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Protective Role of Natural Dietary Antioxidants- A Mini Review

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Abstract

The objective of this review is to study the ameliorative effects of natural dietary antioxidants in the maintenance of health and the prevention and treatment of various pathophysiological disorders, with a focus on data pertaining to L-Ascorbic acid or vitamin C and α- Tocopherol or vitamin E. The current study discusses natural and synthetic antioxidants, its mechanism of action as free radical scavengers, protective role in prevention of some major diseases including lifestyle exposure diseases. There appear to be significant health benefits from dietary antioxidants, have important roles in preventing pathogenic processes related to Diabetic neuropathy, major depressive disorder, inflammation, cataract, age-related muscular degeneration, liver disorders, cardiovascular and neurological disorders, asthma and may enhance immune function. The combined supplementation of vitamins were found to be more beneficial in protection against oxidative stress due to their synergistic effects particularly vitamin C and vitamin E. Thus the findings in the present review will throw considerable light on the use of natural dietary antioxidants against various diseases thus adding more information on therapeutic approaches.

Keywords: Antioxidants, Dietary, Prevention, Vitamin C, Vitamin E

Introduction

Natural antioxidants and therapeutic approach

Antioxidants are substances that lessen or inhibit living organisms from suffering from oxidative damage to a target molecule. Both in the human body and in fruits and vegetables, they are secondary metabolites. Alkaloids, phenolics, and vitamins C and E are just a few of the numerous antioxidants that plants produce that are regarded to be essential to maintain human health. Antioxidants can be generally categorised, and these two types are further classified into smaller groups depending on factors such as bioactivity, solubility, and size. Antioxidants can also be divided into primary and secondary antioxidants, as well as endogenous and exogenous categories (*Ayoka et al, 2020*; *Singh et al, 2020*).

Free radicals are broken down and eliminated by enzyme-based antioxidants, which create hydrogen peroxide from dangerous oxidative waste. Antioxidants that are not enzymes prevent processes involving free radicals. Exogenous antioxidants are received through a diet of an individual, whereas endogenous antioxidants are produced by the human body. Chain-breaking antioxidants, also referred to as primary antioxidants, work with oxidants to convert them into more stable, non-reactive compounds. Secondary antioxidants, also known as preventive antioxidants or hydroperoxide decomposers, can lower the concentration of peroxides while increasing the availability of glutathione and NADPH for the primary antioxidant enzymes (*Sisein et al, 2014; Ifeanyi et al, 2018; Ayoka et al, 2022*).

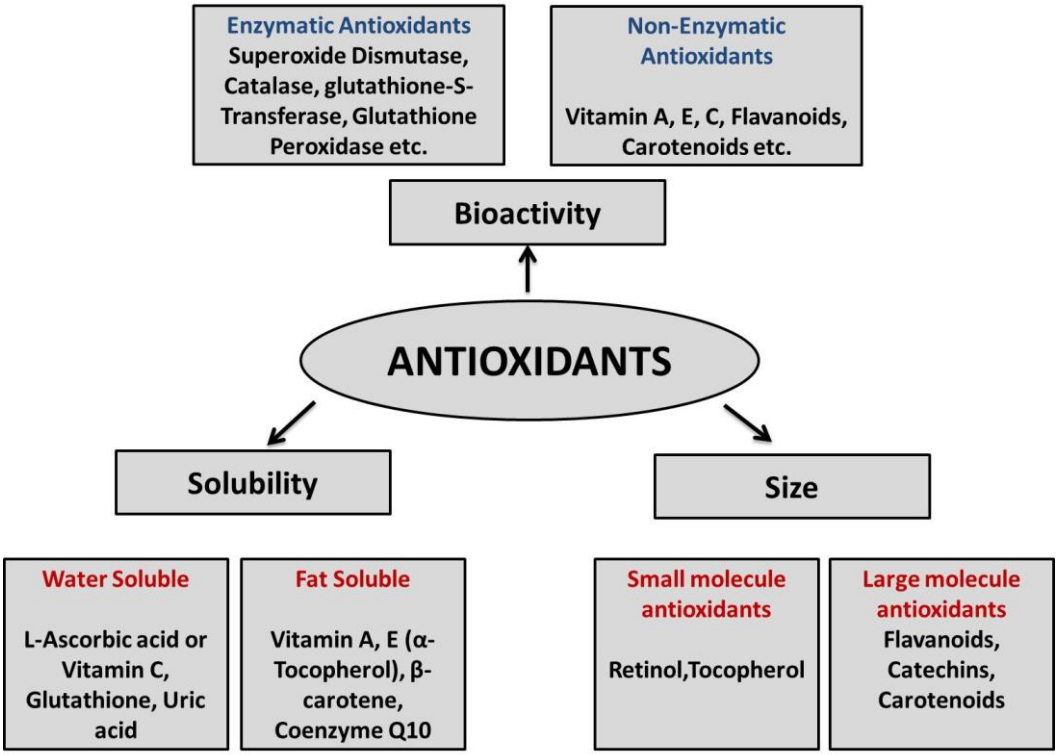

Fig:1 Simplified classification of antioxidants. (Ayoka et al, 2022)

In living organisms, the metabolism of oxygen results in the production of reactive oxygen species (ROS), which are important for cell signalling and homeostasis. Usually, ROS equilibrium is preserved to combat against cell deterioration. However, some environmental factors, such as exposure to heat or UV light, might cause a rise in ROS levels. Oxidative stress is the term used to describe this state (*Raza et al, 2017*).

Due to their anti-inflammatory and antioxidant effects, vitamins are the micronutrients with the strongest evidence for immune support and have been recommended to shorten the length and severity of consequences in viral infections. There is evidence to support their potential for scavenging reactive oxygen species (ROS) and shielding cells from viral infections (*Sorkhabi et al, 2021*).

Plasma and serum total antioxidant capacity (TAC) concentration has been shown to be associated with antioxidant-rich vegetable and fruit consumption, thus the importance of consuming sufficient amount of antioxidants in the diet has been emphasized. Vegetable foods such as whole grains, fruits, and vegetables containing vitamins, minerals, and polyphenols such as A, C, E vitamins, β carotene, lycopene, and Se reduce the risk of chronic illness by protecting the cells from oxidative stresses (*Besagil et al, 2020*).

Natural and synthetic antioxidants

Natural antioxidants are a kind of anti-oxidants that can either be produced by the body or received from the consumption of other natural sources. They have a wide variety of biological effects, including those that are anti-aging, anti-cancer, anti-inflammation, and anti-atherosclerosis. Three types of plant-derived natural antioxidants are categorised: polyphenols, carotenoids, and vitamins (*Lucas et al, 2006; Xu et al, 2017; Anwar et al, 2018*).

Whereas, synthetic antioxidants are chemically created substances that do not exist in nature but can be added to food as preservatives to prevent lipid oxidation, are compounds that do not occur in nature. In fruits and vegetables, synthetic antioxidants including 2-naphthol (2NL), 4-phenyl phenol (OPP), and 2,4-dichlorophenoxyacetic acid (2,4-DA) are utilised, however they have been connected to health problems. It is reported that consuming a lot of synthetic antioxidants in food can harm DNA and hasten senescence (*Kornienko et al, 2019*) which makes crucial to replace synthetic antioxidants with larger natural antioxidants in order to meet dietary demands, but synthetic antioxidants are more affordable, widely accessible, and offer stability advantages over natural antioxidants. Several vitamins have also been found to have antioxidant activity, with vitamins E and C being the most significant. Tocopherols and tocotrienols, which exist in four isomeric forms- α,β,γ and δ but only the α-tocopherol is important nutritionally, make up the lipid known as vitamin E. 22 Legumes and grains contain the α-tocopherols (*Vaca et al, 2012*). 23 Fruits and vegetables include water-soluble vitamin C, which is also found in them (*Goulas et al, 2012*). Fruits and vegetables are also good sources of carotenoids, although β-carotene, α-carotene, lycopene, and lutein are the carotenoids that are known to have antioxidant properties (*Ayoka et al, 2022*).

Antioxidants as free radicals scavengers

An increase in the production of free radicals or a reduction in the quantity of antioxidants causes oxidative stress. The imbalance between free radicals and antioxidants is brought on by oxidative stress. Free radicals are highly reactive and prone to instability when interacting with other species. Free radicals, which can obliterate carbohydrates, lipids, proteins, and nucleic acids, are also produced by metabolic pathways. Similar to this, free radicals function in two different ways depending on their concentration. It can harm living things in high concentrations, but they can also stop infections at low ones. A buildup of free radicals also alters and binds DNA with proteins, degrades single and double strands of DNA, degrades nitrogenous bases, and harms the biological components of proteins, lipids, and DNA (*Ifeanyi et al, 2018*). These faulty DNA alterations can hasten ageing and lead to autoimmune, cardiovascular, neurodegenerative, cancerous, and other illnesses. In light of this, oxidative stress plays a crucial role in the aetiology of various diseases. As such, free radicals can oxidize the backbone and side chains of proteins, which would react with their functional groups to generate the carbonyl function. By disrupting the cellular membrane, free radicals can also break down peptide bonds, oxidize amino acids, as well as cause lipid peroxidation. Thus, the accumulation of free radicals in the body could trigger an array of non-infectious diseases. As a result, antioxidants help to keep them at the lowest concentration in the body (*Nimse et al, 2015; Ifeanyi et al, 2018; Neha et al, 2019; Neha et al, 2019*).

The pool of antioxidant enzymes, not small molecule free radical scavengers, is the main counterbalance of the resultant oxidative stress because reactive oxygen species (RONS) are mostly produced by enzymatic activities. NADPH oxidases, lipoxygenases, cyclooxygenases (COXs), xanthine oxidoreductases (XOR), and cytochrome P (CYP) monooxygenases are some of the enzymes that create ROS. Nitric oxide synthases (NOSs) generate RNS, which then combine with CO2 to form nitrosoperoxycarboxylate. The potentially detrimental effects of RONS are balanced by antioxidant enzymes such catalase, glutathione peroxidase, and superoxide dismutases (SODs) (*Hunyadi, 2019*).

Dehydroascorbic acid (DHA), a form of vitamin C, has been found to inhibit IKKα and IKKβ, which control the transcription factor NF-κB. Ascorbic acid plays a dual role in NF-κB pathway modulation, acting as an antioxidant to lower ROS levels and scavenging ROS to produce DHA. It has

been discovered to selectively kill KRAS or BRAF mutant colorectal cancer embryos and exert an antagonistic influence on the cytotoxic efficacy of numerous antineoplastic medicines (*Yun et al, 2015; Van et al, 2016*). Furthermore, vitamin C has been connected to DHA's antiviral activity, indicating that oxidative stress directly modifies this antioxidant's particular bioactivity through its metabolites (*Furuya et al, 2008*).

Ageing, obesity, nonalcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), depression, and neurodegeneration are all impacted by oxidative stress. Although excessive free radical production can cause tissue oxidative damage, reactive oxygen species (ROS) are necessary for physiological processes. This results in endoplasmic reticulum stress, inflammatory state, and mitochondrial/dysfunction. Plant extracts, such as flavonoids, phenolic acids, and phenolic diterpenes, have been described more and more as readily available dietary antioxidants (*Czarny et al, 2018; Wadhwa et al, 2018; Guo et al, 2020*).

The superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals ($OH^{\bullet-}$), and peroxyl radicals (ROO•) are the most prevalent and physiologically significant ROS. Several cytosolic enzyme systems and regular intracellular metabolism in the mitochondria and peroxisomes both produce ROS. The majority of O_2 produced during electron transport via complexes I and III is produced by mitochondria during their ongoing metabolism of oxygen and production of ROS. Other intracellular enzymes include NADPH oxidases, dopamine oxidation, xanthine oxidase, and lipoxygenases release ROS as part of their typical enzymatic action. Complex II and other mitochondrial and cellular ROS sources may also be relevant. The ability of antioxidant systems to perform tasks like reducing ROS generation or scavenging free radicals is crucial for maintaining intracellular redox equilibrium. Several defence mechanisms, such as antioxidants and antioxidant enzymes like vitamin E, actively reduce ROS-induced oxidative stress (*Murphy, 2009; Willems et al, 2015, Guo et al, 2020*).

Free radical scavenging mechanisms of antioxidants

Despite the fact that numerous small compounds tested as antioxidants showed therapeutic promise in preclinical research, clinical trial outcomes have been underwhelming. A more rational strategy that results in more pharmacological effectiveness may be offered by a better knowledge of the processes by which antioxidants function and where and when they are beneficial (*Forman & Zhang, 2021*).

Antioxidants are also thought to function in two different ways. The primary antioxidant provides an electron to the already-existing free radical in the chain-breaking process, which is the first mechanism. Neutralizing the chain-starting catalyst in the second step eliminates the ROS initiators (secondary antioxidants). In addition to supplying electrons, co-antioxidants, metal ion chelation, and genomic regulation, antioxidants also have an impact on metabolic pathways (*Lobo et al, 2010; Nimse et al, 2015*).

Antioxidant defences are universal but differ depending on the species. Hence, the oxidation reaction is essential for life since it helps to maintain the composite structure of the human body. Nevertheless, it is a chemical process that produces significant ROS, which triggers a series of chain reactions that kill cells. As a result, a number of non-living elements would raise the level of ROS in the body, leading to illnesses and tissue damage. To prevent or treat diseases brought on by oxidative stress, antioxidants can neutralise ROS. They eliminate free radicals and are necessary for preserving healthy cellular processes. Also, they are essential for safeguarding the biological system because they stop new

radicals from forming, capture existing ones to stop chain reactions, and reverse the harm done by free radicals. The defence system function of antioxidant on a number of levels, including prevention, antiradical, repair, and adaptation. Moreover, antioxidants have the ability to neutralise reactive radicals to stop chains from starting and/or stop chains from spreading. The repair antioxidants in the cytosol and mitochondria of mammalian cells recognise, degrade, and remove oxidatively damaged proteins, preventing the accumulation of oxidative proteins. The signal for free radical production and reactions causes the production and distribution of the pertinent adaptive antioxidants to the proper locations (*Xu et al, 2017; Ayoka et al, 2022*).

Superoxide dismutase (SOD), catalase (CAT), selenium, copper, zinc, and other antioxidants work to protect biological systems by three processes- 1)preventing the production of new free radicals, 2) catching free radicals before they can start a chain reaction, and 3) repairing damage caused by free radicals (lipases, proteases) (*Neha et al, 2019*).

Antioxidants in metabolic diseases

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease and oxidative stress (OS) and is a key factor in the pathogenesis and progression of the DN. Different dietary antioxidants, such as resveratrol, curcumin, selenium, soy, catechins, α-lipoic acid, coenzyme Q10, omega-3 fatty acids, zinc, vitamins E and C, have been demonstrated to have beneficial effects on OS and the capacity for antioxidant response (*Escatell e al, 2020*). These interventions could have a positive clinical impact on DN, and factors like hyperglycemia, ROS, AGEs, arterial pressure, insulin resistance, decrease in NO, inflammatory markers, and cytokines are involved in the presence of OS on DN. The increase in antioxidant response by the SOD, GPx, catalase, glutathione, and the Nrf2 has been also seen to be beneficial (*Xu et al, 2014; Wang et al, 2017*).

DN was also studied and reported to be protected by a powerful nephron-protective drug propyl gallate (*Tian et al, 2012*). Additionally, diospyroslotus seed extracts were found to be particularly effective at inhibiting DPPH, chelating iron ions, nitric oxide, reducing power, lipid peroxidation, and scavenging hydrogen peroxide radicals (*Moghaddam et al, 2012*). Curcumin/curcuminoids are phenolic compounds that have been studied for their potential therapeutic benefits as antioxidants and nephroprotectants (*Trujilo et al, 2013*). In patients with low antioxidant levels, vitamin C protects the kidneys by reducing ROS, non-radical oxidants, and oxidative damage. Pre-clinical research has demonstrated that antioxidants support kidney function. Endogenous antioxidant activity of vitamin C and its function as an enzyme co-factor ensure that it has a renoprotective impact (*Dennis, 2017; Neha et al, 2019*).

Major Depressive disorder (MDD) is also accompanied with oxidative stress, therefore antioxidants might contribute to protecting us from MDD. Research into the possible role of dietary factors in depressive symptoms is a common problem in public health (*Huang et al, 2019*). Studies have shown that diet and nutrition play a significant role in the prevention and clinical treatment of depression, implying that the concepts of diet and nutrition could be incorporated into future depression intervention programs. Diet and nutrition can be used as a part of a comprehensive strategy for the prevention of depressive problems (*Roberts & Suzuki, 2021*). Moreover, patients with depression who are not suitable for drug therapy or psychotherapy can use diet and nutrition adjustments as an alternative treatment. Therefore, future research should focus more on understanding the efficacy and

dose responses of foods and dietary patterns upon depression and explore the effects of different dietary patterns for different types of depression patients.

Clinical research has found connections between oxidative stress, inflammation, and nutrition, all of which are likely to contribute to chronic pain. As nutrition can affect pain at the cellular level, dietary interventions are a particularly promising therapeutic approach for treating chronic pain (*Kaushik et al, 2020*). Oxidative stress happens when there are too many free radical species for the body's natural antioxidant defence system to handle, which may be the cause of a number of pain-related symptoms. Hence, dietary antioxidant supplementation naturally emerges as a prospective therapy strategy. Nutritional antioxidants can be obtained in entire foods including berries, fruits, nuts, cocoa, veggies, and green tea as well as a wide range of over-the-counter vitamins and supplements (*Carlsen et al, 2010*). Despite this, there is still data that suggests dietary antioxidants may affect pain, albeit not via the inflammation pathway. In a previous study on people with knee osteoarthritis, those who consumed 40 g of freeze-dried blueberry powder daily over a 4-month period experienced less pain, stiffness, and trouble completing everyday activities than those who consumed a placebo (*Du et al, 2019*). Although an impact on pain may be discernible, antioxidant supplementation may have a bigger impact on reducing oxidative stress than inflammation as no significant changes in inflammatory indicators were discovered (*Frei et al, 2004; Kaushik et al, 2020*).

The main causes of vision loss worldwide are cataract and age-related macular degeneration (AMD). Smoking has been identified as a risk factor for both illnesses by epidemiological studies. Natural antioxidants like flavonoids, vitamins, phenolic acids, and carotenoids can help prevent cataract development. Antioxidant biomolecules in a formulation based on nanotechnology have greater solubility, bioavailability, and stability, as well as an overall increased impact. Dietary additions of natural antioxidant components including vitamin C, curcumin, and vitamin E can improve defenses against free radicals. Although curcumin is a well-known anti-cataract remedy, its bioavailability is low (*Fletcher et al, 2010; Sunkireddy et al, 2013; Weikel et al, 2014*).

A study was performed on the generation of ROS species, their role in vascular dysfunction, and potential therapeutic strategies (*Rodrigo et al. 2011*). Another study was focussed on the detrimental effects of ROS on the heart, where researchers concentrated on coronary artery disease and employed exogenous antioxidants including a-tocopherol, ascorbic acid, and b-carotene (*Leopold et al, 2015*). By lowering oxidized low-density lipoprotein, the Mediterranean diet reduces adverse outcomes by 28%. When it comes to atherosclerosis, hypertension, heart failure, and atherosclerosis-Ischemic heart disease, lipoic acid was protective (*Skibska et al, 2015*). Support for the use of vitamin C supplements to lower cardiac risk was offered by various researchers in different studies (*Moser et al. 2016; Tayebati et al. 2016*). Improvements in lipid profiles, endothelial function, and the suppression of LDL-protein oxidation have all been associated with vitamin C. Lycopene increases HDL, reduces oxidative stress and cholesterol levels in patients, and helps prevent CVDs by lowering nitric oxide and cholesterol levels (*Petyaev, 2016*). It has been demonstrated that alpha lipoic acid and its isomers decrease TBARS levels, limit nucleic acid oxidation, and inhibit adhesion in cardiac and renal vascular endothelium (*Neha et al, 2019*).

A few cross sectional studies reported oxidative stress has a role in the development of liver disorders like non-alcoholic steatohepatitis (NASH), alcoholic liver disease, Wilson's disease, and hepatitis C and revival possibilities were studied with various antioxidants (*Singal et al 2011; Li et al 2015*). Resveratrol was examined for its effectiveness in treating liver problems. According to studies,

resveratrol improves lipid profiles, reduces hepatic steatosis and fibrosis, and suppresses liver steatosis in addition to protecting the liver against cholestasis, alcoholism, and chemical damage (*Faghihzadeh et al, 2015*). Further clinical trials are required to give more solid scientific evidence for the effective management of liver disease. With hepatoprotective and cytoprotective properties in H_2O_2-treated human liver L-02 cells, Q7R is a promising antioxidant for liver damage (*Huang et al, 2018*).

Fistein is a flavonoid that has been found as being active in animal models of CNS diseases as an antioxidant and neuroprotective (*Chiruta et al, 2012*). The polyphenol-rich foods such fruits, herbs, vegetables, and different beverages were described by previous researechers (*Albarracin et al, 2012*). The use of a polyphenolic diet and the prevention of cardiovascular and neurological disorders have been linked by epidemiological studies. Due to the presence of three OH groups in the 3, 40, and 5 positions, a double bond, and aromatic rings in resveratrol, it has been hypothesised that the substance possesses neuroprotective qualities and it protects immune system of the body by proliferating the activities of antioxidant enzymes (*Gerszon et al, 2014*).

Increased nutritional consumption has been linked to a lower risk for diseases where oxidative stress and inflammatory processes are thought to have a pathophysiologic role, according to recent studies. Hence, in addition to their well-known antioxidant properties, new research suggests that these substances also have an anti-inflammatory function (*Halliwell et al, 2015*). Changes in the consumption of antioxidant nutrients have an impact on the development of inflammation mostly through their interaction with the production of ROS and RNS by activated phagocytes. Dietary antioxidants contain reducing structures that inhibit NF-kB activation and promote COX-2, iNOS, and adhesion molecules necessary for phagocyte recruitment (*Marnett et al, 1999; Carter et al, 2002*). The prevention of illnesses in which oxidation and inflammation both play crucial roles may therefore be achieved safely and effectively by dietary modification. Future studies examining the effects of these nutrients on various elements of the inflammatory response require more attention given the intriguing evidence for a protective role of dietary antioxidants in inflammatory processes (*Uysal et al, 1998; Esposito et al, 2002; Shigematsu et al, 2003; Sagin and Sozmen, 2004*).

L-ascorbic acid or Vitamin C as antioxidant

L-ascorbic acid or Vitamin C is a water soluble antioxidant that protects physiology of an individual against oxidative damage by scavenging ROS and RNS. Moreover, it has shown anti-apoptotic actions by preserving the potential of the mitochondrial membrane and shielding the mitochondrial DNA from oxidative damage. Citrus fruits and various green vegetables like broccoli and spinach are dietary sources of this vitamin. Patients with Diabatic neuropathy have been found to have lower vitamin C concentrations (*Varma et al, 2014*). Low plasma concentrations have been linked to elements such as the rise in oxidative stress, serum creatinine, albumin in urine, and the creatinine-albumin interaction in urine. Because of the interaction between glucose and dehydroascorbate, vitamin C is excluded from the tubular epithelial cells, which depletes the cells' antioxidant capacity and increases the risk of ROS buildup in diabetic patients. This deficiency of vitamins activates TGF- signalling, aggravating diabetic mesangial cellular expansion and extracellular matrix deposition (*Ji et al, 2017*). According to a study, vitamin C administration dramatically decreased proteinuria, albuminuria, the amount of apoptotic cells, glomerular and tubulointerstitial sclerosis, and the buildup of renal malondialdehyde in diabetic rats (*Lee et al, 2007*). Another study found that vitamin C intake reduced peroxidation of cellular lipids, enhanced the activity of the antioxidant enzymes SOD, GPx, and

catalase, decreased albuminuria, and thinned the glomerular basement membrane (*Chou et al, 2017*). Another advantageous effect of vitamin C is the improvement of diabatic neuropathy conditions because it lowers blood levels of uric nitrogen, serum creatinine, and the rate at which albumin is excreted in urine. It also improves creatinine clearance rates and protects against renal lesions by inhibiting the expression of collagen type IV. Treatment with vitamins C and E for four weeks significantly reduced albuminuria in patients with type II diabetes who had micro or macroalbuminuria (*Gaede et al, 2001*). Another study found that oral vitamin C supplementation and metformin therapy reduced blood sugar levels and enhanced glycated haemoglobin in type 2 diabetic individuals (*Dakhale et al, 2011*).

Ascorbate serves as a reducing agent in physiologically significant oxidoreduction processes, serving as the first line of defence in the management of the redox state. It modifies the iron's redox chemistry and returns the haem Fe3+ species to the Fe2+ state, inhibiting the peroxide-dependent oxidations brought on by mixes of haemoglobin (Hb) and myoglobin with H2O2. Ascorbate is an antioxidant that inactivates superoxide anion (O_2), hydroxyl (OH^-), peroxyl ($RO2^-$), ozone (O3), and nitric oxide in living organisms ($NO2^-$). It is a potent scavenger and quencher of singlet oxygen ($^1O2$), hypochlorous acid (HOCl), peroxynitrous acid (ONOOH), nitrosating agents, and hypochlorous acid (HOCl) (Halliwell & Gutteridge, 2015). It also stabilises catecholamines by preventing the formation of reactive oxygen species (ROS) and guards plasma lipids against peroxidation by sparing antioxidants found in lipoproteins. By producing α-tocopherol from α-tocopheryl radicals in membranes and lipoproteins, ascorbate works in conjunction with vitamin E. A diet low in vitamin C supplemented to guinea pigs or mutant rat strains have been reported to exhibit lower vitamin E levels in their tissues. Moreover, it has been demonstrated that vitamin C shields LDL from homocysteine-induced oxidation by covalently altering the lipoprotein particle (*Hwang et al, 2000; Alul et al, 2003*).

Due to the high levels of vitamin C in phagocytic cells, status of vitamin C has been widely studied. Prior research found that ascorbic acid in high dosages had negligible benefits on immunological response to colds, although it did lessen the severity of symptoms. After giving the individuals vitamin C along with aspirin, ascorbate went into the leucocytes concurrently with the increase in plasma concentration. Ascorbate was found to have higher amounts of ascorbyl radical than normal mucosa, which shows that inflammation and oxidative stress play a role in the aetiology of H. Pylori-induced ulcers (*Sagin & Sozmen, 2004*).

α- Tocopherol or vitamin E as antioxidant

Vitamin E is a fat-soluble vitamin having antioxidant characteristics. Alpha, beta, gamma, and delta tocotrienol and alpha, beta, gamma, and delta tocopherol are the eight distinct forms of vitamin E, with alpha-tocopherol being the most active form in humans (*Farid et al, 2013*). Olive oil, wheat germ oil, and almond oil are a few of the seed oils that are the main dietary sources of vitamin E. Vitamin E supplementation has been shown to improve lipid peroxidation and the antioxidant defence system in diabetic mouse models by raising levels of GPx, catalase, SOD, glutathione, vitamin A, and beta-carotenes and lowering kidney malondialdehyde levels (*Haidara et al, 2009*). Vitamin E supplementation has positive effects on the development of diabetic neuropathy because it can lower PKC and diacylglycerol levels in the diabetic glomeruli. The downgrading of PKC activation on administering this vitamin seems to induce normalisation of the renal functions as measured by renal hemodynamics and the albumin excretion rate in urine. Similarly, it has been observed that treatment with vitamin E prevents damage to the normal morphology of the podocyte and the loss of podocytes in

mice without α diacylglycerol deficiency when compared to mice with deficiency of α diacylglycerol (*Hayashi et al, 2017*). The levels of proteinuria, tumour necrosis factor, matrix metalloproteinase, matrix metalloproteinase-9, malondialdehyde, AGEs, and insulin concentrations were all found to be lower in a recent study that examined the effects of supplementing diabetic patients with high doses of vitamin E. These findings demonstrate the beneficial effects of this fat-soluble vitamin on the renal injury, inflammatory, and OS biomarkers in these patients (*Khatami et al, 2016*).

Vitamin E is mostly transported in the blood by LDL, which has 6 molecules of the vitamin per particle. Lipoproteins and membranes are more susceptible to peroxidation when vitamin E deficiency is present. Vitamin E is the most significant regulator of the free radical chain reaction that causes lipid peroxidation because it scavenges peroxyl radicals (LO_2^-) (*Halliwell, 2015*). Tocopherols quench and react with $^1O_2$, O_2, and OH^-. It also preserve the NO reservoir by preventing NO from reacting with O_2. Another function is to reduce the Fe3+ to Fe2+ and Cu2+ to Cu+ like vitamin C, generating tocopheryl radical, which can react with PUFAs at a very low rate. These effects of lipid peroxidation go beyond the chain-breaking effect demonstrate a prooxidant effect as a result. But α-Tocopherol is always combined with co-reductants such ascorbate or ubiquinol in vivo, which eliminate the α-tocopheryl radical (*Fuhrman et al, 2002; Sagin & Sozmen, 2004; Bhavnani et al, 2018*)

Many positive effects of vitamin E, including increased nitric oxide (NO) bioactivity, COX-2 inhibition, reduction in platelet aggregation, and suppression of isoprostane synthesis, may help to prevent and/or delay the development of atherosclerotic disease (*Sagin & Sozmen, 2004*). It has been hypothesised that by stabilising brain membranes and synapses, Phoshoplipase A_2 (PLA_2) inhibition may decrease the course of Alzheimer's disease. PLA_2 inhibition is of fundamental therapeutic value in the inflammatory cascade. Vitamin E has been demonstrated to specifically inhibit PLA_2 at 1.8 resolution, which could be exploited to create PLA_2 inhibitors that are more effective (*Li et al, 2001*). Gastro-intestinal system damage, which can be brought on by COX-1 inhibition, is one of the clinical drawbacks of anti-inflammatory drugs now in use (*Marnett & Kalgutkar, 1999*). Although vitamin E also lowers prostanoid levels, this action is not strong enough to prevent the occurrence of macroscopic gastrointestinal damage. Several studies have demonstrated that co-administration of vitamin E helps lessen the gastrointestinal adverse effects of aspirin (*Abate et al, 2000; Sagin & Sozmen, 2004*).

Combined effects of Vitamin C and Vitamin E

Several studies have demonstrated the synergistic antioxidant effects of the combination of vitamins C and E. Particularly, vitamin C altered pro-oxidant status of vitamin E, and this result supports therapeutic trials in which both vitamins C and E are administered together (*Platinga et al, 2007; Ashor et al, 2015*). Vitamin C and vitamin E, a lipid-soluble vitamin with a protective action against lipid peroxidation, have been combined in several studies evaluating the effects of antioxidant supplementation. This combination is of great relevance, as it is known that vitamin E can have pro-oxidant effects and sufficient amounts of vitamin C are necessary for the regeneration of vitamin E. Vitamins C and E work together to provide a synergistic impact, thus it is possible that taking both vitamins together will have a stronger antioxidant effect (*Reaven et al, 1993; Engler et al, 2003; Platinga et al, 2006*). A previous research has highlighted lower concentrations of vitamin C and vitamin E in cerebrospinal fluid of people with Alzheimer's disease as susceptibility of cerebrospinal fluids and plasma lipoproteins to oxidation in brain is increased. However, supplementing AD patients with vitamin C or vitamin E, either separately or together, boosted the levels of both vitamins in their

blood and cerebrospinal fluid. While vitamin E supplementation alone boosted its plasma and CSF concentrations, it was unable to reduce the oxidizability of lipoproteins. These results demonstrate the superiority of vitamin E and vitamin C combination supplementation over vitamin E alone in AD and give a biological justification for its usage (*Kontush et al, 2001*). Another previous research reported that in spite of taking high dose of vitamin C and vitamin E separately, multidose combination therapy at lower doses can be more effective in protecting a chemotherapy drug, cisplatin-induced renal failure (*Ajith et al, 2009*). A recent research on protective effects of L-Ascorbic acid and α-Tocopherol on 1,4-BQ induced toxicity in wistar rats recorded better amelioration by combined supplementation over single treatment (Mishra et al, 2022; Mishra et al, 2023).

Natural antioxidants and lifestyle exposure diseases

The present lifestyle, which includes eating processed food, being exposed to a variety of chemicals, and not exercising, is a significant factor in the development of oxidative stress. Oxidative stress is a result of smoking, drinking alcohol, eating a proper or improper diet, exercising, being undertrained, or not exercising at all. Reactive oxygen species have been found to exist in muscles and to have a part in controlling muscle function, according to some study. Reactive oxygen species are continuously produced at low levels by skeletal muscle fibres, and these levels rise during muscular contraction (*Pingitore et al, 2015*). They are implicated in skeletal muscle fatigue during intense exercise and have numerous direct and indirect impacts on muscle function such as contractility of muscles, excitability, metabolism, and calcium homeostasis. A considerable response to oxidative stress is induced by exhausting workouts, prolonged exercises, overtraining syndrome, and pushing past limitations as a stage in the initial onset of overtraining syndrome. Instead, endogenous antioxidant status is improved by moderate exercise, low intensity training, and sustained training (*Antonioni et al, 2019; Wu et al, 2019*). Reactive oxygen species control the expression of antioxidant genes and are key players in cell signalling. Exercise causes a hyperregulation of nuclear factor kappa B and mitogen-activated protein kinase, which in turn increases the gene production of several enzymes and proteins crucial to maintaining oxidative/antioxidant intracellular equilibrium. Together with lifestyle modifications, physical exercise is regarded as the primary nonpharmacological therapy for a number of chronic conditions, particularly cardiovascular disorders (*Sharifi-Rad et al, 2020a; Sharifi-Rad et al, 2020b*). The findings of a few experimental studies have brought attention to the influence that training has on the cardiovascular system. Autophagy is a conservative kind of catabolism that breaks down and recycles cellular organs and nutrients. Frequent exercise, a special kind of physiological stress, can cause adaptation, but selective mitochondrial autophagy, also known as mitophagy, enables this kind of cardiovascular adaptation. Smoke from cigarettes contains a variety of oxidants, free radicals, and organic substances (such as nitric oxide and nitric superoxide), and when inhaled into the lungs, it activates the buildup of neutrophils and macrophages, which enhances the local production of oxidants (*Valavanidis et al, 2009; Sharifi-Rad et al, 2020b*).

However many researches highlighted use of certain antioxidants through diet can improve scenario of lifestyle exposure deterioration of health (*Lesgards et al, 2002; Naha et al, 2018; Sharifi-Rad et al, 2020c*). Studies on antioxidants revealed that quantity is not always a good indicator of quality. Eating superfoods does not substitute for other poor eating habits or an unbalanced lifestyle. Antioxidants and free radicals both have positive impacts on the body. Importance should be given about a balance and not a negative role attributed to free radicals and a good one to antioxidants (*Salehi et al,*

2018). One of the impacts of an excessive concentration of free radicals is the degradation of nucleic acids, proteins, lipids, or other biological components. Cancer, cardiovascular illness, Alzheimer's disease, and autoimmune diseases are just a few of the conditions that are heavily discussed nowadays (*Poprac et al, 2017*). Air pollution, ionising radiation, extended activity, infections, and an excessive intake of polyunsaturated fatty acids are risk factors that can result in free radicals. Antioxidants, which are molecules that neutralise free radicals, are thought to be the solution to these issues. The ability of a material to give electrons is what is actually meant by the term "antioxidant" in chemistry. Depending on the chemical makeup of the environment they are in, some compounds serve as antioxidants while in other instances they become prooxidants. Antioxidants come in a variety of forms, each with a unique function inside the body and a unique set of physiological mechanisms. One common fallacy is the idea that substituting one antioxidant for another will produce the same results (*Chen et al, 2018*). In fact, each has a distinct biological composition. However, there are notable differences between consuming antioxidants in food and taking an isolated chemical as a supplement. Several drugs that exhibit positive effects in the lab do not function when ingested by humans. There are many antioxidants with poor bioavailability. Sometimes, the blood level of antioxidants such polyphenols is so low that no discernible effect is seen (*Firuji et al, 2011; Fernández et al, 2012*). Bioactive chemicals found in fruits and vegetables often do not function as antioxidants when consumed outside of the body. When present in the body, however, they function as antioxidants because they trigger the natural antioxidant defences of human body. The secret to vegetable consumption is these bioactive compounds. Using antioxidant supplements may provide a variety of health advantages. On the one hand, it is conceivable that other nutrients included in food not necessarily a specific type of antioxidant, but the synergistic effects of several nutrients are to blame for the beneficial impacts on health. On the other hand, the chemical structure of antioxidants found in food and supplements frequently differs. Vitamin E is an instance. While the supplements used in most research only contain one type of vitamin E, the foods we eat include eight different types. Studies typically also include individuals in good health, for whom the effects of oxidative stress on the body are insignificant in predicting a risk of disease (*Firuzi et al, 2011; Aslani et al, 2016*). Antioxidants can help some types of patients who have a real, documented imbalance, but they might not add any additional benefits for someone who consumes enough nutrients from their diet. Observational research examines the patterns or customs of particular sizable population groupings. In many cases, all potential risk variables that could affect the outcome of the study can be controlled, making it challenging to establish a cause-and-effect relationship. Also, none can claim that super-food based solely on limited experiments that were conducted over a brief period of time and using highly concentrated chemicals taken from various plant or animal products. Antioxidant-rich foods cannot make up for an unhealthy lifestyle unless it is consumed with balanced diet and balanced doses of supplementation outside the diet (*Naha et al, 2018; Lesgards et al, 2002; Sharifi-Rad et al, 2020a; Sharifi-Rad et al, 2020b*).

The findings of the present study are expected to throw considerable light on the use of natural dietary antioxidants against various pathophysiological disorders and it can contribute in drug designing and discovery as therapeutic approaches.

REFERENCES

1. Abate A, Yang G, Dennery PA, Oberle S, Schröder H. Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. Free Radical Biology and Medicine. 2000 Dec 1;29(11):1135-42.
2. Ajith TA, Abhishek G, Roshny D, Sudheesh NP. Co-supplementation of single and multi doses of vitamins C and E ameliorates cisplatin-induced acute renal failure in mice. Experimental and Toxicologic Pathology. 2009 Nov 1;61(6):565-71.
3. Albarracin SL, Stab B, Casas Z, Sutachan JJ, Samudio I, Gonzalez J, Gonzalo L, Capani F, Morales L, Barreto GE. Effects of natural antioxidants in neurodegenerative disease. Nutritional neuroscience. 2012 Jan 1;15(1):1-9.
4. Alul RH, Wood M, Longo J, Marcotte AL, Campione AL, Moore MK, Lynch SM. Vitamin C protects low-density lipoprotein from homocysteine-mediated oxidation. Free Radical Biology and Medicine. 2003 Apr 1;34(7):881-91.
5. Antonioni A, Fantini C, Dimauro I, Caporossi D. Redox homeostasis in sport: do athletes really need antioxidant support?. Research in sports medicine. 2019 Apr 3;27(2):147-65.
6. Anwar H, Hussain G, Mustafa I. Antioxidants from natural sources. Antioxidants in foods and its applications. 2018 Apr 8;3.
7. Ashor AW, Siervo M, Lara J, Oggioni C, Afshar S, Mathers JC. Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials. British journal of nutrition. 2015 Apr;113(8):1182-94.
8. Ayoka TO, Ezema BO, Eze CN, Nnadi CO. Antioxidants for the Prevention and Treatment of Non-communicable Diseases. Journal of Exploratory Research in Pharmacology. 2022 Sep 25;7(3):178-88.
9. Beşağıl P, Çalapkorur S, Şahin H. Determination of the relationship between total antioxidant capacity and dietary antioxidant intake in obese patients. Niger J Clin Pract. 2020 Apr;23(4):481.
10. Bhavnani BR, Cecutti A, Gerulath A, Woolever AC, Berco M. Comparison of the antioxidant effects of equine estrogens, red wine components, vitamin E, and probucol on low-density lipoprotein oxidation in postmenopausal women. Menopause. 2018 Nov 1;25(11):1214-23.
11. Carlsen MH, Halvorsen BL, Holte K, Bøhn SK, Dragland S, Sampson L, Willey C, Senoo H, Umezono Y, Sanada C, Barikmo I. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. Nutrition journal. 2010 Dec;9(1):1-1.
12. Carter PH. Chemokine receptor antagonism as an approach to anti-inflammatory therapy:'just right'or plain wrong?. Current opinion in chemical biology. 2002 Aug 1;6(4):510-25.
13. Chen XF, Wang L, Wu YZ, Song SY, Min HY, Yang Y, He X, Liang Q, Yi L, Wang Y, Gao Q. Effect of puerarin in promoting fatty acid oxidation by increasing mitochondrial oxidative capacity and biogenesis in skeletal muscle in diabetic rats. Nutrition & diabetes. 2018 Jun 12;8(1):1.
14. Chiruta C, Schubert D, Dargusch R, Maher P. Chemical modification of the multitarget neuroprotective compound fisetin. Journal of Medicinal Chemistry. 2012 Jan 12;55(1):378-89.
15. Chou ST, Tseng ST. Oxidative stress markers in type 2 diabetes patients with diabetic nephropathy. Clinical and experimental nephrology. 2017 Apr;21:283-92.
16. Czarny P, Wigner P, Galecki P, Sliwinski T. The interplay between inflammation, oxidative stress, DNA damage, DNA repair and mitochondrial dysfunction in depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018 Jan 3;80:309-21.

17. Dakhale GN, Chaudhari HV, Shrivastava M. Supplementation of vitamin C reduces blood glucose and improves glycosylated hemoglobin in type 2 diabetes mellitus: a randomized, double-blind study. Advances in Pharmacological and Pharmaceutical Sciences. 2011 Jan 1;2011.
18. Dennis JM, Witting PK. Protective role for antioxidants in acute kidney disease. Nutrients. 2017 Jul 7;9(7):718.
19. Engler MM, Engler MB, Malloy MJ, Chiu EY, Schloetter MC, Paul SM, Stuehlinger M, Lin KY, Cooke JP, Morrow JD, Ridker PM. Antioxidant vitamins C and E improve endothelial function in children with hyperlipidemia: Endothelial Assessment of Risk from Lipids in Youth (EARLY) Trial. Circulation. 2003 Sep 2;108(9):1059-63.
20. Esposito E, Rotilio D, Di Matteo V, Di Giulio C, Cacchio M, Algeri S. A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes. Neurobiology of aging. 2002 Sep 1;23(5):719-35.
21. Faghihzadeh F, Hekmatdoost A, Adibi P. Resveratrol and liver: A systematic review. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2015 Aug;20(8):797.
22. Farid N, Inbal D, Nakhoul N, Evgeny F, Miller-Lotan R, Levy AP, Rabea A. Vitamin E and diabetic nephropathy in mice model and humans. World Journal of Nephrology. 2013 Nov 11;2(4):111.
23. Fernández-García E, C Aslani BA, Ghobadi S. Studies on oxidants and antioxidants with a brief glance at their relevance to the immune system. Life sciences. 2016 Feb 1;146:163-73.
24. 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.
25. Forman HJ, Zhang H. Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nature Reviews Drug Discovery. 2021 Sep;20(9):689-709.
26. Fuhrman B, Volkova N, Kaplan M, Presser D, Attias J, Hayek T, Aviram M. Antiatherosclerotic effects of licorice extract supplementation on hypercholesterolemic patients: increased resistance of LDL to atherogenic modifications, reduced plasma lipid levels, and decreased systolic blood pressure. Nutrition. 2002 Mar 1;18(3):268-73.
27. Furuya A, Uozaki M, Yamasaki H, Arakawa T, Arita M, Koyama AH. Antiviral effects of ascorbic and dehydroascorbic acids in vitro. International journal of molecular medicine. 2008 Oct 1;22(4):541-5.
28. Gaede P, Poulsen HE, Parving HH, Pedersen O. Double-blind, randomised study of the effect of combined treatment with vitamin C and E on albuminuria in Type 2 diabetic patients. Diabetic Medicine. 2001 Sep;18(9):756-60.
29. Gerszon J, Rodacka A, Puchała M. Antioxidant properties of resveratrol and its protective effects in neurodegenerative diseases. Medical Journal of Cell Biology. 2014;4(2):97-117
30. Goulas V, Manganaris GA. Exploring the phytochemical content and the antioxidant potential of Citrus fruits grown in Cyprus. Food chemistry. 2012 Mar 1;131(1):39-4
31. Guo Q, Li F, Duan Y, Wen C, Wang W, Zhang L, Huang R, Yin Y. Oxidative stress, nutritional antioxidants and beyond. Science China Life Sciences. 2020 Jun;63:866-74.
32. Haidara MA, Mikhailidis DP, Rateb MA, Ahmed ZA, Yassin HZ, Ibrahim IM, Rashed LA. Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rats with streptozotocin-induced Type 1 diabetes. Journal

33. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. Oxford university press, USA; 2015.
34. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. Oxford university press, USA; 2015.
35. Hayashi D, Yagi K, Song C, Ueda S, Yamanoue M, Topham M, Suzaki T, Saito N, Emoto N, Shirai Y. Diacylglycerol kinase alpha is involved in the vitamin E-induced amelioration of diabetic nephropathy in mice. Scientific reports. 2017 Jun 1;7(1):2597.
36. Huang Q, Liu H, Suzuki K, Ma S, Liu C. Linking what we eat to our mood: a review of diet, dietary antioxidants, and depression. Antioxidants. 2019 Sep 5;8(9):376.
37. Huang ZQ, Chen P, Su WW, Wang YG, Wu H, Peng W, Li PB. Antioxidant activity and hepatoprotective potential of quercetin 7-rhamnoside in vitro and in vivo. Molecules. 2018 May 16;23(5):1188.
38. Hwang J, Peterson H, Hodis HN, Choi B, Sevanian A. Ascorbic acid enhances 17 β-estradiol-mediated inhibition of oxidized low density lipoprotein formation. Atherosclerosis. 2000 Jun 1;150(2):275-84.
39. Ifeanyi OE. A review on free radicals and antioxidants. Int. J. Curr. Res. Med. Sci. 2018;4(2):123-33.
40. Ji X, Hu X, Zou C, Ruan H, Fan X, Tang C, Shi W, Mei L, Zhu H, Hussain M, Zeng L. Vitamin C deficiency exacerbates diabetic glomerular injury through activation of transforming growth factor-β signaling. Biochimica et Biophysica Acta (BBA)-General Subjects. 2017 Sep 1;1861(9):2186-95.
41. Kaushik AS, Strath LJ, Sorge RE. Dietary interventions for treatment of chronic pain: Oxidative stress and inflammation. Pain and Therapy. 2020 Dec;9:487-98.
42. Khatami PG, Soleimani A, Sharifi N, Aghadavod E, Asemi Z. The effects of high-dose vitamin E supplementation on biomarkers of kidney injury, inflammation, and oxidative stress in patients with diabetic nephropathy: A randomized, double-blind, placebo-controlled trial. Journal of clinical lipidology. 2016 Jul 1;10(4):922-9.
43. Kontush A, Mann U, Arlt S, Ujeyl A, Lührs C, Müller-Thomsen T, Beisiegel U. Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease. Free Radical Biology and Medicine. 2001 Aug 1;31(3):345-54.
44. Kornienko JS, Smirnova IS, Pugovkina NA, Ivanova JS, Shilina MA, Grinchuk TM, Shatrova AN, Aksenov ND, Zenin VV, Nikolsky NN, Lyublinskaya OG. High doses of synthetic antioxidants induce premature senescence in cultivated mesenchymal stem cells. Scientific reports. 2019 Feb 4;9(1):1296.
45. Lee EY, Lee MY, Hong SW, Chung CH, Hong SY. Blockade of oxidative stress by vitamin C ameliorates albuminuria and renal sclerosis in experimental diabetic rats. Yonsei medical journal. 2007 Oct 31;48(5):847-55.
46. Leopold JA. Antioxidants and coronary artery disease: from pathophysiology to preventive therapy. Coronary artery disease. 2015 Mar;26(2):176.
47. Lesgards JF, Durand P, Lassarre M, Stocker P, Lesgards G, Lanteaume A, Prost M, Lehucher-Michel MP. Assessment of lifestyle effects on the overall antioxidant capacity of healthy subjects. Environmental Health Perspectives. 2002 May;110(5):479-86.

48. 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 2;16(11):26087-124.
49. Li Y, Liu L, Barger SW, Mrak RE, Griffin WS. Vitamin E suppression of microglial activation is neuroprotective. Journal of neuroscience research. 2001 Oct 15;66(2):163-70.
50. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy reviews. 2010 Jul;4(8):118.
51. Lucas SM, Rothwell NJ, Gibson RM. The role of inflammation in CNS disease and injury. Br J Pharmacol. 2006;147(Suppl 1):S232-240.
52. Marnett LJ, Kalgutkar AS. Cyclooxygenase 2 inhibitors: discovery, selectivity and the future. Trends in pharmacological sciences. 1999 Nov 1;20(11):465-9.
53. Moghaddam AH, Nabavi SM, Nabavi SF, Bigdellou RA, Mohammadzadeh S, Ebrahimzadeh MA. Antioxidant, antihemolytic and nephroprotective activity of aqueous extract of Diospyros lotus seeds. Acta Pol Pharm. 2012 Jul 1;69(4):687-92.
54. Moser MA, Chun OK. Vitamin C and heart health: a review based on findings from epidemiologic studies. International journal of molecular sciences. 2016 Aug 12;17(8):1328.
55. Murphy MP. How mitochondria produce reactive oxygen species. Biochemical journal. 2009 Jan 1;417(1):1-3.
56. Naha N, Das M, Banerjee A. Toxic exposure and life style factors on ageing brain neurodegenerative disease, Alzheimer's and Parkinson's: Role of natural antioxidants to ameliorate the condition. Journal of Alcoholism & Drug Dependence. 2018; 6(2):302-309
57. Neha K, Haider MR, Pathak A, Yar MS. Medicinal prospects of antioxidants: A review. European journal of medicinal chemistry. 2019 Sep 15;178:687-704.
58. Nimse SB, Pal D. Free radicals, natural antioxidants, and their reaction mechanisms. RSC advances. 2015;5(35):27986-8006.
59. Petyaev IM. Lycopene deficiency in ageing and cardiovascular disease. Oxidative medicine and cellular longevity. 2016 Jan 1;2016.
60. Pingitore, A., Lima, G. P. P., Mastorci, F., Quinones, A., Iervasi, G., and Vassalle, C. (2015). Exercise and oxidative stress: potential effects of antioxidant dietary strategies in sports. Nutrition 31, 916–922. doi: 10.1016/j.nut.2015.02.005
61. Plantinga Y, Ghiadoni L, Magagna A, Giannarelli C, Franzoni F, Taddei S, Salvetti A. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. American journal of hypertension. 2007 Apr 1;20(4):392-7.
62. Poprac P, Jomova K, Simunkova M, Kollar V, Rhodes CJ, Valko M. Targeting free radicals in oxidative stress-related human diseases. Trends in pharmacological sciences. 2017 Jul 1;38(7):592-607.
63. Raza MH, Siraj S, Arshad A, Waheed U, Aldakheel F, Alduraywish S, Arshad M. ROS-modulated therapeutic approaches in cancer treatment. Journal of cancer research and clinical oncology. 2017 Sep;143:1789-809.
64. Reaven PD, Khouw A, Beltz WF, Parthasarathy S, Witztum JL. Effect of dietary antioxidant combinations in humans. Protection of LDL by vitamin E but not by beta-carotene. Arteriosclerosis and thrombosis: a journal of vascular biology. 1993 Apr;13(4):590-600.

65. Roberts LA, Suzuki K. Anti-Inflammatory and Antioxidant Effects of Dietary Supplementation and Lifestyle Factors. Antioxidants. 2021 Mar 2;10(3):371.
66. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertension Research. 2011 Apr;34(4):431-40.
67. Sagin FG, Sozmen EY. Anti-inflammatory effects of dietary antioxidants. Current Medicinal Chemistry-Anti-Inflammatory & Anti-Allergy Agents. 2004 Mar 1;3(1):19-30.
68. Salehi B, Martorell M, Arbiser JL, Sureda A, Martins N, Maurya PK, Sharifi-Rad M, Kumar P, Sharifi-Rad J. Antioxidants: positive or negative actors?. Biomolecules. 2018 Oct 25;8(4):124.
69. Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, Rajkovic J, Tsouh Fokou PV, Azzini E, Peluso I, Prakash Mishra A. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Frontiers in physiology. 2020b Jul 2;11:694.
70. Sharifi-Rad M, Lankatillake C, Dias DA, Docea AO, Mahomoodally MF, Lobine D, Chazot PL, Kurt B, Boyunegmez Tumer T, Catarina Moreira A, Sharopov F. Impact of natural compounds on neurodegenerative disorders: from preclinical to pharmacotherapeutics. Journal of Clinical Medicine. 2020c Apr 8;9(4):1061.
71. Shigematsu S, Ishida S, Hara M, Takahashi N, Yoshimatsu H, Sakata T, Korthuis RJ. Resveratrol, a red wine constituent polyphenol, prevents superoxide-dependent inflammatory responses induced by ischemia/reperfusion, platelet-activating factor, or oxidants. Free Radical Biology and Medicine. 2003 Apr 1;34(7):810-7.
72. Singal AK, Jampana SC, Weinman SA. Antioxidants as therapeutic agents for liver disease. Liver International. 2011 Nov;31(10):1432-48.
73. Singh B, Singh JP, Kaur A, Singh N. Phenolic composition, antioxidant potential and health benefits of citrus peel. Food Research International. 2020 Jun 1;132:109114.
74. Sisein EA. Biochemistry of free radicals and antioxidants. Scholars Academic Journal of Biosciences. 2014;2(2):110-8.
75. Skibska B, Goraca A. The protective effect of lipoic acid on selected cardiovascular diseases caused by age-related oxidative stress. Oxidative Medicine and Cellular Longevity. 2015 Oct;2015.
76. Sunkireddy P, Jha SN, Kanwar JR, Yadav SC. Natural antioxidant biomolecules promises future nanomedicine based therapy for cataract. Colloids and Surfaces B: Biointerfaces. 2013 Dec 1;112:554-62.
77. Tayebati SK, Tomassoni D, Di Cesare Mannelli L, Amenta F. Effect of treatment with the antioxidant alpha-lipoic (thioctic) acid on heart and kidney microvasculature in spontaneously hypertensive rats. Clinical and Experimental Hypertension. 2016 Jan 2;38(1):30-8.
78. Tian JF, Peng CH, Yu XY, Yang XJ, Yan HT. Expression and methylation analysis of p15 and p16 in mouse bone marrow cells exposed to 1, 4-benzoquinone. Human & experimental toxicology. 2012 Jul;31(7):718-25.
79. Trujillo J, Chirino YI, Molina-Jijón E, Andérica-Romero AC, Tapia E, Pedraza-Chaverrí J. Renoprotective effect of the antioxidant curcumin: Recent findings. Redox biology. 2013 Jan 1;1(1):448-56.
80. Uysal F, Girgin FK, Tüzün S, Aldemir S, Sözmen EY. Effect of Vitamin E on antioxidant enzymes and nitric oxide in ischemia-reperfused kidney injury. IUBMB Life. 1998 May;44(6):1255-63.
81. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects

with other respirable particles. International journal of environmental research and public health. 2009 Feb;6(2):445-62.
82. Van Der Reest J, Gottlieb E. Anti-cancer effects of vitamin C revisited. Cell research. 2016 Mar;26(3):269-70.
83. Varma V, Varma M, Sarkar PD, Varma A, Vyas S, Kulkarni R. Correlation of vitamin C with HbA1c and oxidative stress in diabetes mellitus with or without nephropathy. National Journal of Medical Research. 2014 Jun 30;4(02):151-5.
84. Wadhwa R, Gupta R, Maurya PK. Oxidative stress and accelerated aging in neurodegenerative and neuropsychiatric disorder. Current Pharmaceutical Design. 2018 Nov 1;24(40):4711-25.
85. Wang X, Meng L, Zhao L, Wang Z, Liu H, Liu G, Guan G. Resveratrol ameliorates hyperglycemia-induced renal tubular oxidative stress damage via modulating the SIRT1/FOXO3a pathway. Diabetes research and clinical practice. 2017 Apr 1;126:172-81.
86. Weikel KA, Garber C, Baburins A, Taylor A. Nutritional modulation of cataract. Nutrition reviews. 2014 Jan 1;72(1):30-47.
87. Willems PH, Rossignol R, Dieteren CE, Murphy MP, Koopman WJ. Redox homeostasis and mitochondrial dynamics. Cell metabolism. 2015 Aug 4;22(2):207-18.
88. Wu NN, Tian H, Chen P, Wang D, Ren J, Zhang Y. Physical exercise and selective autophagy: benefit and risk on cardiovascular health. Cells. 2019 Nov 14;8(11):1436.
89. Xu F, Wang Y, Cui W, Yuan H, Sun J, Wu M, Guo Q, Kong L, Wu H, Miao L. Resveratrol prevention of diabetic nephropathy is associated with the suppression of renal inflammation and mesangial cell proliferation: possible roles of Akt/NF-B pathway. International Journal of Endocrinology. 2014 Oct;2014.
90. Xu F, Wang Y, Cui W, Yuan H, Sun J, Wu M, Guo Q, Kong L, Wu H, Miao L. Resveratrol prevention of diabetic nephropathy is associated with the suppression of renal inflammation and mesangial cell proliferation: possible roles of Akt/NF-B pathway. International Journal of Endocrinology. 2014 Oct;2014.
91. Yun J, Mullarky E, Lu C, Bosch KN, Kavalier A, Rivera K, Roper J, Chio II, Giannopoulou EG, Rago C, Muley A. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. Science. 2015 Dec 11;350(6266):1391-6.