152.
82. Miller MD and Morycz RK. preparing for the rise in Alzheimers disease cases: a proposal for training support personnel. J Gerontol Geriatr Res. 2015;4:195.
83. Voziyan PA and Yazlovitskaya EM. Reactive Oxygen Species. J Bioequiv Availab. 2014;6:e57.
84. Niwano Y. how to regulate Reactive Oxygen Species? J Biomol Res Ther. 2014;3:e130.
85. Yadav R, et al. rise and fall of Reactive Oxygen Species (ROS): implications in aging and Neurodegenerative Disorders. Cell Dev Biol. 2013;2:e122.
86. Bajic V, et al. Cyclin Dependent Kinase 11, Neuroinflammation and Alzheimer's Disease: A Review. J Clin Cell Immunol. 2015;6:305.
87. Rosales–Corral S, et al. Cannabinoids in Neuroinflammation, Oxidative Stress and Neuro Excitotoxicity. Pharm Anal Acta. 2015;6:346.
88. Daulatzai MA. Obesity and Gut's Dysbiosis promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: new directions and therapeutic implications. J Mol Genet Med. 2014;S1:005.
89. Mohammad FK and Ridwan BR. medium effect on Solvation Free Energy, Dipole Moment and Molecular Reactivity of Naproxen. J Theor Comput Sci. 2015;2:134.
90. Kundu SP, et al. the study of Analgesic activity of complexes of Magnesium Sulfate with Aspirin, Paracetamol and Naproxen. Clin Pharmacol Biopharm. 2015;4:143.
91. Rajurkar VG, et al. Topical anti-inflammatory gels of Naproxen entrapped in Eudragit based Microsponge delivery system. J Adv Chem Eng. 2015;5:122.
92. Amran S, et al. the Pharmacokinetic study of Aspirin, Paracetamol and Naproxen with Magnesium Sulfate. Pharm Anal Acta. 2015;6:372.
93. Maheswari PD, et al. Micellar Solubilization in the formulation development of poorly soluble Naproxen. Pharmaceut Reg Affairs. 2013;2:108.
94. Rothman KJ and Lanza LL.. estimated risks of fatal events associated with Acetaminophen, Ibuprofen, and Naproxen Sodium used for analgesia. Adv Pharmacoepidem Drug Safety. 2013;2:124.
95. Silva Solon LG, et al. Comparative Bioavailability of a Generic and Two Compounded Naproxen Sodium suspensions administered to rats. J Bioanal Biomed. 2010;2:048-054.
96. Setiawati E, et al. Bioequivalence study with two Naproxen Sodium Tablet formulations in healthy subjects. J Bioequiv Availab. 2009;1:028-033.
97. Reddy YR, et al. rapid simultaneous determination of Sumatriptan Succinate and Naproxen Sodium in combined tablets by validated Ultra Performance Liquid Chromatographic Method. J Anal Bioanal Tech. 2011; 2:121.
98. Abid MR and Sellke FW. antioxidant therapy: is it your gateway to improved cardiovascular health?. Pharm Anal Acta. 2015;6:323.
99. Robles L, et al. role of Oxidative Stress in the pathogenesis of pancreatitis: effect of antioxidant therapy. Pancreatic Dis Ther. 2013;3:112.
100. Azu OO. the male genital tract in the era of highly active antiretroviral therapy (haart): implication for antioxidant therapy. J AIDS Clinic Res. 2012;3:169.