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A COMPREHENSIVE OVERVIEW OF REDOX SYSTEM WITH AN EMPHASIS ON DISEASE PROTECTION AND HEALTH PROMOTION BY MEANS OF NATURAL ANTIOXIDANT PRODUCTS

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ABSTRACT

Our body gradually deteriorates due to various ailments and detrimental conditions. One of them is oxidative stress (OS) which will be caused by an excessive amount of reactive oxygen species (ROS). The redox homeostasis wields an equivalent balance between reactive oxygen and antioxidant. The aim of this review is a comprehensive understanding of redox and antioxidant mechanism and search for strategy to combat various disease and to promote the healthy life through the intake of natural antioxidants products. As far as the structures of antioxidants are concerned a considerable number of antioxidants contains flavonoid skeleton which is polyphenol, the second, unsaturated hydrocarbons. and the third, organic acids. This structure viewpoint assists in developing and synthesizing innovative antioxidant derivatives and/or novel analogs. Electron tunneling between several redox pairs in the establishment of a protonmotive force (PMF) in mitochondria, which contain respiratory chain of five complexes, Complex I to V, cause oxidative phosphorylation. The formation of reactive oxygen species, which is the by-product of electron transfer in mitochondria, is intertwined in the oxidative phosphorylation promoting the production of complex V and adenosine triphosphate (ATP). Cancer is speculated to be caused by the oxidative stress together with the imbalance between ROS and antioxidants. The accumulation of ROS created by metabolic disturbances and signaling aberrations can promote carcinogenesis through gene mutations and pro-oncogenic signaling activation. The disturbance of redox homeostasis leads to intense pathophysiological consequences in cells which regulate the balance between the ROS and antioxidants. To accommodate oxidative stress, cells modify metabolic and genetic reprogramming, thereby leading to increased production of nicotinamide adenine dinucleotide phosphate (NADP), glutathione, superoxide dismutase and thioredoxins, returning ROS to the homeostatic level. Therefore, nonenzymatic antioxidants can be utilized for cancer therapy along with enzymatic antioxidants. Natural antioxidants in general have strong antioxidant activity with little toxicity and side effects. Taking this background into consideration antioxidants from natural sources along with supplemental sources can present a good application prospect in not only the prevention and/or treatment of various diseases but also the promotion of healthy life.

KEYWORDS: Antioxidant, redox homeostasis, mitochondria, oxidation, reduction, reactive oxygen species.

INTRODUCTION AND BACKGROUND

As far as the oxidation reduction system is concerned, it is attributed to the coordination and coupling of various electron gradients which are generated by a serial oxidation-reduction enzymatic reactions.[1] Fundamental biological processes in every cell elicit reduction-oxidation reactions and produce radical oxidant or free radicals.[2,3] The degenerative changes in aging process are referred to production of ROS and reactive nitrogen species (NOS) during cellular metabolism.[4]

Due to the natural physiological process and contact with the external environment and inappropriate diet the human organism suffer from large amount of oxygen free radicals. The antioxidant system of the organism neutralize the generated free radicals in the conditions of normal metabolism. Disturbance in the balance between free radicals and antioxidant reactions are elicited by metabolic disorders leading to the accumulations of an excessive amount of free radicals which result in oxidative stress.[5] The oxidative stress creates substantial damage to proteins, lipids and nucleic acids resulting in the development of neoplastic diseases, disorders in circulatory or nervous systems, tumor, and neurogenerative systems by accelerating degenerative processes.[6,7] The other way of observing oxidative stress is that it is an intricate process related to an imbalance between the production of reactive free radical species and the ability in the body to eliminate these species through the use of exogenous and endogenous antioxidants. In the event of endogenous metabolic process, the reactive oxygen species work as a promoter. A biological system, in which an excess amount of reactive oxygen are accumulated, can cause pathogenically harmful conditions ranging from cardiovascular diseases to cancer.[8] Many signaling pathways altered by oxidative stress include the promotion of inflammation, the impairment of mitochondrial function, the deregulation of autophagy, the induction of apoptosis, the endothelial dysfunction in mesenteric arteries, the fibrosis in the aorta, the development of insulin resistance and so.[9,10]

Redox system and related factors

Reactive oxygen, nitrogen, and chlorine species: There are three types of reactive oxygen species in the endogenous prooxidants. One is reactive oxygen species (ROS), another is reactive nitrogen species (RNS), the other is reactive chlorine species (RCS). Reactive oxygen species, reactive nitrogen species, and reactive chlorine species are shown below.

Reactive oxygen species

Super oxide anion radical, (O_2•–), perhydroxyl radical (HOO•), hydroxyl radical (•OH), peroxyl radical (RO2・) hydrogen peroxide (H2O2), singlet oxygen (1 O2), Super oxide anion (O2—) ozone (O3) reactive nitrogen species nitric oxide radical (NO•), peroxynitrite anion (ONOO－) reactive chlorine species hypochlorite radical (ClO−) hypochlorous acid (HOCl) Reactive oxygen species are highly reactive formed from diatomic oxygen (O_2). The major ROS include peroxides, superoxide, hydroxyl radical, singlet oxygen, [12,] and alpha-oxygen.[13] The reduction of molecular oxygen (O2) produces superoxide (•O−2), which is the precursor to most other reactive oxygen species. Hydrogen peroxide in turn may be partially reduced, thus forming hydroxide ions and hydroxyl radicals (•OH), or fully reduced to water.[14]

Exogenous and endogenous antioxidants

In Figure 2 the structures of antioxidants are shown. The comparison of each structure elucidated that a considerable number of antioxidants contains flavonoid skeleton which is polyphenol. The compounds with flavonoid skeleton include epicatechin gallate, quercetin, fisetin. Epigallocatechin 3,5-digallate. morin, kaempherol, and naringenin. This phenomenon indicates that flavonoid present a vigorous potential as an antioxidant. The second popular antioxidant compounds are unsaturated hydrocarbon which include lutein, lycopene, omega-3. β- carotene, omega-3-acid methyl ester, coenzyme Q10, α- tocopherol, retinol, and curcumin, The third compounds are organic acid which refers to hydroxycinnamic acid, caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, uric acid and gallic acid. This structure classification and overview assist in developing and synthesizing innovative antioxidant derivatives and/or analogs (Table 1).

ROLE OF MITOCHONDRIA

Organisms naturally produce in low concentrations free radicals which are essential for cellular functions and defense systems.[15,16] In order to produce necessary energy in the form of adenosine triphosphate (ATP) O2 is used by mitochondria. This process is intertwined with the formation of ROS during the mitochondrial electron transport chain called oxidative phosphorylation.[46,17] During energy metabolism to generate adenosine triphosphate (ATP), the redox system plays an important role while within the cell reactive oxygens are generated at different sites.[18] Glucose, which is transformed into pyruvate via glycolysis, is the most important source of energy. The mitochondrial respiratory chain consists of five complexes. Complex I is NADH dehydrogenase, complex II, succinate dehydrogenase, complex III, cytochrome c reductase, complex IV cytochrome oxidase and complex V, ATP synthase. Furthermore, the electrons are transported from complex I, through II and III, to complex IV to reduce oxygen to water.[13,14] Mitochondria are considered to be the main source of ROS because ROS is generated as a byproduct of electron transfer. The respiratory chain (mainly complexes I and III) is the predominant origin of ROS in the case of ATP synthesis. An adaptor protein with proapoptotic activity, p66shc, is involved in the production of ROS. It is reported that this protein can generate ROS by oxidizing cytochrome C.[15-18] Another source of ROS is NADPH oxidase (NOX) family of enzymes. NOX makes a use of NADPH as an electron donor to reduce oxygen, resulting in the generation of superoxide.[11,19] Figure 3 shows the electron transport chain and the source of reactive oxygen species (ROS's). ROS's are produced from respiratory chain complexes I and III as a byproduct of electron transfer in mitochondria. Enzymes in Krebs cycle are implicated as sources of ROS. Several enzymes involved in the Krebs cycle are also reported as sources of ROS. P66shc, by oxidizing cytochrome c (Cyt C), is able to generate ROS within the mitochondria intermembrane space. The NADPH oxidase (NOX) family of enzymes are another important source of ROS by reducing oxygen to generate superoxide.

Overview of Redox system

Oxidative stress induced by high level of reactive oxygen species result in the upregulation of antioxidant capacity which maintains redox homeostasis by metabolic rerouting or activation of genetic programs.[20,21] Lettner et al. investigated the effect of cocktail therapy for disused vastus lateralis muscle The cocktail containing polyphenols, omega-3, vitamin E, and selenium was intended to counteract the increased redox homeostasis and enhance the antioxidant defense response. They elucidated that decreased antioxidant nitrosative defense response was mitigated by treatment with the antioxidant cocktail and advocate positive effects of the nutritional intervention protocol for the patient on bed-rest dis used versus lateralis muscle dysfunction.[22] A free radical is an atom or molecule of on or more unpaired electron in its valiance shell. They are highly reactive because they show a strong radical productions. One is redox reaction, i. e. the gain of an electron from a molecule (reduction) or the loss of an electron from a molecule (oxidation). The other is a homeolytic cleavage of a covalent bond in which each fragment gets one of the shared electron of the bond; electron-gaining is called prooxidant and electron-donating, antioxidant. [24] ONOO− is a powerful RNS that can irreversibly inhibit electron transport, which is pathological.[18,22 −24] Both ROS and RNS are necessary for normal cell function as they modulate cell-signaling pathways and cellular processes. However, overproduction of any of them is pathological since it can bemacromolecules like proteins, lipids, or DNA.[25]

Mechanism of antioxidant

Significantly effective antioxidant against oxidizing agents is intracellular law molecular weight non-enzymatic antioxidant, i. e. coenzyme Q10 vitamin A, glutathione, bilirubin, albumin, uric acid.[25] Tocopherols (vitamin E) β-carotene (precursor of vitamin A), lycopene, vitamin C, lutein, and various polyphenols, (flavonoids, and other related compounds) are the main dietary antioxidants.[26] Oxidase and antioxidant enzymes are referred to act on the free radicals. As far as antioxidant enzymes, which are superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT), are concerned, they fulfill a significant function in the induction of reactive oxygen-scavenging enzymes. On the other hand, glutathione (GSH) synthase can induce the synthesis of endogenous antioxidant enzymes. Looking at the counter part of those enzymes, monoamine oxidase (MAO), lipoxygenase (LOX), NADPH oxidase (NOX), and xanthine oxidase (XO) promote the production of ROS.[27] Monoamine oxidase is one of the important enzymes in the redox system. MAO catalyzes the oxidation of monoamines, employing oxygen to clip off their amine group.[27,28] MAOs are bound to the outer membrane of the most of cell types of the body. MAO inactivate monoamine neurotransmitters which are involved in psychiatric and neurological diseases. MAOs are flavin-containing amine oxidoreductases and breakdown monoamines ingested in food. They inactivate monoamine neurotransmitters and cause psychiatric and neurological diseases. Because of these physiolosical reasons, monoamine osxidase inhibitors can be used to treat these diseases.[29]

Antioxidant activity of selected antioxidant

Protein hydrolysates

Antioxidant potency of five protein hydrolysates derived from Decapterus maruadsi was investigated by assaying scavenging activity (DPPH, O_2•) and reducing power assays by way of redox linked colorimetric reactions and electron-transfer evaluations by Jiang et al. They elucidated that DPPH scavenging effect revealed an increase whose extent depended on the enzyme used: neutral (32.33%) < pepsin (32.63%) < alcalase (39.36%) < trypsin (39.37%) < papain (40.21%).[30] Czelej et al. elucidated antioxidant activity of protein hydrolysates obtained from various animals and plants on their review article.[31] Those protein hydrolysates include pepsin, trypsin, neuroses, neutral protease, papain, Protex 6L, Seabzyme L 20, alcalase, flavoenzyme, αamylase, pancreatin, bromelain, proteinase, cellulase, thermolysin, peptidase, and chymotrypsin. They concluded that protein hydrolysates, which exhibit antioxidant, immunomodulatory, anticancer and antimicrobial properties, could constitute a valuable natural component for future applications not only in food products but also in the pharmaceutical, nutraceutical, and cosmetic areas.

Polyherbal Formula

Traditional herbal species used for ROS-involved ailments include the extracts of Populus alba L. leaf and shoots, Populus nigra L. and Populus berolinensis Dipp. leaf-buds (Populi gemmae), Poplar species belonging to the Salicaceae family, and Populus deltoides W. Bartram ex Marshall leaf extract.[32-35] Grigore et al. pursued a study of the antioxidant–anti-inflammatory effects of a patented preparation based on Populus nigra and Rosmarinus officinalis extracts. They tried to elucidate its applicative potential as a dietary supplement, or complementary medicine. Antioxidant–anti-inflammatory effects of a patented preparation based on Populus nigra and Rosmarinus officinalis extracts was studied to highlight its applicative potential as a dietary supplement, complementary medicine or cosmetic ingredient v and High-Performance Thin-Layer Chromatography (HPTLC) analysis revealed the presence of salicins in the formula and poplar extract. Furthermore, triterpenoid (ursolic and oleanolic) and polyphenolcarboxylic (chlorogenic and caffeic) acids were identified in the formula. They concluded that a natural product based on rosemary and poplar extracts can exhibit both antioxidant and anti-inflammatory activities that could be used as complementary treatment for relevant ailments.[36]

Lactiplantiibacillus pluntarum

Tian et al. investigated antioxidant mechanism of Lactiplantiibacillus pluntarum (LpLop) KM1 screened from natural product containing probiotic properties and antioxidant function.[37] The antioxidant mechanism of L. plantarum KM1 was deeply analyzed by using the proteomics method. The results demonstrated that a total of 112 differentially expressed proteins (DEPs) were screened, 31 DEPs were upregulated and 81 were downregulated. The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis indicated that DEPs participated in various metabolic pathways which were related to oxidative stress caused by H_2O_2 in L. plantarum KM1. Therefore, the antioxidant mechanism of L. plantarum KM1 under H_2O_2 stress provided a theoretical basis for its use as a potential natural antioxidant.[37] Free radical generation has been linked in studies to the development of CVD. It has been demonstrated that several strains of Lp. plantarum achieve antioxidant capacity by scavenging free radicals. Therefore, it is speculated that the Lplap. plantarum strains with antioxidant capacity may have the potential to mitigate CVD. Antioxidant activities L. plantarum are complex.[38,39] Dietary polyphenols include phenolic acids, flavonoids, lignans, stilbenes, catechins, tannins, and anthocyanidins. Dietary polyphenols exert powerful antioxidant action against reactive oxygen species reducing cellular oxidative stress for the prevention of pathological conditions or diseases caused by oxidative stress.[18] It is now noteworthy that dietary polyphenols/flavonoids exhibit powerful antioxidant activity for the protection against reactive oxygen species (ROS)/cellular oxidative stress (OS) towards the prevention of OS-related pathological conditions or diseases.

Beneficial role of the antioxidants against major diseases caused by oxidative stress

Antioxidants attract attention not only to basic scientists but also to clinical professionals. In this sense we should keep an eye on antioxidants from comprehensive points of view. We will examine contribution and benefits of antioxidants in various diseases. Electron tunneling between several redox pairs in the respiratory complexes and establishment and protonmative force (PMW) cause oxdative phospholidation (OXPHOS), including power complex V and the production of ATP.

Ischemic stroke

Brain dysfunction caused by variety of vascular diseases is related to cardiovascular diseases which are a common neurological disease. Atherosclerosis has been recognized as one of the main culprits for the rising incidence of stroke related mortality.[10] Cerebral ischemic/reperfusion is a pathological process involving inflammation, oxidative stress, C+ overload, and mitochondrial damage leading to neural necrosis and apoptosis.[11,12] It is imperative to regulate oxidative stress on the biological effects. Three major antioxidant systems responsible for removing over produced free radicals are grutathion, thioredoxin, and neuclernuclear factor 2-related factor 2.[13]

Osteoarthritis

Bilobalide, which is a sesquiterpenoid derived from Ginkgo biloba L., wields anti-inflammatory, antioxidant, neuroprotective activities among others.[42-44] In particular, bilobalide exhibits antioxidant and anti-matrix degradation effects by activating the nuclear factor erythroid-2 related factor 2/HO-1 Nrf2-/HO-1 pathway in the cartilage, resulting in inhibiting and improving cartilage degeneration in rabbits.[45] The initiation and progression of osteoarthritis incur osteoclastogenesis and angiogenesis in subchondral bone. Wu et al. synthesized, methoxypolyethylene glycol amine (mPEGNH2) modified polydopamine nanoparticles (PDA-PEG NPs) for treating early osteoarthritis. And then they evaluated the cytotoxicity and reactive oxygen species (ROS) scavenging ability of PDA-PEG NPs. PDA-PEG NPs were administrated to anterior cruciate ligament transection (ACLT)-induced OA mice. The results showed that PDA-PEG NPs had low toxicity both in vitro and in vivo and they elucidated that PDA-PEG NPs could inhibit osteoclastogenesis via regulating nuclear factor kappa B (NFκB) and mitogen-activated protein kinase (MAPK) signaling pathways. In vivo, PDA-PEG NPs inhibited subchondral bone resorption and angiogenesis, resulting in rescuing cartilage degradation in OA mice. They concluded that PDA-PEG NPs development could be a potential therapy for OA.[46]

Cancer

Cancer is speculated to be caused by the oxidative stress increase, and the imbalance between reactive oxygen species (ROS) and antioxidants. The accumulation of ROS created by metabolic disturbances and signaling aberrations can promote carcinogenesis and malignant progression by inducing gene mutations and activating pro-oncogenic signaling,[47] Redox homeostasis is essential function in biological system and its disturbance leads to intense pathophysiological consequences in cells, which regulate the balance between the relative reactive oxygen species (ROS) and antioxidants.[48] Oxidative stress arises when ROS are excessively produced, while antioxidants are relatively insufficient. The ROS levels are tightly regulated by antioxidant systems, including both enzymatic antioxidant and nonenzymatic antioxidant systems. To accommodate oxidative stress, cells modify metabolic and genetic reprogramming, thereby leading to increased production of NADPH, glutathione (GSH, L-γ-glutamyl-L-cysteinyl-glycine), superoxide dismutases (SODs) and thioredoxins (TRXs), returning ROS to homeostatic levels [6–8]. When the high ROS level exceeds non-toxic doses, ROS may cause oxidative damage. Luo et al. state that the treatment with weak.SOD mimic, which act as pro-oxidants, to boost antioxidant activity might be one of promising ways for cancer therapy.[48,49] Nonenzymatic Antioxidants can be utilized for cancer therapy. Those include NF-E2 p45- related factor 2 (NRF2) activators, N-acetylcholine, glutathione esters., and. On the other hand, enzymatic antioxidants which can be utilized for cancer therapy include NADPH oxidase inhibiters, SOD, and SOD mimics.[50-52] In scopolamine-induced neurotoxic mice experiment they administered orally two doses (2.5 mg/kg and 5 mg/kg) in the mice. Ex vivo experiments exerted that the mouse with the higher dose of 4b (5 mg/kg) increased reduced glutathione (GSH) levels by 46%, catalase (CAT) and superoxide dismutase (SOD) activity by 57%, and glutathione peroxidase (GPx) activity by 108%, compared with the SC-treated group. They elucidated that GCH acted as an antioxidant agent with rain protection.[92,143]

Cardiovascular disease

Alzheimer's disease (AD)

The pathogenesis of AD is well-reported in the literature.[53] The gene mutations, ROS mitochondrial dysfunction and the impairment in the antioxidant defense system have all been implicated.[53,54] The high amounts of intracellular oxygen are consumed by neuronal mitochondria to perform essential functions including not only the metabolism of amino acids, fatty acids and lipids, and energy metabolism, but also intracellular calcium homeostasis, ROS generation and ROS regulation.[55,56] Cellular and animal-based models of AD have been shown that compounds such as vitamins, carotenoids, polyphenols, and minerals have been promising their investigation in human clinical trials for their neuroprotective effects, both alone and in combination with other antioxidants and drugs.[57] Compounds such as vitamins, carotenoids, polyphenols and minerals have shown promise in cellular and animal-based models of AD, prompting their investigation in human clinical trials for their neuroprotective effects. In general, results from previous and ongoing clinical trials remain inconclusive. The role of oxidative stress in the pathogenesis of AD is well-established in the literature.[58-72] To this effect, the oxidative stress hypothesis of AD development postulates potential mechanisms by which oxidative damage causes and/or contributes to the development and progression of AD.[73,203] This hypothesis is supported by findings from molecular, genetic, and biochemical studies and highlights the detrimental role of ROS in AD onset and progression. Heightened levels of biomarkers of oxidative stress, impairments in the antioxidant defense system, gene mutations and mitochondrial dysfunction have all been implicated.[64,66] As previously mentioned, highly reactive molecules such as ROS target biomolecules such as DNA, proteins, and lipids in the instance of AD, mitochondrial dysfunction is proposed to underlie the increase in ROS.[61-73] Neuronal mitochondria consume high amounts of intracellular oxygen to perform essential functions including energy metabolism, the metabolism of amino acids, fatty acids and lipids, intracellular calcium homeostasis, ROS generation and regulation and more.[74] During mitochondrial respiration, O_2 •−, a by-product of adenosine triphosphate production, is created. In large amounts, O_2 •− induce oxidative stress by oxidizing cellular targets directly or indirectly by reacting with other molecules and oxidants to form additional ROS and reactive nitrogen species.[74] Mitochondria also produce H_2O_2, which can further exacerbate oxidative stress by the endogenous conversion reaction of H_2O_2 to •OH by Fe_2+ via the Fenton reaction.[60,74] Although the primary generation sites of O_2 •− are mitochondrial respiratory transport chains I and III, additional cellular sources that could contribute to neuronal oxidative stress include xanthine oxidase, NADPH oxidase and cytochrome P450 enzymes. To prevent a cascade of ROS production, O_2 •− is neutralized by SOD (Figure 1). Oxidative stress does not exist alone as a potential cause or contributing factor to AD.[75-79] Oxidative stress is reported to associated with other hypotheses of AD, which implicate the aggregation of intracellular tau, elastin degradation, N-methyl-D-aspartate receptor (NMDAR)-mediated cell stress and abnormal extracellular amyloid accumulation as the primary cause.[58-72,80-91] To this effect, the oxidative stress hypothesis of AD development postulates potential mechanisms by which oxidative damage causes and/or contributes to the development and progression of AD.[202] This hypothesis is supported by findings from molecular, genetic, and biochemical studies and highlights the detrimental role of ROS in AD onset and progression. - Heightened levels of biomarkers of oxidative stress, impairments in the antioxidant defense system, gene mutations and mitochondrial dysfunction have all been implicated.[64,66] As previously mentioned, highly reactive molecules such as ROS target biomolecules such as DNA, proteins, and lipids in the instance of AD, mitochondrial dysfunction is proposed to underlie the increase in ROS.[61-73] Again, neuronal mitochondria consume high amounts of intracellular oxygen to perform essential functions including energy metabolism, the metabolism of amino acids, fatty acids and lipids, intracellular calcium homeostasis, ROS generation and regulation and more.[74] Sineonova et al. investigated antioxidant inhibitory effect of galantamine-carcumin hybrid (GCH), named 46, on scopolamine-induced neurotoxic mice. In this experiment they administered orally two doses (2.5 mg/kg and 5 mg/kg) in the mice. Ex vivo experiments exerted that the mouse with the higher dose of 4b (5 mg/kg) increased reduced glutathione (GSH) levels by 46%, catalase (CAT) and superoxide dismutase (SOD) activity by 57%, and glutathione peroxidase (GPx) activity by 108%, compared with the SC-treated group. They elucidated that GCH acted as an antioxidant agent with brain protection.[92]

Cardiovascular disease

Among cardiovascular diseases (CVD), stroke and acute myocardial infarction are the main causes of death. Either partial or complete occlusion of the coronary arterial circulation produce myocardial infarction, The occlusion of the coronary arterial circulation causes atheromatous plaques that are vulnerable to rupture or erosion leading to thrombotic alterations that block blood flow to cardiac tissue.[93,94] Higher dietary intake of nonenzymatic antioxidants derived from ferric reducing antioxidant power and oxygen radical absorbance capacity decrease risk of mortality from heart disease, and cerebrovascular disease.[95] Nirmiran et al. reported an inverse association of Vitamin E and the risk of cardiovascular disease and emphasized the protective effect of fruits and vegetables in the prevention of CVD.[96]

Hepatic Disease

Aghemo et al reviewed literatures on the role of silymarin as antioxidant in the clinical management of chronic hepatic disease.[97] The review elucidated that 5 clinical trials involving 602 patients with alcoholic liver disease (ALD) and liver cirrhosis showed a 57.8% reduction in liver-related mortality in patients taking silymarin compared to placebo.[98] The review also noted that meta-analysis conducted by de Avelar et al. advocates the use of silymarin in reducing serum levels of ALT and AST,[99] wherein randomized and controlled clinical trials were included. Furthermore, the review revealed that the meta-analysis conducted by Saller et al. wherein 36 articles were used for the examination, also confirmed the use of silymarin in liver diseases, and reduction in mortality rates following the administration of silymarin due to the improvement in liver function tests.[100]

Diabetic mellitus

Mahnaashi et al. investigated the phytochemicals regarding to antidiabetic and antioxidant capacities of Allium consanguineum. Allium consanguineum is species of the Amaryllidaceae family. Several species of the Allium genus are reported to exert significant pharmacological activity including anti-viral, antidiabetic and antioxidant activities. In vivo anti-diabetic results of investigated compound 1 (s (E)-4-(3-hydroxyprop-1-en-1- yl)-2-methoxyphenol) and compound 2(6-allyl-4,5-dimethoxybenzo [d][1-3] dioxole) in albino experimental mice were noteworthy in lowering the blood glucose levels. The observed decrease in blood glucose level for the mice groups treated with the compound 1 extracted from Alliium. Consanguineum were 119, 205, 47, 37 and 36 mg/dl against the groups for which 500 to 31.25 μg/ kg were administered in 15 days experiments. Similarly, the decrease in blood glucose levels with the compound 2 were 201, 112, 68, 59 and 33 mg/dl for the five groups. The observed plant exhibits dose-dependent inhibitory action against alpha glucosidase and alpha amylase enzymes. They claim that they provides a baseline guideline for the use of crude extract and isolated compounds from Allium consanguineum for the management of diabetes.[101]

Lioa et al. elucidated that Polysaccharide from Okra (OP, Abelmoschus esculentus L. Moench) enhances antioxidant capacity in a Type 2 diabetes model. They observed that the levels of fasting blood glucose level FBG in the model group were remarkably higher than the control group ($p < 0.001$). However, after the administration of Okra (200 or 400 mg/kg) for eight weeks, the fasting blood glucose levels decreased significantly ($p < 0.05$, $p < 0.001$). They observed that the amount of superoxide dismutase, catalase, and glutathione peroxidase decreased significantly in the livers of the diabetes mice compared with the blank group ($p < 0.01$, $p< 0.01$, and $p < 0.05$, respectively). After eight weeks of treatment with Oka (400 mg/kg) improved this reduction ($p < 0.05$). The opposite results were observed regarding the level of malondialdehyde in the model mice, which was significantly increased compared with the level in the control group ($p < 0.001$), and treatment with OP (400 mg/kg) could reverse this change ($p < 0.05$). OP alleviated the type 2 diabetic mellites characteristics through the activation of the phosphoinositide 3- kinase(PI3K)/protein kinase B (AKT)/glycogen synthase kinase 3 beta (GSK3β) pathway, enhanced the nuclear factor erythroid-2 expression. And promoted Nrf2- medicated heme oxygenase-1(HO-1). Okra also relieved mitochondrial dysfunction by inhibiting NOX2 activation. They proposed that a polysaccharide isolated from Okra exerts anti-type 2 diabetic mellites effects partly by modulating oxidative stress through PI3K/AKT/GSK3β pathway-medicated Nrf2 transport. Polysaccharide wields hypoglycemic activity, as well as its underlying mechanism.[102]

Cytotoxicity

Alhoshani et al. tested the antioxidant and anti-inflammatory effects of lycopene against 5FU-induced cytotoxicity in Caco2 cell line. Lycopene enhanced 5FU-induced SOD activity and GSH level compared to control group. Lycopene supplementation with 5FU therapy resulted in improvement in antioxidant parameters such as catalase and GSH levels giving the cell capacity to cope with 5FU-mediated oxidative stress.[110]

Natural foods and diet groups

Vegetables

Generally speaking, vegetables are abundant in vitamins and provitamins which encompass ascorbic acids, tocopherols, and carotenoids. They also contain phenolic substances that exert strong antioxidant properties.[73] These vegetables are abundant in polyphenol Compounds. A question here is whether those antioxidant capacities remain active by thermal treatments or not. Ismail et al. investigated this thermal effects on antioxidants of vegetables under the title of " total antioxidant activity and phenolic content in selected vegetables."[74] They elucidated that spinach had the highest phenolic content, followed by swamp, kale, shallot and cabbage. After a 1-min blanching in boiling water, swamp cabbage lost the highest amount of phenolic content (26%), followed by cabbage (20%), spinach (14%), shallot (13%) and kale (12%). The statistical analysis showed significant differences in the total phenolic content between fresh and treated vegetables. They concluded that phenolic compounds were very sensitive to heat treatment even in a short period of cooking. Increasing attention has been paid for natural pigments such as carotenoids, β-xanthine, β-cyanins, anthocyanin, betalains, and chlorophylls from the stand point of safety, and esthetic food. Amaranthus (red amaranth) is a unique source of battalions, β-xanthine, and β-cyanins that have potential free radical detoxifying ability. Red beet and amaranth are edible vegetables and contain natural pigments such as betalain, β-cyanins, β-xanthine. Red morph Amaranthus is a spectacular source of color pigments such as β-cyanins, β-xanthine, betalain, anthocyanin, amaranthine, carotenoids, and chlorophylls. These pigments exhibit free radical detoxifying ability as a potent antioxidant.[75] Vegetable amaranth is a bioactive compound that exert a prominent significance as a food natural antioxidants and ROS scavenger.[76] Sarker et al. pursued a research on the antioxidant activity in selected red morph Amaranthus leafy vegetables. They concluded that red morphs amaranth leaves can be a potential leafy vegetable as a source of natural antioxidant pigments having strong antioxidant activity in our daily diet to combat with the hidden hunger attaining nutritional and antioxidant insufficiency.

Fish

Functional materials fish can provide include polysaccharides, essential minerals, vitamins (A and E), antioxidants, enzymes, bioactive peptides and polyunsaturated fatty acids (PUFA) such as eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA exert protective effects against such diseases as cardiovascular diseases, colon cancer, and disorder in immune systems.[77] It is recommended to consume two meats of fish per week considering these beneficial effects of fish.[78] Aghakhan Kheiri1 et al. investigated the antioxidant potential and fatty acid profile of fish fillet: effects of season and fish species. The fillet extracts of zander and bream in summer and common carp in winter had the highest antioxidant activity. In summer, the highest levels of total PUFA, n3 PUFA and n3/n6 ratio were observed in zander. In winter, the highest amounts of total PUFA and n3 PUFA were detected in silver carp, followed by zander. They concluded that seasonal variation changed the antioxidant potential and fatty acid composition of fish fillets. River fishes, especially zander, exhibited the excellent antioxidant activity and high nutritional quality.[79]

Fruits

Fruits are imperative to maintain a healthy diet because of the content of antioxidant compounds such as vitamins (Vitamin C, Vitamin E), minerals (selenium, manganese, and zinc), polyphenols (flavonoids and anthocyanins) and other components such as fiber (pectin and cellulose). Their activity is associated with the scavenging of free radicals and nonradical reactive oxygen species.[80] The intervention programs have been promoted on fruit and vegetable consumptions considering the association of their low consumption with the high risk of various diseases. Those diseases include noncommunicable diseases, cancers, osteoporosis, type 2 diabetes, osteoarthritis, obesity, cardiovascular illnesses, degenerative diseases, high blood pressure and strokes.[86-90] Pavlina Drogoudi et al. investigated phenotypic variation in fruit antioxidant contents in European and Japanese plum.[91] The hexaploidy European plum and diploid Japanese plum are two most crucial commercial plum cultivars. Plum contributes to prevention of osteoporosis, and memory improvement with anti-inflammatory, antioxidant, and laxative effects. They found that both the Japanese plums and the European plums were characterized by particularly rich dietary sources of phytochemicals and the plums are a rich source of phenolic compounds, being ranked superior to various other fruits such as apple, banana, peach, pear, and watermelon. They also found that the large variation in the peel/flesh antioxidant content ratios among the studied cultivars and that the peel can have significance equal to that of flesh in providing nutritive value in a plum fruit. This is a valuable study in that we tend to pear off the peel without eating.

Grains

lJoanne Slavin pointed out four mechanisms to which the protectiveness of the body in the whole grains intake are associated. Those four mechanisms are large-bowel effects, glucose and insulin changes, the antioxidant capacity for protectiveness, and other effect of bioactive compounds. The primary protective function of antioxidants in the body is their reaction with free radicals. Cellular membrane damage is caused by free radical attack and the resulting peroxidation is considered to be a principal responsible ill factor. Whole grain products are relatively abundant in antioxidant activity. Antioxidants found in wholegrain foods are water- soluble and fat-soluble with approximate half and half in ratio. Soluble antioxidants include phenolic acids, flavonoids, tocopherols and avenanthramides in oats. A majority of the insoluble antioxidants are bound to arabinoxylan side chains of hemicellulose as cinnamic acid esters. Covalently-bound phenolic acids are beneficial free radical scavengers. In the colon hydrolysis by microbial enzymes liberates bound phenolic acids. Colon endothelial cells absorb the released phenolic acids to gain antioxidant protection property, and these phenolic acids also enter the portal circulation. Eventually, wholegrain foods provide antioxidant protection capacity over a long period of time through the entire gastrointestinal digestive trac.[104-106] Natural raw materials sufficient in dietary fiber and high in antioxidant capacity serve not only as functional ingredients for the food industry but also as functional food in our daily life. As a matter of fact, the use of cheap and nutritionally valuable raw materials which may otherwise go as waste products is being encouraged to utilize.[107] Tingting Song et al. explored antioxidant activities of seven types of grains fermented with Sanghuangporus sanghuang fungus.[108] Sanghuangporus sanghuang (SS) is a rare medicinal polypore fungus. Seven grains they investigated are oats, barley, millet, rice, buckwheat, corn, and coix seed. Oats were one of the best grains for SS fermentation, SS- Oat produced 6.23 mg QE/g polyphenols, 21.8 mg rutin/g flavonoids, and 2.3% triterpene. They elucidated that grain can produce more antioxidants when fermented with SS and that there was a high correlation between antioxidant capacity and bioactive compound levels after fermentation.

Selected individual natural foods and diets

Dioscorea

It is a common practice to use several Dioscorea species for various medicinal purposes considering the property of phytochemicals with antioxidant properties. They are related mainly to radical scavenging capacity in chemical assays and positive effects on the endogenous antioxidant system in cell-based and in vivo assays.[109] The analysis of anthocyanins using LCMS-IT-TOF mass spectrometry in the vines of purple yams (D. alata) revealed that two investigated accessions from 8 months old had cyanidin or peonidin nuclei, while their glycosides were nonacylated, monoarylated, or diacylated with sinapicsynaptic or ferulic acid. Cyanidin 3-(6-sinapoyl gentio bioside (alatanin C) was the major yam anthocyanin. [110] Padhan et al. reported that the flavonoid, total antioxidant capacity and in vitro antioxidant activity of eight wild Dioscorea species (D. oppositifolia, D. hamiltonii, D. bulbifera, D. pubera, D. pentaphylla, D. wallichii, D. glabra, D. hispida) and one cultivated (D. alata) yam tuber from Koraput (India): TPC, TFC, and total antioxidant capacity ranged from 2.19 to 9.62 mg GAE/g pdw, 0.62– 0.85 mg QE/g pdw and 1.63–5.59%, respectively; meanwhile, the IC_{50} values were 77.9–1164, 101.2–1031.6, 27.0–1022.6 and 47.1–690 µg/mL for DPPH• , ABTS•+ ,•O2−, and •NO scavenging capacity, respectively.[111]

Sesame

Sesame oil has been reported to use for the treatment of a number of diseases including oxidative-induced various ailments. By modulating the antioxidant enzymes as well as of oxidative stress markers, sesame seeds and its oil can reduce oxidative stress.[112] Sesame is a popular ethnomedicinal plant and its oil has been reported to use against a number of diseases including oxidative different ailments. Experimental studies have been reported that sesame seeds and its oil can reduce oxidative stress by modulating the antioxidant enzymes as well as oxidative stress markers. In rat model, oxidative stress induced by lipopolysaccharide (LPS) was reduced.[113] Furthermore, oxidative stress induced by lipid peroxidation, hydroxyl radical and nitrite levels in rat model was reduced by the antioxidant enzyme superoxide dismutase (SOD) and catalase.[114,115]

Green Tea

Nonalcoholic fatty liver disease (NAFLD) is one of the most important public health issues induced without alcohol consumption.[116] The estimated morbidity of NAFLD is about 17–33%, 75% in obese individuals, and even more in patients with type 2 diabetes mellitus (T2DM).[93,94] Beneficial effect of green tea with its most abundant catechin EGCG against NAFLD have been reported. The mode of action of green tea may include, not only alleviating oxidative stress, but also promoting lipid metabolism, inflammation cascades, fibrotic response, and HCC tumorigenesis. It is noted that oxidative stress mediated by excessive accumulation of reactive oxygen species has associated with the signaling pathway of nonalcoholic liver diseases acting as an accelerator. Green tea is one of the most imperative natural dietary antioxidant with EGCG as a notably contributing resource.[117] It is proposed that green tea extract possibly attenuate liver steatosis in NAFLD by improving lipid metabolism via targeting SIRT1 and AMPK signaling pathways.

Melatonin

The generation of reactive oxygen takes place, when inflammatory cytokines concentration increase after lymphocyte and macrophage infiltrated into the central nervous augments. This circumstance occurs when the organism's defense mechanism of antioxidant is deficient because of the unwarranted release of oxidants.[118] Consequently, the large amount of lipid peroxidation products (LPO) are generated, and then the nuclear and mitochondrial DNA as well as cell tissues and walls are damaged.[119] Since ROS possess unpaired electrons they can capture electrons from other molecules. At the same time, they can react with some unsaturated fatty acids existing in the cell membranes resulting in activating the lipid peroxidation process, and triggering the modification of proteins and the changes in the membrane gradient leading to a loss of their integrity and irreversible damage.[120] Since melatonin exert the distinctive antioxidant property, it can conquer the oxidative stress produced by multiple sclerosis (MS) reducing not only macromolecular damage in all the organs but also the principal oxidative stress biomarkers such as carbonylated proteins (CP), lipid peroxidation products (LPO), nitric oxide (NO) and malondialdehyde (MDA).[121-123] Escribano et al. demonstrate that melatonin has the capacity to restore the body's antioxidant defenses mechanism decreasing the main oxidative stress biomarkers.[104]

Cranberry

Inflammation in the body inhibit urinary tract infections, reduce inflammation in the body, maintain a healthy digestion system, and decrease cholesterol levels.[125] Cranberry fruit is rich in an imperative source of antioxidants, such as ascorbic acid, triterpene, and polyphenols (flavonoids, phenolic acids), with electrons in their outer orbit but also remove reactive oxygen species that oxidize biological organisms.[128] Their role is indispensable to preventing the incidence of chronic diseases such as diabetes, inflammation and so on.[129] There are two types of cranberries, large cranberry and small cranberry. Both of them contain large number of phenolic compounds including tannins, phenolic acids, and flavonoids (anthocyanins and flavonoids).[130] Cranberry fruits are divided into three species, Vaccinium macrocarpon Ait., Vaccinium oxycoccos L., and Vaccinium vitisidaea (lingonberry grown in North America and Europe), and 4624 compounds were identified with about 8000–10,000 phytochemicals found in each type.[131]Phytonutrients of cranberry include anthocyanins, phenolic acids, flavonoids, flavan-3-ols, proanthocyanidins, and triterpenoids with antioxidant activities. Nenzer et al. states that consumption of cranberry offers a reliable protection from and prevention of many chronic diseases such as cardioprotective, anti-carcinogenic, anti-diabetic, anti-inflammatory, antipyretic, antiseptic, antibacterial, antiviral, and other effects. An increase in demand for functional foods has led to development of food products with added protein.[127]

Capsicum

Capsicum is mainly distributed in tropical and temperate areas and it is reported that five species exist including *Capsicum annuum L., Capsicum accatum L., Capsicum chinese Jacq., Capsicum frutescens L., and Capsicum pubescens, Among Capsicum* baccatum L., Capsicum chinese Jacq., Capsicum frutescens L., and Capsicum pubescens, Capsicum annuum L, (Bell pepper) is beneficial and has pharmacological characteristics such as antioxidative, anti-inflammatory, and anticarcinogenic characteristics.[132]Leng Z. et al. conducted in Vitro assays on pulps and peppers of yellow, green, and red bell peppers and elucidated that they are abundant in phenolic compounds.

Dragon fruit

Dragon fruit (Hylocereus spp.) is a tropical fruit which contains an abundant amount of phenolic compounds. The pulp of dragon fruits are particularly rich in phenolic compounds which reveal antioxidant activity contributing to exhibit various health benefits. White dragon fruit has red peel and white pulp which is used for healing wounds and bruise as indigenous medicine in Mexico. Chen et al. pursued an examination on Australian dragon fruits and elucidated that dragon fruit pulp had a total of higher phenolic content and stronger antioxidant capacity than peel. On the other hand, the dragon peel had a higher content of flavonoids and tannin content.[134] Overall, pulps and seeds of yellow, green, and red bell peppers were proved to be abundant in phenolic compounds with considerable antioxidant potential. They concluded that different parts of bell peppers could be good sources of phenolic compounds with remarkable antioxidant capacity as, cosmetics, pharmaceutical, and nutraceutical industries.[133]

Fermented Food Products

Lactiplantibacillus pluntarum scavenge free radicals and exert antioxidant activities which are additionally attributed to intracellular enzyme system. In case oxidative stress encountered, antioxidant enzymes such as catalase, NADPH peroxidase, and thioredoxin reductase are activated to resist oxidative stress.[135]Tang et al. identified that L. plantarum MA2 exerts the antioxidant capacity in vitro and that the antioxidant-related genes including cat, gshR, and npx were upregulated under hydrogen peroxide (H_2O_2) challenge.[136] The gshR and npx were upregulated in L. plantarum AR113 with probiotic activities after H_2O_2 treatment.[137] Furthermore, in response to H_2O_2 many genes in various pathways changed from the global transcriptomics perspective of L. plantarum CAUH2.[138] Tian et al. pursued a proteomics assay on the antioxidant activities of L plantarum KB 1 under H_2O_2 stress and concluded that differentially expressed proteins participated in various metabolic pathways including pyruvate metabolism, carbon metabolism, TCA cycle, amino acid metabolism, and microbial metabolism in response to oxidative stress caused by H_2O_2 in L plantarun KB1. Therefore, it is noteworthy to acknowledge that L plantarun KB1 which was derived from natural fermented food exerted good antioxidant activity in vitro.

Cereal

Cereal contains 0.1 – 0.5 % of ferulic acid which is known to exhibit antioxidant activity.[139] The phenolic ring of ferulic acid exert rather strong resonance stability and can accept the electron more easily from free radical. Moreover, hydrogen peroxide, superoxide, hydroxyl radical, nitric oxide and ABTS radical, nitrogen dioxide free radicals and hydroxyl radicals in a reaction system are scavenged very well by ferulic acid.[140,141,92,93] NADPH (nicotinamide adenine dinucleotide phosphate) oxidase system present in the vasculature is the major source of free radicals. Angiotensin II stimulates the reactive oxygen species generation via NADPH oxidase in SHR rats and DOCA-salt rats aorta.[142-144,94-96] It is reported that NADPH might inhibit the NADPH oxidase in SHR rat aorta,[145,97] Polyphenolics extract of whole wheat grains and ferulic acid protected in rat cardiomyocytes with doxorubicin induced cardio-toxicity. Therefore. ferulic acid might prevent the increased iNOS expression, NADPH oxidase activation, and Nrf-2/HO-1 impairment in this rat.[146]

Mushroom

The oxidation process is essential for various living organisms to produce energy necessary for the various physiological functions leading to oxidative stress. The scavenging of free radicals is a technique for lipid oxidation inhibition generally used for evaluating antioxidant potential.[147] Throughout this oxidative stress, freely radicals attack cells, tissues, and organs in addition to their proteins, RNA, and DNA resulting in apoptosis, necrosis, body disorders and illnesses such as cardiovascular diseases, diabetes, aging, and various forms of cancers. The inhibitive potency of mushrooms fungal species against premature mortality is closely linked to their large quantities of potent antioxidants such as ergothioneine and grutathione.[147-149] Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay is useful in predicting antioxidant activities by inhibiting lipid oxidation. Hasnat et al. reported that the ethanol and aqueous extracts of Russula virescens demonstrated scavenging potential against DPPH radicals in a dose-dependent fashion.[150] At a concentration of 6.4 mg/mL, the Pleurotus ostreatus methanol extract showed 81.8% scavenging activity against DPPH radicals.[151] Fung et al. pursued an investigation on a DPPH scavenging ability of Lignosus rhinoceros with the concentrations ranged between 1 and 16 mg/mL and the DPPH scavenging potential was elucidated to be dose-dependent.[152] Mau et al. reported scavenging effects using Antrodia camphorata methanol extracts at a concentration of 2.5 mg/m and elucidated the concentration ranging between 96.3% and 99.1%.[153]

Mwangi et al. stated that mushrooms equipped with antioxidant bioactive compounds such as flavonoids, phenolics, polysaccharides, glycosides, phenols, tocopherols, ascorbic acid, organic acids besides other compounds exhibit inhibitory and immunological potency. These biomolecules play vital roles such as scavenging free radicals in the body and thus inhibiting carcinogenesis. Phenolic biomolecules are therefore naturally occurring substrates for oxidative enzymes, which are abundant in large amounts in mushrooms. Mushrooms synthesize various chemically assorted substances which contain comprehensive range of physiological functions. Therefore, mushrooms exhibit significant health benefits which improve the quality of life of human beings.[154]

Fresh-cut fruits and vegetables

Hu et al. reviewed and reported the effects of chopping modes and intensities of fresh-cut fruits and vegetables.[155] They showed the comparison of phenolic contents of whole and fresh-cut fruits and vegetables such as Carrot, Potato Dragon, Broccoli, Onion, Lettuce, Sweet potato and celery and indicated the degree of increase times ranged from 5.21 of carrot to 1.13 of celery.[156.157] They also explored the contents comparison of phenolic compounds in fresh- cut fruits and vegetables with different cut-wounding intensities. The degree of increase times of florets cutting (10 × 10 cm) of broccoli against the whole broccoli was 1.27 while that of florets cutting (2.5 × 2.5 cm) was 1.46.[158] The degree of increase times of slices of carrot against the whole carrot was 1.67 while that of shreds was 5.21.[159,22] The degree of increase times of slices of onion against the whole onion was 1.36 while that of pies was 1.44.

The degree of increase times of slices of pitaya against the whole pitaya was 1.43 while that of pies was 1.76.[160] suggested that fresh-cut processing to exert wounding stress can be used as an effective way to improve the nutritional composition and function of fresh-cut fruits and vegetables.

Pecan

Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans, pine nuts, pistachio nuts, and walnuts which are low in saturated fat and cholesterol may reduce the risk of heart disease.[161] Turgut et al. examined the chemical composition and antioxidant properties of the extracts obtained from two byproduct streams generated at a commercial pecan nut shelling operation. They elucidated that ASE extraction of byproduct is the optimal process for obtaining a water extract with high DPPH, TPC, ABTS and FRAP activities.[162] The antioxidant properties of various plant extracts are commonly attributed to their phenolic content.[163]

Buckwheat

Because of the limitation of various nutrients, the fortification of basic gluten-free formulations is recommended to develop value-added products including pseudocereal flour such as buckwheat to produce gluten-free bread.[164] Since buckwheat flour contains total higher phenolic constituent, especially rutin, the antioxidant activity of buckwheat flour is superior to that of rice flour.[165] Furthermore, the incorporation of light buckwheat flour in gluten-free cookie formulation contribute to increase antioxidant activity of the enriched gluten-free cookies.[166] Hou et al. investigated relationships of changes between antioxidant capacities and major non-enzymatic antioxidant compounds including vitamin C, vitamin E, flavonoids, carotenoids, and chlorophyll of tartary buckwheat during germination. They found that although a germination decreased the vitamin E activity, a good accumulation in the content of vitamin C (0.71 mg/g), total flavonoids (19.53 mg rutin/g), and rutin (11.34 mg/g) was found after 7-day germination. Furthermore, they elucidated that germination improved the activities of buckwheat extracts to scavenge DPPH, ABTS, and superoxide free radicals by 107, 144, and 88 %.[167] Živkovi et al. investigated the influential consequences of the cold dehulling of buckwheat seeds on their germination, total phenolic content (TPC), antioxidant activity (AA) and phenolics composition. The high levels of orientin, vitexin and other phenolic compounds were detected for dehulled germinated seeds (e.g., isoorientin, rutin; 1402, 967 µg/g dry weight, respectively).[168]

Oat

Vanillic acid, and p-coumaric acid are the major antioxidants in oat. Carotenoids may act as oxygen quenchers and can transfer an electron to the radicals to give rise to a stable carotenoid radical cation.[169] Thus, it is note-worthy to assess the quality and contribution of carotenoids to antioxidant activity of oat. Oat oil extract obtained with ethanol was found to contain all the phenolic acids they studied, and these components were present in the highest concentrations among all of the oil extracts. As the polarity of the extraction solvent increased, the oat oil extracts contained more antioxidant components. They demonstrated that oat oil has the potential to act as an antioxidant agent for the preservation of oil.[165]

Esfandi Rsjandai et al. investigated antioxidant properties of oat bran protein hydrolysates in stressed hepatic cells. The Cellulase Protein Isolate (CPI) and the Viscozyme Protein Isolate (VPI) were obtained after solubilization of oat bran at pH 9.5. Each protein isolate was digested with proteolytic enzymes to produce eight protein hydrolysates. The CPI-derived hydrolysates were named CPI-Al, CPI-Fl, CPI-Pa, and CPI-Pr, respectively while the ones from VPI were named VPI-Al, VPI-Fl, VPI-Pa, and VPI-Pr, respectively. The hydrolysates, CPI-Fl, VPI-Al, VPI-Fl, VPI-Pa, and VPI-Pr were selected because they were either cytoprotective, produced less ROS, or had a higher amount of glutathione (GSH). The induction of oxidative stress by 2,20 -azobis (2-amidinopropane) dihydrochloride (AAPH) reduced the activity of catalase, glutathione peroxidase (GPx), and superoxide dismutase (SOD) to 87.5% ± 6.1%, 75.7% ± 0.7% and 55.2% ±1.1%, respectively in relation to normal cells. The change was not significant in the case of catalase. The activity of catalase increased by up to 3-fold when cells were pre-treated either of the five hydrolysates with VPI-Pa having the most up-regulation. A similar increase was reported in human hepatic carcinoma HepG2 cells (ATCC® HB-8065™)HepG2 due to the action of peptide GLVYIL.[170]

Chickpea

Plant-based proteins are gaining popularity since they are low cost, healthier, and sustainable sources with reduced environmental impacts quality and safety.[171] Furthermore, legume protein products are becoming the most appropriate alternative due to their high nutritive quality, and good techno-functional properties. While there are many legumes, chickpeas are a very important part of the human diet due to their nutritional and bioactive composition. Mesfin et al. investigated the effect of germination, roasting on physicochemical, techno-functional, and antioxidant properties of chickpea. Chickpea protein isolates prepared from native Arerti and Natoli flours were 179.8 and 186.0 mg GAE/100 g, and roasting significantly increased the total phenol content of the isolate, and this could be attributed to the production of Maillard reaction products during roasting. Germination also improved the total phenolic content by 16.2–51.6% for CPIs obtained from Arerti chickpea and by 39.1–76.6% for CPIs obtained from Natoli chickpea.[172] Dulce-María et al. investigated the role of sprouting of black chickpea seeds on the synthesis of isoflavones to evaluate the impact of the soluble isoflavone on cellular antioxidant activity (CAA) and antiproliferative activity in breast cancer cells. In sprouted black chickpea, six isoflavones such as formononetin, biochanin-A, and its glycosides were identified and the total isoflavones content increased by 0.31 to 35.72 mgBA/mg of extract. The CAA was increased five times from 137.2 to 788.2 mMEQ/100 g of sample. They proposed that bioactive compounds, as isoflavones, in sprouted black chickpea showed a potential antioxidant and antiproliferative activity.[173] León-López et al. investigated antioxidant activity in chickpea sprouts through elicitation with hydrogen peroxide. They applied multi-response optimization means by response surface methodology (RSM) with desirability function (DF) to modulate the elicitor concentration (hydrogen peroxide (H_2O_2)) and germination time in order to maximize total phenolic content (TPC), total flavonoids content (TFC), and antioxidant activity (AOX) of chickpea sprouts. They elucidated that the optimum attributes in chickpea sprouts can be achieved by the application of 30 mM H2O2 and 72 h of germination time, with global desirability value D = 0.893. They substantiated elicitation with H2O2 as an effective approach to improve phytochemical content and antioxidant activity in chickpea sprouts.[174]

Egg White

In recent years a note-worthy attention has been paid for natural antioxidant compounds including protein-derived bioactive peptides such as egg white hydrolysates (EWH) against oxidative imbalance preventing dysfunction in hypertensive and obese experimental models,[175,] Wiggers et al. examined whether the antioxidant properties of EWH have a protective effect against vascular damage caused by exposure to $HgCl_2$ in mesenteric resistance arteries (MRA).They elucidated that egg white hydrolysate intake prevented the increased contractile responses to noradrenaline and the reduced endothelium dependent vasodilator response to acetylcholine induced by $HgCl_2$ exposure. EWH taken as a functional food at low concentrations reversed the increase in systolic blood pressure induced by chronic exposure to $HgCl_2$ which is attributed to the reduction of contractile responses and the vascular dysfunction induced by the metal in MRA. They postulated that EWH benefits could be contributed by its ND-induced by vasodilation capacity and its antioxidant and anti-inflammatory properties.[176] Nowadays, increasing demands for bioactive protein hydrolysate derived from natural sources have been observed by nutraceutical and health food industries. Furthermore, immunity is among people's utmost concern in this period and therefore, consumers are keen to change their diets to healthier alternatives.[177] The production and characterization of protein hydrolysates from various food sources with different bioactivities including antioxidant activity have been investigated.[178] The productions of bioactive hydrolysate peptides from egg white proteins through enzymatic hydrolysis have been reported.[179] Johny et al. investigated the process optimization, production and evaluation of whole egg white protein hydrolysate (WEWPH) using pineapple bromelain through the Box-Behnken design.[180] They analyzed the DPPH, ABTS, HO_2, O_2 - scavenging activity, ferric reducing antioxidant power (FRAP) and singlet oxygen quenching ability of the WEWPH. They advocate that the WEWPH can be used as a promising functional ingredient in the development of health food and nutraceutical products to benefit human health and that the application of bromelain from the pineapple crown discard/waste to the development of bioactive WEWPH would raise the extra value and usage to improve agricultural environment.

Pearl millet

Pearl millet is nutritious staple food grains worldwide, especially in the hottest and driest rainfed farming regions of Africa and Asia and it is one of the four most important cereals grown in the tropical semi-arid regions of the world. Since the crop can easily survive on marginal lands, in harsh climatic conditions it has excellent sustainability credentials. It has a short growing period to complete its life cycle and, 8–15 times greater α-amylase activity compared with wheat. Furthermore, pearl millet has a low glycemic index (50) and is gluten-free, exhibiting an ideal candidate grain for use in the functional-food market worldwide.[181] It also contains several phenolic compounds such as benzoic and cinnamic acid derivatives, anthocyanidins, flavonoids, lignans, and phytoestrogens, which play an important role in preventing various diseases.[182] Yadav et al. pursued a study to identify the total antioxidant content of pearl millet flour and to apply it to evaluate the antioxidant activity of its 222 genotypes drawn randomly from the pearl millet inbred germplasm association panel (PMiGAP), a world diversity panel of this crop. Pearl millet is an important antioxidant food resource exhibiting with a wide range of phenolic compounds that are good natural antioxidants. They elucidated that the total phenolic content (TPC) is significantly correlated with DPPH (1,1-diphenyl-2- picrylhydrazyl) radical scavenging activity (% inhibition), which ranged from 2.32 to 112.45% and ferric-reducing antioxidant power (FRAP) activity ranging from 21.68 to 179.66 (mg ascorbic acid eq./100 g). They were able to explore the genetic architecture of the antioxidant contents in pearl millet using LD-based GWAS, manipulating historical recombination in a natural germplasm population. Resequencing data and phenotyping of DPPH and FRAP resulted in the identification of highly significant SNP markers associated with antioxidant contents. The gene analysis of SNP region has identified potential candidates which will provide a great resource to select these important traits in pearl millet breeding programs.[183] Pushparaj et al. investigated the effect of various processing methods such as milling, boiling, pressure cooking, roasting and germination on the antioxidant components as well as the antioxidant activities in the commonly used pearl millet cultivars. They elucidated that the antioxidant activity of pearl millet was affected not only by the processing methods but also by the cultivar types. Kalukombu (K) and Maharashtra Rabi Bajra (MRB) exhibited low inhibition values of DPPH (about 60%), RPA (about 0.32) and FRAP (about 2.69). The Bran Rich fraction revealed high antioxidant activity RPA owing to high tannin, phytic acid and flavonoid levels. Heat treatments processing manifested significantly higher antioxidant activity (DPPH scavenging activity and RPA) reflecting the high flavonoid content. It was noteworthy that significantly high radical scavenging activity in heat treated pearl millet had the lowest yield. On the contrary, germinated millet which demonstrated the lowest activity had the highest yield.[184] This is an interesting observation because production yield and antioxidant activity of any other antioxidant natural resources will be influenced by their processing methods.

Rice residue

Rice residue is considered to be a source of high-quality protein since rice dreg proteins are rich in methionine and cysteine, which are different from other plant or animal proteins.[2] It is elucidated that many active peptides derived from rice exert antioxidant, anti-inflammatory, antiaging, lipid-lowering and blood pressure-lowering effects.[185,187] It has a valuable significance to increase the fringe benefits of by-products of rice processing and to promote the sustainable development of the rice usage. Although rice residue has so many advantages, a large amount of rice residue is used as animal feed or directly discarded and has not been fully exploited and utilized. Therefore, microbial fermentation of rice residues to obtain active peptides with certain physiological functions can provide an important basis for better utilization of rice residues. Rice residue is the by-product of rice in the processing of starch sugar and monosodium glutamate, which contains more than 50% protein and about 40% polysaccharide and dextrin.[188] Tian et al. investigated antioxidant properties of rice residue hydrolysates from fermented broth. Antioxidant activity of ethyl acetate extracts from rice leaven exhibited a significant antioxidant activity on radical scavenging. and inhibitory effect on peroxidation of linoleic. Since rice residue contains abundant amount of carbon and nitrogen, the rice residue is supreme raw materials producing hydrolysates by fermentation. Rice residue hydrolysates (RRHs) were evaluated using ferric reducing antioxidant power (FRAP) assay which is simple, precise, sensitive and inexpensive method, and gives fast and reproducible results. They evaluated the antioxidant potency of five different RRHs fermented by various strains of molds and all the RRHs had antioxidant capacity. They mentioned that rice residue is an abundant resource and not efficiently utilized and RRHs may be developed as a new food additive.[189] Their investigation is impressing in the fact that they caught an eye on a popular grain of rice in a way of fermentation and hydrolysates which exhibited antioxidant activity.

Duck

Heat shock proteins (Hsps) are ubiquitously expressed under stress or normal physiological conditions. The 90 Kda heat shock protein (Hsp90), an important member of Hsps family, exert versatile functions in regulating cellular homeostasis and promoting cell survival. The amount of Hsp increase from 1% to 2% to 4% to 6% level in response to stress.[190] Hsp90 is alluded to an inhibitor of programmed cell death during oxidative stress.[191] and play a protective role against oxygen free radical damage induced apoptosis in human gastric mucosal cells.[192] Zhang et al. investigated the direct antioxidative effect of Hsp90 obtained from duck muscle. They conducted SPR, TBARS, DPPH, and ABTS assays. By SPR assay they elucidated that Hsp90 could bind with both phospholipids and oxidized phospholipids, and prevent their further oxidation. The DPPH and ABTS scavenging activity increased by adding 50µM of Hsp. They advocated that their findings contribute to the understanding of direct antioxidative role of Hsp90 and, broaden characterization and screening of oxidized phospholipids. Their binding proteins may be exhilarating area of research and have potential in the prevention of lipid oxidation and improvement of meat quality. In the present study, the antioxidative ability of Hsp90 isolated from meat was assessed. Results showed that Hsp90 could bind with oxidized phospholipid, and prevent their further oxidation to secondary products.

Sea cucumber

Sea cucumbers are valuable marine invertebrates found in deep seas across the world. These animals have been recognized ss folk medicine in many countries for centuries and have gained increasing attention among researchers in recent years for their diverse biological capacities including antioxidant, anticancer, anti-diabetic, anti-inflammatory, anti-obesity, anti-atherosclerotic, antithrombotic and immunomodulatory activities.[193,194] These bioactivities of sea cucumbers can be attributed to their sequence of compounds such as polysaccharides, triterpenes, lactones, glycosaminoglycans, chondroitin, cerebrosides, fucoidans, various organic acids and other secondary metabolites.[195,196] Polysaccharides from sea cucumber are attributed to be one of its main components and can be divided into two main types, fucosylated glycosaminoglycan and sulfated fucoidan. These biological macromolecules have shown multiple pharmacological capabilities such as antioxidant, anti-hyperlipidemia, anti-hyperglycemia, antitumor, antivirus, anti-inflammation, anticoagulation and antithrombosis, and may therefore serve as promising agents for some disease treatment and prophylaxis. Qin et al. explored enzyme-assisted extraction optimization along with the characterization and in vitro antioxidant activity of polysaccharides from sea cucumber Phyllophorus proteus (PPP). They elucidated that the optimal extraction conditions were extraction time of 2.89 h, ratio of extraction solvent to raw material of 16.26 mL/g, extraction pH of 6.83, extraction temperature of 50 ◦C and papain concentration as enzyme of 0.15%. They secured three purified fractions, PPP-1a, PPP-1b and PPP-2 with molecular weights of 369.60, 41.73 and 57.76 kDa and from PPP. PPP, PPP- 1a, PPP-1b and PPP-2 showed palatable scavenging activity of superoxide radical, DPPH radical, hydroxyl radical, and ABTS radical, which may be closely related to their structures such as monosaccharide compositions, and contents of carboxyl and sulfate groups. They suggested that polysaccharides from PPP will be able to exert protective effects as a potent antioxidant.[197]

Sea Buckthorn

In recent years, antioxidant food additives and dietary supplements have been popular globally. As the utilization of amounts and species of antioxidants have been increasing, consumers' concern on their safety and quality increasing as well. Consequently. there is a growing demand for manufacturing and concocting antioxidants from natural sources such as herbs, spices, seeds, cereals, fruits, grains, sea foods and vegetables. Pengfel et al. scrutinized antioxidant properties of isolated isorhamnetin from the sea buckthorn marc.[198] Isorhamnetin is a flavonoid with four hydroxy groups. Hydroxy groups at position three enhance its antioxidant activity.[58] The antioxidant capacity of flavonoids depends on the number of hydroxyl groups in the ring A, B, C and; that is, the greater the number of hydroxyl groups in the three rings especially in ring B, the greater the radical scavenging capacity of flavonoids.[59] By applying the processing method of obtaining isorhamnetin from marc of sea buckthorn they secured high purity (92.1%) of isorhamnetin and the yield was 25.6%. Isorhamnetin had strong antioxidant activities in all of the three assays, DPPH radical scavenging assay, ion IIIP to ion II reducing assay, and ion chelating assay. Good linear correlation coefficients (R2) between the amount of substance and the antioxidant activity were obtained in these assays.[178] Sea buckthorn is a hardy plant with drought- and cold- resistant. Berries of sea buckthorn have long been used for gastrointestinal disease, asthma, hepatitis, skin disorders, and rheumatisms. It has been reported that oil extracts of sea buckthorn contains bioactive compounds including monounsaturated fatty acids, vitamins, carotenoids, and phytosterols.[59] Consequently, sea buckthorn oils are gaining considerable attention in the manufacturing of antioxidant products.[60] Zheng et al. explored the effect of oil content and emulsifier type on antioxidant properties of sea buckthorn.[61] They elucidated that higher radical scavenging activity could be obtained in emulsions with bigger droplets, higher oil content, by using soy protein isolate as the emulsifier. This observation is worth inspecting from the standpoint of the relationship between the antioxidant activity and their formulation. In other way of saying is that antioxidant activities could increase by applying a proper formulation strategy.

Berries, Especially Strawberry

Generally speaking, berries include blackberry (Rubus spp.), black raspberry (Rubus occidentalis), red raspberry, blueberry and strawberry which is abundant in phenolic compounds comprised of phenolic acids, tannins, stilbenes, flavonoids and anthocyanins. The dietary intake of berry fruits plays an important role on human health from a standpoint of performance, and disease protection.[63] Rios de Souza et al. investigated in the bioactive compounds, antioxidant activity and chemical composition of Brazilian blackberry, red raspberry, strawberry, blueberry and sweet cherry fruits. They elucidated that the blackberry revealed the highest antioxidant activity and the highest levels of phenols, flavonoids, anthocyanins and carotenoids. The phenolic content of the strawberry was higher than reported, the blackberry presented higher levels of flavonoids, and the blackberry, strawberry and blueberry fruits showed lower anthocyanin contents than those found in the literature.[64] It is worth recognizing that the chemical compositions depend on the climate, location, and other environmental factors of berries cultivation. Skrovankova et al. reviewed bioactive compound and antioxidant activity in different types of berries. Grape berries are great sources of bioactive compound. Other relevant types of berries with low to medium bioactive compound are bilberries, elderberries, oseberries, capegooseberries, chokecherries, arctic brambles, cloudberries, crowberries, lingonberries and so on.[62]

Grapes

Since grape pomace (GP) is available globally as a remnant of the wine industry it can contribute as a very reliable source of polyphenol. Grape pomace are rich in polyphenols, mainly flavanols, procyanidins anthocyanins, and resveratrol which exert antioxidant and anti-inflammatory properties. The GP polyphenols exhibit a direct antioxidant activity by acting as a free radical scavenger or donating a hydrogen atom. In addition, it dominates not only an indirect antioxidant and anti-inflammatory activities by reducing mitochondrial reactive oxygen species (ROS) generation, malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1β), interleukin-6 (IL-6), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κβ), but also inhibitor of nuclear factor kappa-B kinase subunit beta (Iκκβ) levels or nitrate oxide-4 (NOX4) expression by increasing the levels of antioxidants enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GRx) and glutathione peroxidase (GPx).[62] An isotonic beverage that is designed to rehydrate, replenish and enhance electrolytes could be more effective when by diluting the sugar content of grape juice to 40–50 g/L to obtain a beverage with beneficial health properties. In other words, rehydrated isotonic grape drinks have more benefits in terms of antioxidant activity because of the abundant phenolic content which acts against oxidative stress. Developing new and natural isotonic beverages of grape juice with antioxidant capacity and increased sensory properties with the aid of anthocyanin will be a novel product in the field of healthy beverages.[65] Barreto de Andrade et al. conducted a study on the influence of different extraction parameters (temperature and ultrasound time) of bioactive compounds from the skin of the Syrah grapes. The application of ultrasound-assisted extraction (UAE) showed a positive effect on the extraction of total flavonoids, and a negative effect on total polyphenols. The temperature of 40 ◦C and 60 ◦C without the UAE caused an increase of 260% and 287% of the total polyphenols, respectively. The anthocyanin concentration exhibited high variation, to a lesser extent for phenolic acids, flavonoids, procyanidins and stilbenes due to the UAE means. The Syrah grape skin residue has a high concentration of total phenolic compounds and a total flavonoid content. The results of free radical scavenging activity by grape skin extract (UAE 40:20) indicate high antioxidant and antibacterial activities.[67]

Beans

Common bean (Phaseolus vulgaris L.) contains beneficial phytochemicals which wield protective effects against various diseases.[68,198] Phenolic compounds of phytochemical families in bean possess antioxidant activity associated with anti-diabetic, anti-obesity, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties.[69] Madrera et al. investigated on phenolic content and antioxidant activity in seeds of common bean.[70] They utilized two hundred and fifty-five lines of Phaseolus vulgaris, all of which are included in the Spanish Diversity Panel (SDP). The lines are classified according to the main seed coat color, into white, white with speckle, yellow, cream, brown, red, pink, grey or black. Beans with more strongly colored coats (red, cream, black, pink and brown) exert higher levels of total phenolic compounds, reducing power and radical scavenging activity. The phenol antioxidant index (PAOXI) showed that, in general, phenolic compounds in beans with colored coats wield a higher efficiency as antioxidants than those in completely white ones.[70]The most abundant nutritional component of adzuki beans is carbohydrates and vitamins. Fatty acids, minerals, protein, and fibers are also ample in the seeds. The non-nutritional secondary metabolites encompass saponins and polyphenolic compounds such as azukisaponins, flavonoids, proanthocyanidins, and anthocyanins. Pharmacological in vivo and in vitro investigations confirmed the antidiabetic, anti-obesity, antioxidant, and anticancer properties of adzuki bean seeds.[71] Desta et al. investigated variability of anthocyanin concentrations, total metabolite contents and antioxidant activities in adzuki bean cultivars.[72] The anthocyanins were detected only in the black seed-coated cultivars and delphinidin-3-O-glucoside was dominant in both Geomguseul and Chilbopat followed by delphinidin 3-O-galactoside. Total saponin content (TSP) and total phenolic content (TPC) were in the ranges of 16.20– 944.78 mg DE/g and 0.80–57.35 mg GAE/g, respectively, and each decreased in the order of seed coats > whole seeds > dehulled seeds regardless of extract type. The antioxidant activities also showed similar patterns of variation. Geomguseul seed coats outweighed the remaining cultivars in terms of TPC and ferric reducing antioxidant power (FRAP) activity ($p < 0.05$). Significant variations of metabolite contents and antioxidant activities were observed between cultivars and across their seed parts. Black seed-coated adzuki beans could be marvelous sources of anthocyanins and antioxidants.

Sea squirt protein

Gunasinghe et al. investigated vanadium binding proteins purified from the sea squirt Halocynthia roretzi on antioxidant and antidiabetic activities.[199] They determined the 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity of all the crude and the purified VBPs and found that they increased in a dose-dependent manner. IC_{50} values of the VBP blood plasma and VBP intestine on DPPH radical scavenging activity were 367.38 and 119.29 lg/ml, respectively, whereas that of ascorbic acid was 41.76 lg/ml, which indicated that vanadium binding proteins purified from the sea squirt Halocynthia roretzi are a fairly strong antioxidant.[200] Ma et al. verifies the novel antioxidant peptides from sea squirt (Halocynthia roretzi). and elucidated the neuroprotective effect in 6-OHDA-induced neurotoxicity.[200] After gel filtration, they secured six peptides such as Phe-Gly-Phe (FGF), Leu-Gly-Phe (LGF), Leu-Phe-VAL (LFV), Val-Phe-Leu (VFL), Trp-Leu-Pro (WLP), and Ile-Ser-Trp (ISW). Among them, WLP and ISW showed higher oxygen radical absorbance capacity (ORAC) values (2.72 ± 0.47 and 1.93 ± 0.01 μmol L−1 of Trolox equivalent (TE) per μmol L−1 of peptide) than glutathione (GSH). Furthermore, WLP effectively increased cell viability, dramatically attenuated 6-Hydroxydopamine (6-OHDA)-induced cell apoptosis and decreased reactive oxygen species (ROS) levels to nearly two-fold, and significantly boosted glutathione peroxidase (GSH-Px) activity.

Sheep

Chengli Hou et al. pursue an investigation on purification and identification of antioxidant alcalase derived peptides from sheep plasma proteins. They submitted sheep plasma to alcalase-hydrolysis and peptides with better antioxidant properties measured through both the ferric-reducing antioxidant power (FRAP) and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging ability assays. After hydrolysate, nine fractions (F1–F9) were obtained, with the two first (F1 and F2) showing the greatest antioxidant potential. Using liquid chromatography-tandem mass spectrometry, three antioxidant peptides were identified. From their amino acid sequences (QTALVELLK, SLHTLFGDELCK, and MPCTEDYLSLILNR), which include amino acids that have been previously reported as key contributors to the peptide antioxidant properties, it can be maintained that they come mainly from sheep serum albumin.[199] Kerasioti et al. explored antioxidant effects of sheep whey protein on endothelial cells.[200]

Suggested general intakes of antioxidant foods

Our natural antioxidant search alluded to abundant resources not only in groups but also in species. The next exhilarating area of investigation is how often and how much human beings should intake those natural antioxidants. Table 2 lists the suggested intake of natural antioxidant foods based on the relevant searched literature.

Evaluation of antioxidant assays and ranking of antioxidant capacity

Antioxidant capacities of natural products varies from species to species, and it is difficult to compare the real antioxidant capacity in a global sense. Apak et al. reported USDA data on ORAC per serving value (μmol TE: 100-1) on common foods. [201] The one with highest value is ground cinnamon (100g, 27,653), followed by aronia black chokeberry (100g, 16062), aronia black chokeberry (100 g, 16,062), small red bean (½ c. dried beans, 13,727), wild blueberry (1 c., 13 427), red kidney bean ½ c., dried beans 13 259), pinto bean (½ c.< 11,864), blueberry (1 c. berries, 9,019), cranberry (1c. berries, 8,983). artichoke hearts (1 c. cooked, 7,904), blackberry (1 c. berries, 7,701), prune (½ c., 7291), raspberry (1 c. 6058), strawberry (1 c., 5,938), red delicious apple (1 apple, 5,900), Granny Smith apple (1 apple, 5,381), pecan (1 oz., 5,095), sweet cherry (1 c., 4,873), black plum (1 plum, 4,844), russet potato (1 cooked, 4,649), black bean (½ c. dried beans, 4,181), plum (1 plum, 4,118), and gala apple (1 apple, 3903). Among the list eight berries are ranked, and four beans are included. This is worthwhile information for the human beings in that they should select as much berries and beans in their daily diets.

Molecular docking

In the molecular docking method, which is a structure-based computational approach, the method is applied to generate and seek for opposite binding pose and affinity between ligands and targets which are usually proteins. Theoretically molecular docking is to predict the ligand-receptor protein complex structure by using various computation methods. In particular, the initial stage of molecular docking is sampling the conformation of the ligand in the active site of the target protein via particular algorithm and then ranking those conformation through the scoring function either by binding affinity energy (E, kcal/mol) or free energy (ΔG, kcal/mol). Sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it from the highest to the lowest among all generated conformations.[202] Essentially, the aim of molecular docking is to give a prediction of the ligand-receptor complex structure using computation methods. Docking can be achieved through two interrelated steps: first by sampling conformations of the ligand in the active site of the protein; then ranking these conformations via a scoring function. Ideally, sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest to lowest among all generated conformations.

CONCLUSIONS

Fundamental biological processes in every cell elicit reduction-oxidation reactions and produce radical oxidant or free radicals. The degenerative changes in aging process are referred to production of excess reaction oxygen species (ROS) during cellular metabolism. The antioxidant system of the organism neutralizes the generated free radicals in the normal metabolism. However, disturbance in the balance between free radicals and antioxidant reactions is elicited by metabolic disorders leading to the accumulations of an excessive amount of free radicals which result in oxidative stress. The oxidative stress creates substantial damage to proteins, lipids and nucleic acids leading to the development of neoplastic diseases, disorders in circulatory or neurogenerative systems by accelerating degenerative processes.

The comparison of each exogenous antioxidant structure elucidated that a considerable number of compounds contains flavonoid skeleton which is polyphenol. Catechin is a representative antioxidant in this group. The second major group is unsaturated hydrocarbon represented by Coenzyme Q10. The third group is organic acid represented by ascorbic acid. This structure characteristic assists not only in the selection of antioxidant intake but also in development of innovative antioxidants and/or novel antioxidant analogs.

In order to produce necessary energy in the form of adenosine triphosphate (ATP) oxygen is used by mitochondria. This process is intertwined with the formation of ROS during the mitochondrial electron transport chain called oxidative phosphorylation. Pyruvate entered in Krebs cycle reduces nicotinamide adenine dinucleotide (NAD) to NADH which is oxidized again in the mitochondrial respiratory chain. Mitochondria are considered to be the main source of ROS because ROS is generated as a byproduct of electron transfer. Oxidative stress induced by high level of reactive oxygen species result in the upregulation of antioxidant capacity which maintains redox homeostasis by metabolic rerouting or activation of genetic programs.

Oxidative stress causes various diseases among which cancer is most serious. Cancer is speculated to be caused by the oxidative stress together with the imbalance between reactive oxygen species (ROS) and antioxidants. The accumulation of ROS created by metabolic disturbances and signaling aberrations can promote carcinogenesis through gene mutations and pro-oncogenic signaling activation. The disturbance of redox homeostasis leads to intense pathophysiological consequences in cells. To accommodate oxidative stress, cells modify metabolic and genetic reprogramming, thereby leading to increased production of NADPH, glutathione, superoxide dismutase and thioredoxins, returning ROS to the homeostatic level. Therefore, nonenzymatic antioxidants can be utilized for cancer therapy along with enzymatic antioxidants.

It is reported that some synthetic antioxidants have produced toxicity and side effects.[83] On the contrary, natural antioxidants in general have strong antioxidant activity with little toxicity and side effects. [83] Taking this background into consideration antioxidants from natural sources can present a good application prospect in the prevention and/or treatment of various diseases.[85] Toxicity-related problems should be avoided by all means while utilizing and/or intaking endogenous and exogenous antioxidants. In this regard, one of the shrewd choices is to utilize antioxidants in natural origin. However, since it is difficult to take all necessary antioxidants of natural origin, taking supplemental antioxidants is a wise choice.

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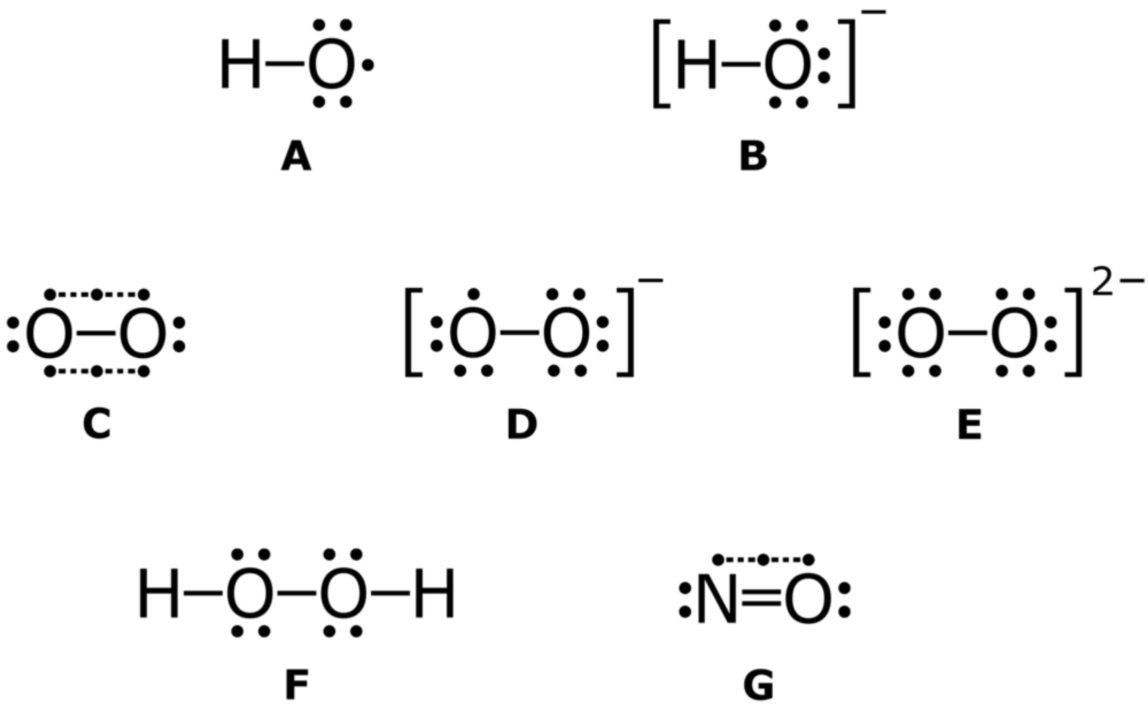
Table 1: Various antioxidants of endogenous and exogenous origins.

Antioxidants	Endogenous	Enzymatic	Superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, peroxiredoxin, ascorbate peroxidase
		Non-enzymatic	Coenzyme Q10, Vitamin A, glutathione, bilirubin, albumin, uric acid,
	Exogenous	Non-enzymatic	Vitamin E, Vitamin C, selenium, zinc, polyphenolic acid, carotenoids, curcumin, lutein, lycopene, betalains, omega-3, zeaxanthin、βcarotin, eicatechin gallate, epigallocatechin gallate, quercetin, fisetin, epigallocatechin, catechin, epicatechin, rutin, morin, kaempherol, hesperidin, hesperidin, naringenin, naringin, hydroxycinnamic acid, caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, gallic acid, synaptic acid, vanillic acid, syringic acid α－tocopherol

Table 2: Suggested intake of antioxidant foods [3,4,13,78]

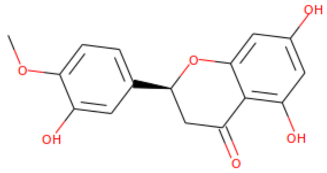
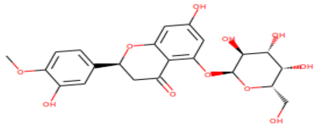
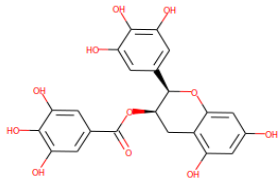
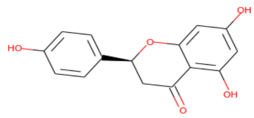
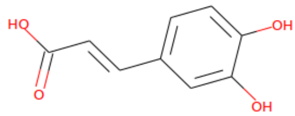
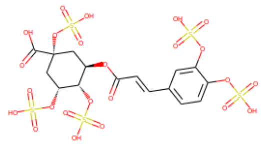
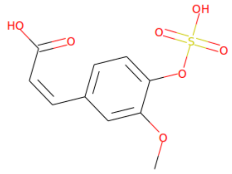
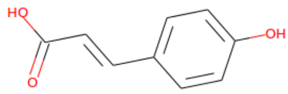
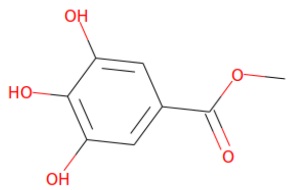
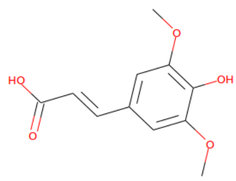
Natural antioxidant foods	Frequency of intake
Fruits and vegetables	800 gram a day, minimum of 5 servings/week
Whole-grain	225 g/day
Nuts	15–20 g/day
	5 to <6 servings/day for cardiovascular ailments 1 to <4 servings/day for all-cause mortality Note: 1 serving is defined as 125 g/day,
Fish	15g/day increment, or 2 fish meals / week
Fermented dairy (i.e. sour milk products, cheese, yogurt)	20g/day

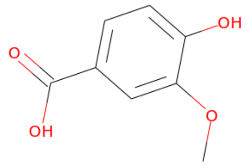
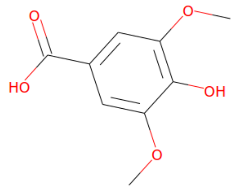
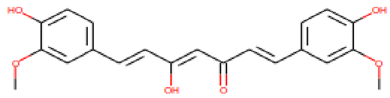
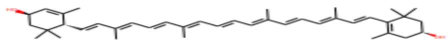
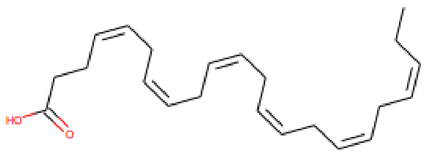
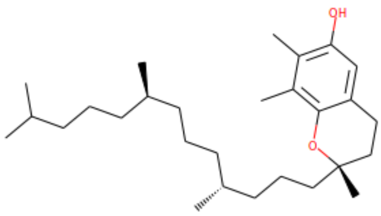
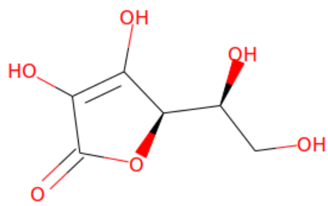
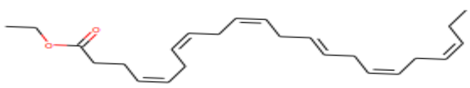
Figure 1: Lewis structure of major reactive oxygen species.[11]



A: hydroxyl radical ($HO^{\bullet}$);
B: hydroxide ion (HO^{-});
C: triplet oxygen ($O_2^{2\bullet}$);
D: superoxide anion ($O_2^{\bullet -}$);
E: peroxide ion (O_2^{-2});
F: hydrogen peroxide (H_2O_2);
G: nitric oxide ($NO^{\bullet}$)

Figure 2: Chemical structure of nonenzymatic antioxidants.

Antioxidant origin	Molecular name	Molecular structure
	hesperidin	
	hesperetin5-glucoside	
	epigallocatechin gallate	
Exogenous, Nonenzymatic	naringenin	
	caffeic acid	
	chlorogenic acid persulfate	
	ferulic acid 4-sulfate	
	P-coumarate	
Exogenous, Nonenzymatic	gallic acid methyl ester	
	O-methylsinapate	

	yanillate	
	cedar acid	
	curcumin	
	lutein	
	lycopene	
	Omega-3	
Exogenous, Nonenzymatic	B-Carotene	
	Tocopherol	
	Ascorbic acid	
	Omega-3-Acid Ethyl Ester	
Endogenous, Nonenzymatic	Coenzyme Q10	

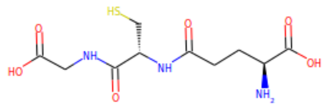
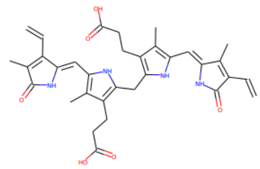
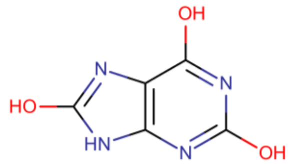
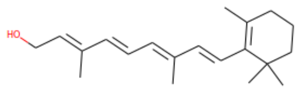
	Glutathione	
	Bilirubin	
	Uric acid	
	Vitamin A (Retinol)	

Figure 3: The electron transport chain and the source of reactive oxygen species (ROS's)