Dietary Antioxidant and Metabolic Syndrome

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Reactive oxygen radicals (ROS) are highly reactive and the overproduction of ROS could induce the pathogenesis of endothelial dysfunction, and might serve as a main cause of the life style diseases, such as hypercholesterolemia, hypertension, atherosclerosis, diabetes mellitus, and several cancers. These life style diseases are currently called as metabolic syndromes. The plant polyphenols as ROS scavengers have been widely studied and dietary antioxidants like tea and wine are well known as antioxidant foods. In order to look for the effective natural antioxidants which possess a health benefit function, we have collected and assayed numerous medicinal herbs and plant materials like agricultural by products. Some strong antioxidant polyphenols which had been isolated and identified from these plants extracts are presented here.

1. Reactive oxygen radicals (ROS) and metabolic syndrome

1.1 Reactive oxygen radicals (ROS)

Molecular oxygen has two unpaired electrons, one on each oxygen atom. The spins of these electrons are parallel, and so reduction of oxygen to water must proceed via a series of sequential one electron transfers, yielding superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\cdot}OH$) as intermediates. These radicals which is called Reactive oxygen radicals (ROS) are highly reactive to the nearby biomolecules like lipid, protein, carbohydrate and DNA, and induce several degenerative diseases such as diabetes, coronary heart diseases, and inflammation. Hydrogen peroxide and superoxide can injure some biologic targets, whereas hydroxyl radical attacks biomolecules with almost unlimited reactivity. In 1956, Harmann (1) demonstrated that free radicals produced during aerobic respiration cause cumulative oxidative damage, resulting in aging and death. In 1968, McCord and Fridovich (2,3) reported that superoxide anion was produced during the oxidation of purines by xanthine oxidase. In fact, up to 2% of oxygen reduction by normal cells has been shown to occur via univalent pathways. Because of the potential for these reduction products of oxygen to cause toxicity, cells have evolved pathways to eliminate superoxide and hydrogen peroxide, thereby limiting formation of hydroxyl radical. These include superoxide dismutases (SOD) for superoxide anion, peroxidases and catalase for hydrogen peroxide.

Mitochondria is 'the powerhouses of the cell' because they link the energy releasing activities of electron transport and proton pumping with the energy conserving process of oxidative phosphorylation, to transform the foods in the form of ATP. Over 95% of all the oxygen we breathe undergoes a concerted tetravalent reduction to produce water catalyzed by cytochrome oxidase (cytochrome c, oxygen, oxidoreductase) of complex IV in the mitochondrial electron transport chain. With estimates of 1~ 2% of the total daily oxygen consumption going to mitochondrial $O_2^{\cdot -}$ generation, a 60 kg woman would produce some 160~320 mmol of superoxide each day from mitochondrial respiration alone (based on an O_2 consumption of 6.4 L/kg/day) (4).

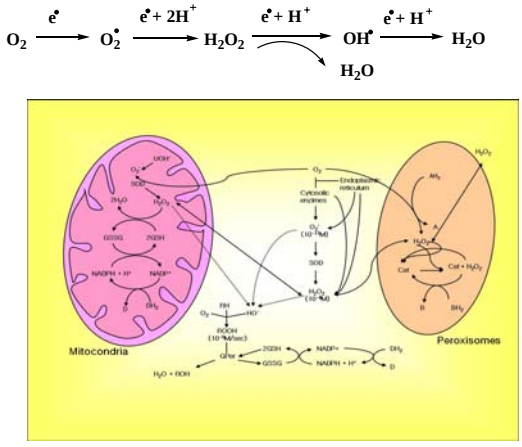

Fig. 1. Scheme of cellular oxygen free radical generation and metabolism.
(Modified from Biol. Res.v.33(2). Santiago.2000).

ROS cause damage to mitochondrial components and initiate degradative processes. During the respiration, the tetravalent reduction of oxygen is carried out by mitochondrial cytochrome oxidase in a process coupled to energy generation and ATP synthesis. The products of the univalent reduction of oxygen are also generated in mitochondria. A small fraction of the total electron transfer is used to univalently reduce oxygen to superoxide anion by ubisemiquinone and the flavin semiquinone of NADH dehydrogenase of the mitochondrial electron transfer chain (5). Superoxide anion dismutates to hydrogen peroxide by the enzymatic action of Mn superoxide dismutase (Mn-SOD) specifically located in the mitochondrial matrix. It was recently estimated that O_2^- and H_2O_2 account for approximately 2% and 1% respectively, of the O_2 uptake by liver and heart mitochondria under physiological conditions (6). The primary production of O_2^- and H_2O_2 is able to initiate the free radical chain reaction due to hydroxyl radical formation ($^{\cdot}OH$) by the Fenton and Haber Weiss chemical reactions.

$$O_2^{\bullet -} + O_2^{\bullet -} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

$$H_2O_2 + RH_2 \xrightarrow{Peroxidase} 2H_2O + R$$

$$H_2O_2 + H_2O_2 \xrightarrow{Catalase} 2H_2O + O_2$$

1.2. Metabolic syndrome

Metabolic syndrome, such as cardiovascular diseases (CVD), osteoporosis, and several degenerative diseases are closely related with aging progressed by ROS. Oxidative damage to cell components, DNA, proteins, and lipids increases with age and contributes to the degeneration of the cells and to the pathogenesis. ROS mediated metabolic syndrome occurred in human are shown in the following Table 1.

CVD is the leading cause of death worldwide, especially in western countries. Considerable studies have been made over recent years to identify mechanisms involved in the development of atherosclerosis,

including oxidative stress, a characteristic symptom in patients with main cardiovascular risk factors such as diabetes mellitus, hypertension, hypercholesterolaemia and smoking. The epidemiological studies demonstrated that antioxidant supplementation could protect against the deleterious effects of oxidative stress on the cardiovascular system, and preventing the development of atherosclerosis and CVD.

The consumption of tea and red wine have been associated to a lower risk of myocardial infarction in both case control and cohort studies (7,8). Comparing American, French has lower rate of CVD due to wine intake, and this health benefit effect by wine has been called as French paradox. An inverse association between flavonol and flavone intake and the risk of coronary heart diseases or non fatal myocardial infarction has been also observed in several studies. Catechin intake has also been related to a lower risk of coronary death but not to stroke (9,10).

The main cause of CVD might be the development atherosclerosis associated with multifactors of outer and inner factors which is partly inherited. One of the first recongnized signs in atherosclerotic plaque development is endothelial cell injury, whether it might be a consequence of the free radical damage, or the toxic effect of the lipid peroxidation. Loss of endothelial integrity predisposes to platelet adherence, and release of chemotactic agents and enhances sub endothelial accumulation of cholesterol and cholesterol esters. Under the influence of local oxidants, sub endothelial native LDL is converted to oxidized LDL, which is a potent chemoattractant stimulus for macrophage migration and smooth muscle proliferation. And it is toxic to the endothelium, promoting further LDL deposition and atheromators plaque propagation. Sub endothelial macrophages ingest native LDL cholesterol via a receptor mediated pathway, while

Table 1. Metabolic syndromes developed by Reactive oxygen species (ROS)

Liver	**Muscle**
Reperfusion	Muscular dystrophy
Kidney	Multiple sclerosis
Autoimmune nephrosis : inflammation	Exercise
Lung	**Skin**
Normobaric hyperoxic inhury	Radiation (UV or ionizing)
Bronchopulmonary displasia	Thermal injury
Idiopathic pulmonary fibrosis	Contact dermatitis
Heart and cardiovascular system	porphyria
Atherosclerosis	**Brain and nervous system**
Hemochromatosis	parkinson's disease
Reperfusion : after infraction or transplant	Alzheimer's disease
Selenium deficiency (keishan disease)	Tardive dyskinesia
Myocardial infarction	Neuronal ceroid lopofuscinosis
Gastrointestinal tract	Hypertensive cerebrovascuar
Reperfusion	Allergic encephalomyelitis
Toxic effects of chemicals : nonsteroidal	**Inflammatory-immune system**
Pancreatitis, Colitis	Glomerulonephritis
Blood	Vasculitis (hepartitis β virus, drugs)(
Malaria	Autoimmune disease
Various anemias	Reumatroid arthritis
Protoporphyrin photooxidation	**Aging**
Eye	**AIDS, Cancer, Diabetes**
Retionopathy of prematurity	**Inflammation**
Photic retionpathy	**Trauma**
Macular degeneration	**Ischemia/reperfusion**
Ocular hemorrhage	**Radiation injury**
Cataracts	**Theumatioid arthritis and lupus**

oxidized LDL is ingested by a separate 'scavenger' pathway that results in formation of cholesterol saturated macrophages, or foam cells, a characteristic pathological finding in atherosclerotic plaques (11). Therefore sub endothelial LDL oxidation is a key step in the oxidative modification model of atherosclerosis (12).

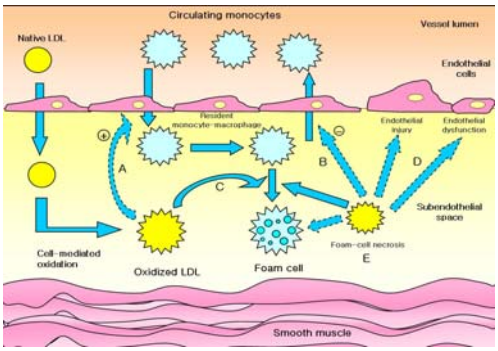

Fig. 2. Initiation of atherosclerosis.
(Modified from Macro *et al*., New Engl. J. Med. 7: 408-416).

2. Dietary antioxidant polyphenol

As oxygen and its radicals are continuously utilized and metabolized, aerobes could survive with the aid of its biological antioxidant defense system. Antioxidant is a term used so widely and diversely, therefore it can not be defined clearly. Among our food technologists it means inhibitors of lipid oxidation. But in organisms, it is the more appropriate definition such as 'any substance that significantly delays or prevent oxidation of biomolecules of intra and extracellular components'. Halliwell and Gutteridge (13) demonstrated that antioxidants act at several different levels in the oxidative sequences, therefore they might have multiple mechanism of action.

Antioxidant defense system consists of :

- Biological agents that catalytically remove ROS ; superoxide dismutase (SOD), peroxidase and glutathione peroxidase family.
- Proteins that minimize the availability of pro oxidants like Fe, Cu ; transferring, haptoglobins, metallothionein
- Low molecular weight agents that scavenge ROS; glutathione, vitamin E, bilirubin, uric acid, ascorbic acid and plant polyphenolics.

The composition of antioxidant defenses differ from tissue to tissue and cell to cell in any living organism.

Polyphenols are a group of chemical compounds that are widely distributed in nature, with benzene ring substituted with more than one phenolic group. They are essential to the plant's physiology being involved to the diverse function such as coloring, structure, pollination, pathogen, predeator resistance, growth and development. The two main types of polyphenols are phenolic acids and flavonoids. Over the past decade, most research on the health benefit function of the fruit and vegetables has focused on the dietary flavonoids. Flavonoids consist of two aromatic rings linked through an oxygenated heterocycle, having C6-C3-C6 structure. Major classes include flavans, flavanols, flavones, flavonols, isoflavone and anthocyanidins. They are responsible for the colours of many flowers, leaves and fruits. Others are complex compounds such as tannin, present in bark, roots and leaves of plants that are used for tanning hides and skins to give leather.

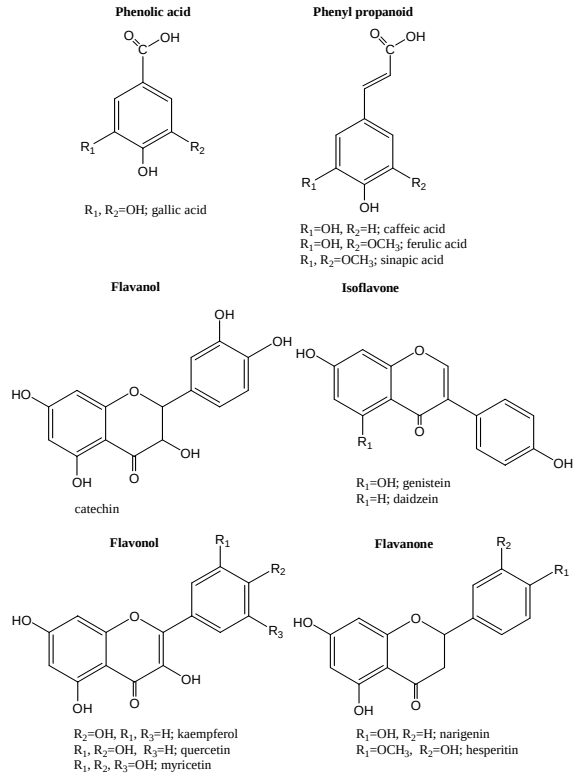

Fig. 3. Chemical structure of the typical polyphenol compounds

Antioxidants contained in the dietary food can help reduce this damage by scavenging directly on reactive oxygen species or by inducing endogenous defense systems. The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, thereby cleavaging chain oxidation reactions in cellular components. Several kinds of dietary polyphenols have been evaluated their antioxidant activities in vitro, although their efficacy in vivo are uncertain. Polyphenol rich foods, such as tea (14, 15), wine (16-18) and beer (19) as well as fruit and vegetables, increase the antioxidative capacity of plasma. Apple juice and chocolate by healthy volunteers significantly reduced the plasma concentrations of malondialdehyde (MDA) (20, 21). A lot of studies have also reported the protective effect of polyphenol consumption against DNA damage (22).

We had also isolated and identified dozens of antioxidant polyphenol compounds, such as phenyl propanoids, flavonoids and lignans from herbs, agricultural by products and medicinal plants, including novel ones (23-31). Depends on the chemical structures, they exhibited different antioxidant activities and patterns. However, polyphenols with o dihydroxy moiety, such as caffeic acid, chlorogenic acid and quercetin reacted as strong antioxidants (31, 32). The plant extract as well as the polyphenol compounds also could be utilized as useful health benefit antioxidant materials.

Acknowledgement

We would like to thank to all the collaborators.

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