IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2021 Vol.:21, Issue:4

Role of Antioxidants in Oxidative Stress Associated Diseases

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Diksha Mehta[1], Kapil Kumar Verma[1], Kalpana Thakur[1], Amit Chaudhary[1]*

[1]School of Pharmacy, Abhilashi University, Chail Chowk, Mandi, Himchal Pradesh-175028 India.

Submitted: 21 June 2021
Accepted: 27 June 2021
Published: 30 July 2021

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Free radicals, Antioxidant, Cellular damage, Oxidative Stress

ABSTRACT

Free radicals are one or more unpaired electrons containing reactive molecules, which can damage nucleic acids, proteins, carbohydrates, and lipids, leading to several diseases including early aging, cancer and atherosclerosis. Free radicals generated due to exposure of radiation, environmental pollutants and as by-products of metabolised drugs. Antioxidants can antagonize these free radicals to prevent cellular damage by ultimately reducing oxidative stress and thus have a beneficial effect on human health. Antioxidants are substances which inhibit oxidation. An Antioxidant reduces the occurrence of different disorders like: aging, cancer, diabetes, inflammation, liver disease, cardiovascular disease, cataract and nephrotoxicity and neurodegenerative disorders. Dietary antioxidants are deliberation to have possible capacities to turn aside oxidative induced diseases.

INTRODUCTION

Antioxidants are molecules that can reduce and neutralize reactive oxygen species (ROS), which are generated by a variety of chemical and biochemical processes.[1] Oxidative stress is linked to enlarged inception of free radicals or else due to decrease in concentration of antioxidant. It shows a disruption in the steadiness of pro-oxidant and antioxidant molecules. [2] Free radicals, i.e. reactive oxygen species (ROS) are involved in the pathogenesis of a number of processes mainly including carcinogenesis, cardiovascular disease, ischemia, Alzheimer's disease, early aging, arteriosclerosis, liver injury, inflammation, diabetes mellitus, skin damages, and arthritis. [3] Free radical could be any atom or molecule (e.g. oxygen, nitrogen) with at least one unpaired electron in the outermost shell, which may exist independently. A free radical is formed when a covalent bond between two entities is destroyed and one electron remains with each newly formed atom. Free radicals are extremely reactive due to the presence of unpaired electron(s).

Two types of free radicals; reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generally involved in human physiology [4]. ROS plays dual behaviour, as at higher concentration it is harmful to biological system while moderate amount shows valuable effect like guard against infection. [2] ROS can also break down the peptide chains, oxidize few amino acids and bring lipid peroxidation by disturbing the biological membrane [5]. ROS can oxidize DNA bases and cause DNA strand breakages, which can lead to mutations. ROS also play vital roles in the promotion and progression of cancer and other diseases. [6,7] Oxidation reaction is vital to life as they are supportive in retaining the composite system of our body and it can be destructive also. Generally, oxidation is a process to change a chemical substance, which produces free radicals (highly reactive) leading to numeral chain reactions which may destruct cells. A number of abiotic stress cause abundance of Reactive Oxygen Species (ROS) and damages the tissue which results in various diseases including heart disease, liver disease, cancer, neurodegenerative disease and aging [8].

Antioxidants may potentially slow down or prevent the oxidation of other molecules. In oxidation reaction, an electron is transferred from a substance to the oxidizing agent. Thus, oxidation reaction can generate free radicals, which start chain reactions to damage the cells. Antioxidants terminate these chain reactions by eliminating or stabilizing free radicals and obstruct other oxidation reactions by self-oxidation [3]. Antioxidant systems exist in the cells

to protect them against ROS. Cellular aqueous compartments like cytosol or extracellular fluids consist of low molecular weight antioxidants e.g. glutathione and ascorbate (vitamin C) along with some antioxidant enzymes namely: superoxide dismutases (SOD), catalases and peroxidases to prevent oxidative cell damage [9].

Oxidative Stress Associated Diseases

Cardiovascular diseases

Cardiovascular diseases (CVDs) are considered as the major reason for mortality and morbidity worldwide. Substantial evidence suggests that increased oxidative stress plays a significant role in the pathogenesis of CVDs, including atherosclerosis, hypertension, vascular endothelial dysfunction and ischemic heart disease. Cellular oxidative stress results in the release of toxic free radicals by endothelial cells and vascular smooth muscle cells that interact with cell components such as protein, DNA or lipid resulting in cardiovascular pathology. Silymarin has antioxidant activities against CVDs and offers protection against oxidative stress-induced hypertension, atherosclerosis and cardiac toxicity [10].

Alzheimer's disease

Oxidative stress was initially proposed to be a major factor in AD in 1986. Since then many other researchers have found that oxidative stress is implicated in AD in various stages of the disease. Overwhelming evidence exists that the cells in the Alzheimer's brain undergo abnormally high levels of oxidative stress and that amyloid plaques are a focus of cellular and molecular oxidation. Oxidative stress is perhaps not the primary aetiology of AD; however, it precedes specific cellular and tissue damage, which underlies the onset of this disease [11]. Since 1994 various studies have established that oxidative stress is present in dying neurons and not just in (Aβ) deposits. Since oxidative stress is thought to play an important role in AD it follows that antioxidants may provide a useful therapy in the disease [12].

Inflammatory bowel disease

The global incidence of inflammatory bowel disease (IBD), a group of chronic gastrointestinal disorders, has been rising. The preponderance of evidence demonstrates that oxidative stress (OS) performs a critical function in the onset of IBD and the manner of its development. The purpose of this review is to outline the generation of reactive oxygen species and antioxidant defense mechanisms in the gastrointestinal tract and the role played

by OS in marking the onset and development of IBD. Furthermore, the various ways through which OS is related to genetic susceptibility and the mucosal immune response. The experimental results suggest that certain therapeutic regimens for IBD could have a favorable impact by scavenging free radicals, reducing cytokine and prooxidative enzyme concentrations, and improving the antioxidative capabilities of cells. However, antioxidative activity characterized by a high level of specificity may be fundamental for the development of clinical therapies and for relapsing IBD patients. Therefore, additional research is required to clarify the ways through which OS is related to the pathogenesis and progression of IBD [13].

Atherosclerosis

Atherosclerosis is now considered a chronic inflammatory disease. Oxidative stress induced by generation of excess reactive oxygen species has emerged as a critical, final common mechanism in atherosclerosis. Reactive oxygen species (ROS) are a group of small reactive molecules that play critical roles in the regulation of various cell functions and biological processes. Although essential for vascular homeostasis, uncontrolled production of ROS is implicated in vascular injury. Endogenous anti-oxidants function as checkpoints to avoid these untoward consequences of ROS, and an imbalance in the oxidant/anti-oxidant mechanisms lead to a state of oxidative stress. The role of ROS and antioxidant mechanisms in the development and progression of atherosclerosis, the role of oxidized low-density lipoprotein cholesterol, and highlight potential anti-oxidant therapeutic strategies relevant to atherosclerosis. There is growing evidence on how traditional risk factors translate into oxidative stress and contribute to atherosclerosis. Clinical trials evaluating anti-oxidant supplements had failed to improve atherosclerosis. Current studies focus on newer ROS scavengers that specifically target mitochondrial ROS, newer nanotechnology-based drug delivery systems, gene therapies, and anti-miRNAs. Synthetic LOX-1modulators that inhibit the effects of Ox-LDL are currently in development. Research over the past few decades has led to identification of multiple ROS generating systems that could potentially be modulated in atherosclerosis. Therapeutic approaches currently being used for atheroslcerotic vascular disease such as aspirin, statins, and renin-angiotensin system inhibitors exert a pleiotropic antioxidative effects. There is ongoing research to identify novel therapeutic modalities to selectively target oxidative stress in atherosclerosis [14].

Diabetic kidney disease

Diabetes Mellitus (DM) remains one of the most challenging global epidemics of the twenty first century. More than 350 million people worldwide are estimated to be affected by this metabolic disorder [15]. Diabetic kidney disease (DKD) currently ranks as the first cause of endstage kidney disease (ESKD), accounting for approximately 50% of cases in the developed world [16]. As many as 50% of individuals with longtime DM usually develop some degree of renal damage during their lifetime [17]. Progressive impairment in renal function is associated with an increased risk of cardiovascular events and hospitalizations, particularly in ESKD patients needing chronic renal replacement therapy by dialysis or kidney transplantation. Current strategies available for slowing-down DKD progression largely failed to achieve stable results in the long term. Alternative or additive approaches for maximizing reno-protection are thus eagerly advocated [18]. It is nowadays well recognized that oxidative stress plays a major role in the genesis and worsening of DKD [19]. A persistent state of hyperglycemia and the increase in advanced glycation end products (AGEs) elicit the generation of reactive oxygen species (ROS) which, in turn, enhance chronic inflammation and glomerular and tubular hypertrophy, eventually impairing overall renal function. Sparse evidence has now accrued indicating that antioxidant supplements may bring significant benefits to DKD patients, including the reduction of urinary albumin and total protein excretion and the normalization of glomerular filtration rate [20]. This raises the question as to whether such supplements should be systematically recommended for improving reno-protection in diabetic patients, particularly with early signs of renal damage.

Infertility

Infertility is a global health problem and it is one of the most stressful conditions amongst married couples. Even though not lethal, it has been described as a radical life changing problem that carries with it significant psychological trauma. Infertility can be caused by various problems and sometimes it is not possible to establish a cause. Oxidative stress, which arises from an imbalance between reactive oxygen species (ROS) and protective antioxidants, influences the entire reproductive lifespan of men and women. ROS can modulate cellular functions, and oxidative stress can disturb the intracellular milieu, resulting in diseased cells or endanger cell survival. Under normal conditions, antioxidants act to oppose ROS production, scavenging existing free radicals and promoting the repair of ROS-induced damage to cell structures. At controlled levels, oxidative stress facilitates some

physiological reproductive functions but at higher levels it is implicated in pathological processes in the reproductive tract that contribute to infertility and poor pregnancy outcomes. As high levels of reactive oxygen species and low antioxidant status have been implicated in conditions contributing to infertility, treatment based on strategies to boost the exhausted antioxidant defense of the reproductive microenvironment is intuitive. Glutathione is a natural body antioxidant, which helps preserve all other antioxidants. It is present in both the male and female gametes and its level varies widely. The role oxidative stress plays in both male and female infertility, and the antioxidant action of glutathione on infertility [21].

Cancer

Extensive research over the past half a century indicates that reactive oxygen species (ROS) play an important role in cancer. Although low levels of ROS can be beneficial, excessive accumulation can promote cancer. One characteristic of cancer cells that distinguishes them from normal cells is their ability to produce increased numbers of ROS and their increased dependence on an antioxidant defense system. ROS are produced as a byproduct intracellularly by mitochondria and other cellular elements and exogenously by pollutants, tobacco, smoke, drugs, xenobiotics, and radiation. ROS modulate various cell signaling pathways, which are primarily mediated through the transcription factors NF-κB and STAT3, hypoxia-inducible factor-1α, kinases, growth factors, cytokines and other proteins, and enzymes; these pathways have been linked to cellular transformation, inflammation, tumor survival, proliferation, invasion, angiogenesis, and metastasis of cancer. ROS are also associated with epigenetic changes in genes, which is helpful in diagnosing diseases. Numerous studies from preclinical and clinical models have indicated that antioxidants are helpful in reducing cancer risk [22].

Inflammation

Inflammation is a comprehensive array of physiological response to a foreign organism, including human pathogens, dust particles, and viruses. Inflammations are mainly divided into acute and chronic inflammation depending on various inflammatory processes and cellular mechanisms. Recent investigations have clarified that inflammation is a major factor for the progression of various chronic diseases/disorders, including diabetes, cancer, cardiovascular diseases, eye disorders, arthritis, obesity, autoimmune diseases, and inflammatory bowel disease. Free radical productions from different biological and environmental sources are due to an imbalance of natural antioxidants which further leads to

various inflammatory associated diseases. In this review article, we have outlined the inflammatory process and its cellular mechanisms involved in the progression of various chronic modern human diseases. In addition, we have discussed the role of free radicals-induced tissue damage, antioxidant defence, and molecular mechanisms in chronic inflammatory diseases/disorders. The systematic knowledge regarding the role of inflammation and its associated adverse effects can provide a clear understanding in the development of innovative therapeutic targets from natural sources that are intended for suppression of various chronic inflammations associated diseases [23].

Neurodegenerative diseases

The pathophysiologies of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD), are far from being fully explained. Oxidative stress (OS) has been proposed as one factor that plays a potential role in the pathogenesis of neurodegenerative disorders. Clinical and preclinical studies indicate that neurodegenerative diseases are characterized by higher levels of OS biomarkers and by lower levels of antioxidant defense biomarkers in the brain and peripheral tissues. In this article, we review the current knowledge regarding the involvement of OS in neurodegenerative diseases, based on clinical trials and animal studies. In addition, we analyze the effects of the drug-induced modulation of oxidative balance, and we explore pharmacotherapeutic strategies for OS reduction [24-26].

Liver disorders

Liver is a major organ attacked by ROS [Sánchez-Valle et al., 2012]. Parenchymal cells are primary cells subjected to oxidative stress induced injury in the liver. The mitochondrion, microsomes and peroxisomes in parenchymal cells can produce ROS, regulating on PPAR gamma, which is mainly related to the liver fatty acid oxidation gene expression. The oxidative stress not only triggers hepatic damage by inducing irretrievable alteration of lipids, proteins and DNA contents and more importantly, modulating pathways that control normal biological functions. [27] A complex antioxidant system has been developed in mammals to relieve oxidative stress. However, excessive reactive species derived from oxygen and nitrogen may still lead to oxidative damage to tissue and organs. Oxidative stress has been considered as a conjoint pathological mechanism, and it contributes to initiation and progression of liver injury. A lot of risk factors, including alcohol, drugs, environmental pollutants and irradiation, may induce oxidative stress in liver, which in turn results in severe

liver diseases, such as alcoholic liver disease and non-alcoholic steatohepatitis. Application of antioxidants signifies a rational curative strategy to prevent and cure liver diseases involving oxidative stress. Although conclusions drawn from clinical studies remain uncertain, animal studies have revealed the promising in vivo therapeutic effect of antioxidants on liver diseases. Natural antioxidants contained in edible or medicinal plants often possess strong antioxidant and free radical scavenging abilities as well as anti-inflammatory action, which are also supposed to be the basis of other bioactivities and health benefits [28].

Aging

Aging is commonly related to functional decline of the organism and progressive deleterious alterations leading to increased risk of disease and death with advancing age [29]. Aging also presents motor and cognitive deficits. Free radicals and oxidative stress have been considered as important factors in the biology of aging and in many age-associated degenerative diseases since the antioxidant systems are under deterioration during aging [30]. Antioxidant phytochemicals have the potential to fight against aging and its related disorders. For example, coffee, which contains high levels of antioxidant phytochemicals, reduced both motor and cognitive deficits in aged rats [31], and methanol extract of Elaeis guineensis leaves with high antioxidant activities also showed potential ability as an anti-aging agent [32]. In addition, antioxidant phytochemicals showed anti-ageing activities by different mechanisms. For example, epigallocatechin gallate (EGCG) extended lifespan of healthy rats by reducing the damage of liver and kidney and improving age-associated inflammation and oxidative stress through inhibiting NF-_B signaling [33], and tetrahydroxystilbene glucoside showed protective effect against the D-galactose-induced aging process by regulating Klotho gene in mice [34].

Skin Diseases

Oxidative stress plays an important role in the development of numerous cutaneous diseases via various redox-sensitive pathways; conflicting results have been reported regarding the oxidant/antioxidant states in these diseases. This discordance can be explained by the following: (1) the innate levels in different tissue samples differ; (2) ROS can affect different complex signaling and biochemical pathways; and (3) oxidative stress can be the result of inflammation, not the cause. The efficacy of antioxidative treatments remain still elusive. But there have been many reports about effective antioxidant treatment for cutaneous disease, as

well as conventional drugs that have antioxidant activity. Targeting oxidative stress may be an effective strategy for various skin diseases; thus, further studies are required to establish a framework for antioxidative therapeutic plans for each disease [35].

Role of Antioxidants

Antioxidant molecules prevent oxidation of body metabolites. Oxidation promotes transfer of electrons or hydrogen to oxidants, predominantly to oxygen. Oxidation generates free radicals. These jump-start a chain of events that compromise the cells. Antioxidants block these chain reactions by removing the reactive oxygen species (ROS). ROS are believed to cause or aggravate several human pathologic processes such as heart disease, stroke, cancer, neurodegenerative diseases and many other disorders. As part of their adaptation from marine life, terrestrial plants began producing antioxidants such as ascorbic acid, polyphenols, tocopherols and innumerable other antioxidants. [36] Antioxidants, such as *tert*-butyl-4-hydroxyanisol, 3,5-di*tert*- butyl-4-hydroxytoluol, members of the vitamin E family, ascorbic acid, and citric acid, are frequently used food additives. They protect items which are susceptible to oxidative degradation and prevent them from a premature loss of quality. Their efficiency, even at dosages of 0.1% or lower, has been proven since a long time [37, 38] and explained by either. Scavenging of free radicals (phenols may donate a hydrogen atom to a fatty acid radical, forming a reconstituted fatty acid and a more stable phenol radical, thus breaking the chain reaction), low redox potential (sacrificing themselves in favor of other, less easily oxidized food constituents) or complexing of catalytic trace metal ions (which would otherwise accelerate lipid oxidation by facilitating electron transfer reactions). Supported by advances in high-performance liquid chromatography coupled to mass spectrometric techniques and rapid bioassays, such as ORAC (oxygen radical absorbance capacity), a wealth of compounds with anti-oxidative properties has been detected and identified in foods including fruits, vegetables, oilseeds, nuts, teas, cocoa, coffee, spices, meat, and cereals [39]. Starting in the late 1990s food producers have transformed this knowledge into the idea that antioxidants in food could also protect sensitive constituents of human cells from oxidation, thereby obviating severe diseases, such as atherosclerosis, cancer, and cataract [40].

REFERENCES

1. Yang CS, Ho CT, Zhang J, Wan X, Zhang K, Lim J. Antioxidants: Differing meanings in food science and health science. Journal of agricultural and food chemistry. 2018 Mar 10;66(12):3063-8.

2. Husain N, Kumar A. Reactive oxygen species and natural antioxidants: a review. Adv Biores. 2012;3(4):164-75.
3. Valentao P, Fernandes E, Carvalho F, Andrade PB, Seabra RM, de Lourdes Bastos M. Antioxidant activity of Hypericum androsaemum infusion: scavenging activity against superoxide radical, hydroxyl radical and hypochlorous acid. Biological and Pharmaceutical Bulletin. 2002;25(10):1320-3.
4. Bhattacharya S. Reactive oxygen species and cellular defense system. InFree radicals in human health and disease 2015; 17-29.
5. Firuzi O, Miri R, Tavakkoli M, Saso L. Antioxidant therapy: current status and future prospects. Current medicinal chemistry. 2011 Sep 1;18(25):3871-88.
6. Siti, H. N.; Kamisah, Y.; Kamsiah, J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vasc. Pharmacol. 2015, 71, 40−56.
7. Yang, C. S.; Chen, J. X.; Wang, H.; Lim, J. Lessons learned from cancer prevention studies with nutrients and non-nutritive dietary constituents. Mol. Nutr. Food Res. 2016, 60 (6), 1239−1250.
8. Kim GH, Kim JE, Rhie SJ, Yoon S. The role of oxidative stress in neurodegenerative diseases. Experimental neurobiology. 2015 Dec;24(4):325.
9. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. European journal of medicinal chemistry. 2015 Jun 5;97:55-74.
10. Taleb A, Ahmad KA, Ihsan AU, Qu J, Lin N, Hezam K, Koju N, Hui L, Qilong D. Antioxidant effects and mechanism of silymarin in oxidative stress induced cardiovascular diseases. Biomedicine & Pharmacotherapy. 2018 Jun 1;102:689-98.
11. Smith MA, Harris PL, Sayre LM, Perry G. Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. Proceedings of the National Academy of Sciences. 1997 Sep 2;94(18):9866-8.
12. Veurink G, Perry G, Singh SK. Role of antioxidants and a nutrient rich diet in Alzheimer's disease. Open Biology. 2020 Jun 17;10(6):200084.
13. Guan G, Lan S. Implications of antioxidant systems in inflammatory bowel disease. BioMed research international. 2018 Oct;2018.
14. Kattoor AJ, Pothineni NV, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. Current atherosclerosis reports. 2017 Nov;19(11):1-11.
15. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27(5):1047-53.
16. Martinez-Castelao A, Navarro-Gonzalez JF, Gorriz JL, de Alvaro F. The Concept and the Epidemiology of Diabetic Nephropathy Have Changed in Recent Years. J Clin Med. 2015; 4(6):1207-16.
17. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016; 12(2):73-81.
18. Lacava V, Pellicano V, Ferrajolo C, Cernaro V, Visconti L, Conti G, et al. Novel avenues for treating diabetic nephropathy: new investigational drugs. Expert Opin Investig Drugs. 2017:1-18.
19. Miranda-Diaz AG, Pazarin-Villasenor L, Yanowsky-Escatell FG, Andrade-Sierra J. Oxidative Stress in Diabetic Nephropathy with Early Chronic Kidney Disease. J Diabetes Res. 2016; 2016:7047238.
20. Bhattacharjee N, Barma S, Konwar N, Dewanjee S, Manna P. Mechanistic insight of diabetic nephropathy and its pharmacotherapeutic targets: An update. Eur J Pharmacol. 2016; 791:8-24.
21. Adeoye O, Olawumi J, Opeyemi A, Christiania O. Review on the role of glutathione on oxidative stress and infertility. JBRA assisted reproduction. 2018 Jan;22(1):61.
22. Prasad S, Gupta SC, Tyagi AK. Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals. Cancer letters. 2017 Feb 28;387:95-105.
23. Arulselvan P, Fard MT, Tan WS, Gothai S, Fakurazi S, Norhaizan ME, Kumar SS. Role of antioxidants and natural products in inflammation. Oxidative medicine and cellular longevity. 2016 Oct 10;2016.
24. Niedzielska E, Smaga I, Gawlik M, Moniczewski A, Stankowicz P, Pera J, Filip M. Oxidative Stress in Neurodegenerative Diseases. Mol Neurobiol. 2016 Aug;53(6):4094-4125.
25. Niedzielska E, Smaga I, Gawlik M, Moniczewski A, Stankowicz P, Pera J, Filip M. Oxidative stress in neurodegenerative diseases. Molecular neurobiology. 2016 Aug;53(6):4094-125.
26. Simonian N, Coyle JT. Oxidative stress in neurodegenerative diseases. Annual review of pharmacology and toxicology. 1996 Apr;36(1):83-106.

27. Singal AK, Jampana SC, Weinman SA. Antioxidants as therapeutic agents for liver disease. Liver International. 2011 Nov;31(10):1432-48.
28. Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, Feng Y. The role of oxidative stress and antioxidants in liver diseases. International journal of molecular sciences. 2015 Nov;16(11):26087-124.
29. Kolosova NG, Stefanova NA, Muraleva NA, Skulachev VP. The mitochondria-targeted antioxidant SkQ1 but not N-acetylcysteine reverses aging-related biomarkers in rats. Aging (Albany NY). 2012 Oct;4(10):686.
30. Garrido M, Terron MP, Rodriguez AB. Chrononutrition against oxidative stress in aging. Oxidative medicine and cellular longevity. 2013 Jun 18;2013.
31. Shukitt-Hale B, Miller MG, Chu YF, Lyle BJ, Joseph JA. Coffee, but not caffeine, has positive effects on cognition and psychomotor behavior in aging. Age. 2013 Dec;35(6):2183-92.
32. Soundararajan V, Sreenivasan S. Antioxidant activity of Elaeis guineensis leaf extract: An alternative nutraceutical approach in impeding aging. APCBEE Procedia. 2012 Jan 1;2:153-9.
33. Niu Y, Na L, Feng R, Gong L, Zhao Y, Li Q, Li Y, Sun C. The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. Aging cell. 2013 Dec;12(6):1041-9.
34. Zhou XX, Yang Q, Xie YH, Sun JY, Qiu PC, Cao W, Wang SW. Protective effect of tetrahydroxystilbene glucoside against D-galactose induced aging process in mice. Phytochemistry Letters. 2013 Aug 1;6(3):372-8.
35. Baek J, Lee MG. Oxidative stress and antioxidant strategies in dermatology. Redox Report. 2016 Mar 31.
36. Young IS, Woodside JV. Antioxidants in health and disease. J Clin Pathol. 2001 Mar;54(3):176-86.
37. Pokorny J. Antioxidants in food preservation. In Handbook of food preservation 2007 Jul 16:pp. 277-304.
38. Pokorný J. Are natural antioxidants better–and safer–than synthetic antioxidants?. European Journal of Lipid Science and Technology. 2007 Jun;109(6):629-42.
39. Hall C. Sources of natural antioxidants: oilseeds, nuts, cereals, legumes, animal products and microbial sources. Antioxidants in food. Practical Applications. Pokorny, J., Yanishlieva, N. y Gordon, M.(Editores). CRC Woodhead Publishing Limited. Cambridge, Inglaterra. 2001 Jan 1.
40. Sánchez-Valle V, C Chavez-Tapia N, Uribe M, Méndez-Sánchez N. Role of oxidative stress and molecular changes in liver fibrosis: a review. Current medicinal chemistry. 2012 Oct 1;19(28):4850-60.