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## Diabetes, Oxidative Stress and Tea

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### 1. Introduction

Diabetes mellitus is the most common serious metabolic disorder in the world. Diabetes is characterized by a hyperglycemia that results from an absolute or relative insulin deficiency and is associated with long term complications affecting the eyes, kidneys, heart and nerves (Baydas *et al.*, 2003). Oxidative stress is defined as imbalance between the generation of reactive oxygen species and antioxidant defense capacity of the body that is closely associated with aging and a number of diseases including cancer, cardiovascular diseases, diabetes and diabetic complications (Atalay *et al.*, 2002). Irregular cellular metabolism in diabetes leads to production of free oxygen radicals and imbalanced antioxidant capacity (oxidative stress) of the body (Vincent *et al.*, 2004).

Recent studies have shown that both types of diabetes can increase oxidative stress in blood and treatment with antioxidants such as vitamin E and flavonoids may be used for decreasing of oxidative stress and diabetic complications (Baydas *et al.*, 2003; Vincent *et al.*, 2004). There is good evidence that tea flavonoids intake have a role in protection against degenerative diseases and long-term intake of tea flavonoids can prevent obesity in high fat diet. Also it has positive effects against glucose metabolism disorders and diabetes-induced fat disorders that lead to lowering the risk of diabetes complications (Crespy *et al.*, 2004). Flavonoids have antioxidant properties, and tea is one of the main sources of flavonoids. Tea (from the plant *Camellia Sinensis*) is the most popular beverage next to water, consumed by over two-thirds of the world's population. About three billion kilograms of tea are produced and consumed yearly (Yang, 2000; Gupta *et al.*, 2002; Crespy *et al.*, 2004). Regular intake of tea is associated with an improved antioxidant status in vivo conditions that may contribute to the lowering risk of certain types of cancer, coronary heart disease, atherosclerosis, stroke, reduced mutagenicity and inflammation, protection against neurodegenerative diseases and increasing insulin sensitivity (Luximon-Ramma *et al.*, 2005; Alipoor *et al.*, 2011).

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## 2. Diabetes

Diabetes resembles fasting, especially regarding the responses of the liver, muscle cells, and adipose tissues. With low serum ratios of insulin to glucagon and high levels of fatty acids, the liver produces glucose, whereas other tissues use fatty acids and ketones instead of glucose. Muscle cells and adipose tissue respond by using ketones and fatty acids. Although these resemblances between fasting and diabetes are striking, pathologically low serum insulin levels disrupt the efficiency seen during fasting. With low insulin levels, key glycolytic enzyme activities decrease. Glucose use decreases to levels far below those seen during fasting. Concurrently, hepatic gluconeogenic enzyme activities and gluconeogenic rates increase. Bombarded with free fatty acids, the liver increases gluconeogenesis, secreting large amounts of very low density lipoproteins (VLDLs) and accumulating fatty acids in droplet form. A long-term toxic effect of diabetes is the accumulation of 25% more lipid than normal. In the diabetic state, the liver oxidizes these fatty acids and produces acetone, acetoacetate, and  $\beta$ -hydroxybutyrate. Muscle cells and adipose tissue also show major metabolic changes in diabetes. Muscle glycogen almost disappears, and muscle protein is broken down to support gluconeogenesis. Cardiac and skeletal muscles meet their energy needs from ketones and fatty acids. Fat cells actively release fatty acids under the lipolytic stimuli of glucagon, catecholamines, and insulin deficiency (Shils *et al.*, 2006).

### 2.1 Historical overview

Diabetes mellitus is a chronic disease that has affected mankind throughout the world. The records of the ancient civilizations of Egypt, India, Japan, Greece, and Rome describe the symptoms of the disease and usually include recommendations for treatment. The wasting away of flesh, copious urination, and the sweet taste of the urine were frequently noted by the ancient medical writers. Aretaeus of Cappadocia, who lived between A.D. 30 and 90, not only named the disease diabetes, which means “to run through or to siphon” but also recommended, “The food is to be milk and with in the cereals, starch, autumn fruits and sweet wines”. The term mellitus, which means honey like, was added by a London physician, Willis, in 1675 (Robinson, 1972).

### 2.2 Epidemiology and etiology

Diabetes mellitus has reached epidemic proportions worldwide. There is an apparent epidemic of diabetes which is strongly related to lifestyle and economic change (WHO). Over the next decade the projected number will exceed 200 million. Most will have type 2 diabetes, and all are at risk of the development of complications. Diabetes mellitus is a heterogeneous group of diseases that develops dangerously and characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic. Diabetes mellitus is increasing due to population growth, aging, consequences of industrialization and urbanization, preference of high fat containing fast foods, sedentary life and obesity. Given the enormous public health and economic burden posed by the global epidemic of type 2 diabetes mellitus (T2DM), intervention in the pre-diabetes stage of disease to prevent progression to T2DM and its vascular complications seems the most sensible approach. Prudent lifestyle changes have been shown to significantly reduce the risk of progression in individuals with impaired fasting glucose (IFG) and impaired glucose

tolerance (IGT). Although lifestyle modifications are difficult to maintain, there is evidence that intensive intervention results in continued preventive benefit after the stopping of structured counseling (Bharati *et al.*, 2011).

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Quantifying the prevalence of diabetes and the number of people affected by diabetes, now and in the future, is important to allow rational planning and allocation of resources (Wild *et al.*, 2011).

### 2.3 Classification and diagnosis

Diabetes is a heterogeneous disorder both genetically and clinically and is hyperglycemia, attributable to either insulin insufficiency or insulin resistance. The traditional classification separates out hyperglycemic conditions into these groups: insulin-dependant diabetes mellitus (IDDM or type 1), non-insulin-dependent diabetes mellitus (NIDDM or type 2), other specific types of diabetes and gestational diabetes mellitus (GDM). Type 1 diabetes accounts for approximately 5% of diabetes and is manifested by insulin deficiency caused by destruction of the pancreatic  $\beta$  cells. Type 2 diabetes accounts for about 90% of diabetes and is characterized by two primary defects: insulin resistance (diminished tissue sensitivity to insulin) and impaired  $\beta$ -cell function (delayed or inadequate insulin release). Other causes account for the remaining 5% of diabetes. Classic symptoms such as polydipsia, polyuria, and rapid weight loss associated with gross and unequivocal elevation of blood glucose ( $\geq 200$  mg/dl) make the diagnosis of Diabetes mellitus. A fasting plasma glucose level greater than or equal to 126 mg/dl on two occasions is diagnostic of diabetes (Shils *et al.*, 2006).

### 2.4 Diabetic complication

Associated to insulin-dependent diabetes (type 1), makes the disease one of the worst by considering the human suffering and the socio-economic trouble. In developed countries the number of diabetic patients is increasing all the time and both inability and mortality values are staggering. There is a dedication of studies aiming first to block or slow down the onset of type 1 diabetes, secondly to identify the numerous environmental and genetic factors causing type 2 diabetes and thirdly to suggest possible ways for the prevention or the postponement of crippling complications. The initial problem of diabetes is the hyperglycemia due to the inability of several control systems to maintain a normal glycemic plasma level. A first question is: can diabetic complications be prevented or delayed by normalizing hyperglycemia? This can be achieved at least in part if a meticulous control of glycemia is kept with an appropriate diet, oral anti-diabetic drugs, or insulin administration associated with daily exercise and a correct lifestyle. However, owing to genetic factors and in spite of a serious control, complications are found even in patients with a transitory and slight hyperglycemia. Circulatory abnormalities are the common denominator and they are present under the form of micro- and macro-vascular disease. Throughout the years the following complications may develop with different intensity and localization:

1. Diabetic retinopathy is a leading cause of blindness in about 85% of patients aged 20-75 years.
2. Diabetic nephropathy occurs in 20-40% of patients and when the GFR is <15 ml/min, the end stage renal disease (ESRD) is a leading cause of disability and premature death.
3. Diabetic foot disease normally caused by several factors such as peripheral vascular disease (PVD), altered biomechanics, possibly polyneuropathy and infected foot ulcers.
4. Neuropathy involving both the somatic and autonomic nervous system with neuromuscular dysfunction and muscular wasting is another major cause of morbidity.
5. Accelerated atherosclerosis frequently manifests itself with myocardial infarction, stroke and limb vascular occlusion complicated with necrotic ulcers.
6. Lipodystrophy, seemingly due to ineffective leptin activity or/and fatty acids dysmetabolism, represents another aspect of the metabolic syndrome (Bocci *et al.*, 2011).

Early detection and appropriate management of diabetes is essential to reduce major morbidity and mortality, however these strategies are not implemented in many countries of the world. In the diabetes centre in Isfahan, I.R. Iran, the rate of complications among approximately 4000 type 2 diabetes patients have been recorded as: ischemic heart disease 34%, hypertension 50%, congestive heart failure 12%, retinopathy 44%, cataract 5%, bacteriuria 27%, nephropathy 19%, neuropathy 27%, depression 60%, diabetic foot 2.5%, hypercholesterolemia 37%, and hypertriglyceridemia 37%. Among 296 cases of non-traumatic amputations, 38% were diabetes-related; 27% of stroke cases (cerebrovascular accident), 15% of patients with acute myocardial infarction and 15% of dialysis patients were also diabetics (Azizi *et al.*, 2003).

### 3. Oxidative stress

Oxidative stress happens in a cellular system when the production of free radical moieties exceeds the antioxidant capacity of that system. If cellular antioxidants do not remove free radicals, radicals attack and damage proteins, lipids and nucleic acids. The oxidized or nitrosylated products of free radical attack have decreased biological activity, leading to loss of energy metabolism, cell signaling, transport, and other major functions. These altered products also are objected for proteosome degradation, further decreasing cellular function. Accumulation of such injury ultimately leads a cell to die through necrotic or apoptotic mechanisms (Vincent *et al.*, 2004).

#### 3.1 Historical overview

The presence of free radicals in biological materials was discovered less than 50 years ago. Thereafter, Denham Harman hypothesized that oxygen radicals may be formed as by-products of enzymatic reactions in vivo. In 1956, he described free radicals as a Pandora's Box of evils that may account for gross cellular damage, mutagenesis, cancer, and last but not least, the degenerative process of biological aging. The science of free radicals in living organisms entered a second time after McCord and Fridovich discovered the enzyme superoxide dismutase (SOD) and, finally convinced most colleagues that free radicals are important in biology. Numerous researchers were now inspired to investigate oxidative damage inflicted by radicals upon DNA, proteins, lipids, and other components of the cell. A third period began with the first reports describing advantageous biological effects of free radicals. Mittal and Murard provided suggestive evidence that the superoxide anion,



through its derivative, the hydroxyl radical, stimulates the activation of guanylate cyclase and formation of the “second messenger” cGMP. Similar effects were reported for the superoxide derivative hydrogen peroxide. It was discovered that nitric oxide (NO) has independently role as a regulatory molecule in the control of smooth muscle relaxation and in the inhibition of platelet adhesion (Droge, 2002).

Also it is found that in activated T-cells the superoxide anion or low micromolar concentrations of hydrogen peroxide increase the production of the T-cell growth factor, interleukin-2 which is an immunologically important T-cell protein. Studies have shown that hydrogen peroxide induces the expression of the heme oxygenase (HO-1) gene and hydrogen peroxide has induction effects on various genes in bacteria, as well as activation of the transcription factor nuclear factor  $\kappa$ B (NF- $\kappa$ B) in mammalian cells. At the beginning of the 21st century, there is a large amounts of evidence showing that living organisms have not only adapted to an unfriendly coexistence with free radicals but have, in fact, developed mechanisms for the advantageous use of free radicals. Important physiological functions that involve free radicals or their derivatives include the following: regulation of vascular tone, sensing of oxygen tension and regulation of functions that are controlled by oxygen concentration, enhancement of signal transduction from various membrane receptors including the antigen receptor of lymphocytes, and oxidative stress responses that ensure the maintenance of redox homeostasis (Droge, 2002).

The field of redox regulation is also receiving growing attention from clinical colleagues in view of the role that oxidative stress has been found to play in numerous disease conditions. These pathological conditions demonstrate the biological relevance of redox regulation. The delicate balance between the advantageous and detrimental effects of free radicals is clearly an important aspect of life. The science of biological “redox regulation” is a rapidly growing field of research that has impact on diverse disciplines including physiology, cell biology, and clinical medicine (Droge, 2002).

### 3.2 Biomarkers of oxidative stress

Measuring biomarkers of oxidative stress is an essential step toward better understanding the pathogenesis and developing treatments for diabetic. There are several approaches that may be adopted, including measurements of the depletion of antioxidant reserves, changes in the activities of antioxidant enzymes, free radical production, and presence of protein, lipid, and DNA free radical adducts. For the purposes of clinical assessment, measurements of end products of free radical attack may be the most reliable determination of the occurrence of oxidative stress because enzyme activities and cellular antioxidants are likely to display transient changes. The enzymes responsible for detoxifying free radicals or regenerating antioxidant molecules can provide an indication of the stress level experienced in a cell or tissue. These enzymes are usually measured by *in vitro* activity assays, although changes in transcription can also provide evidence of cell stress. In long-term diabetes, catalase, GSH reductase, GSH peroxidase, and SOD decrease in complication-prone tissue (Vincent *et al.*, 2004).

### 3.3 Oxidative stress and disease

There is a growing awareness that oxidative stress plays a role in various clinical conditions. Malignant diseases, diabetes, atherosclerosis, chronic inflammation, human immunodeficiency

virus (HIV) infection, ischemia reperfusion injury, and sleep apnea are important examples. These diseases fall into two major categories. In the first category, diabetes mellitus and cancer show commonly a pro-oxidative shift in the systemic thiol/ disulfide redox state and impaired glucose clearance, suggesting that skeletal muscle mitochondria may be the major site of elevated reactive oxygen species (ROS) production. These conditions may be referred to as “mitochondrial oxidative stress.” Without therapeutic intervention these conditions lead to massive skeletal muscle wasting, reminiscent of aging-related wasting. The second category may be referred to as “inflammatory oxidative conditions” because it is typically associated with an excessive stimulation of NAD(P)H oxidase activity by cytokines or other agents. In this case increased ROS levels or changes in intracellular glutathione levels are often associated with pathological changes indicative of a dysregulation of signal cascades and/or gene expression, exemplified by altered expression of cell adhesion molecules (Droge, 2002).

3.4 Oxidative stress and diabetes

Increased oxidative stress is widely accepted as a major role player in both development and progression of diabetes (Maritim *et al*, 2002). Figure 1 summarizes the relationship between oxidative stress, development of diabetes and resulting complications.

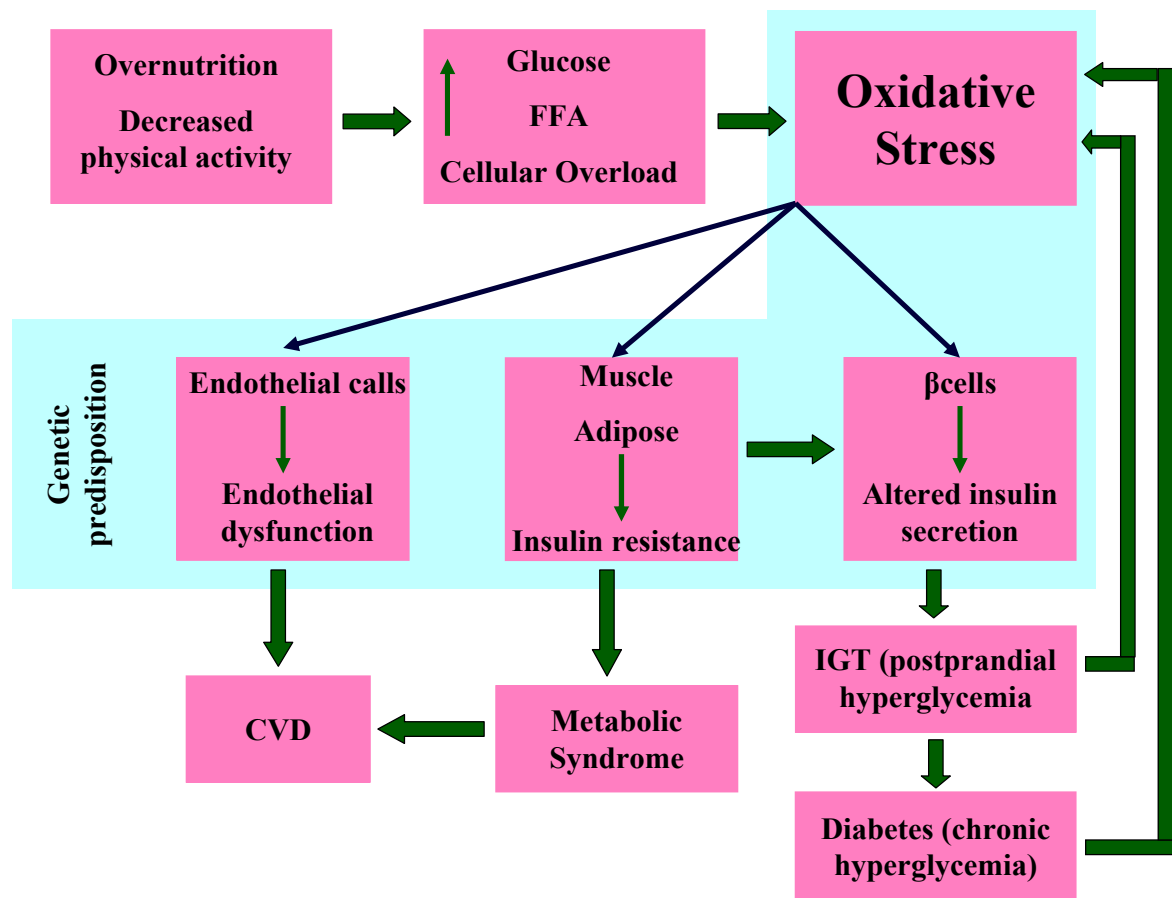


Fig. 1.Overnutrition leads to oxidative stress which in turn results in diabetes and its complications (FFA: Free Fatty Acids, IGT: Impaired Glucose Tolerance, CVD: Cardiovascular Disease)

To better understand the role of tea antioxidants in either preventing diabetes or reducing its complications, one must first know the mechanisms through which oxidative stress contributes to the development of this chronic disease and disorders following it. Some evidence on how tea antioxidants, in particular, can prevent diabetes development and its progression will be presented next.

As mentioned previously, type 1 diabetes mellitus which is less prevalent than type 2 is a genetic autoimmune disorder affecting the islet cells leading to insulin deficiency and thus hyperglycemia. Type 2 diabetes however is a multi-factorial disease. Insulin resistance most often precedes the onset of this type by many years and can be caused by acquired factors. Elevations in glucose and free fatty acids have been shown to induce oxidative stress which in turn can play a key role in causing insulin resistance and  $\beta$ -cell dysfunction (Evans *et al.*, 2002).

One most favored hypothesis on how hyperglycemia and elevated free fatty acids (FFA) can lead to oxidative stress is that as energy intake exceeds energy expenditure, generation of excess mitochondrial NADH (mNADH) and the level of reactive oxygen species (ROS) is increased due to the greater activity of citric acid cycle, induced by the abundance of substrates. Reducing ROS formation or increasing its removal is the way through which cells can protect themselves. The mechanism of preventing excessive mNADH generation may be inhibiting insulin-stimulated nutrient uptake and preventing the entrance of pyruvate and fatty acids into the mitochondria. Either of glucose or FFA enters the citric acid cycle after being converted to acetyl-CoA which then combines with oxaloacetate to form citrate. Greater availability of substrates will result in greater production of mNADH which is beyond the capability of oxidative phosphorylation to dissipate it all, leading to increased mitochondrial proton gradient. Thus single electrons are transferred to molecular oxygen forming free radicals, especially superoxide anion.

One way the cells can reduce free radical generation is inhibition of FFA oxidation. This will increase intracellular FFA which in turn leads to reduced GLUT4 translocation to the plasma membrane resulting in resistance to insulin-stimulated glucose uptake in muscle and adipose tissue. *In vitro* studies have shown that antioxidants may have role in reducing insulin resistance (Ceriello *et al.*, 2004).

Chronic exposure to abnormally high levels of glucose and FFA leads to toxic effect on  $\beta$ -cells of pancreas. Furthermore as aforementioned, hyperglycemia and high levels of FFA leads to increased oxidative stress.  $\beta$ -cells are particularly susceptible to the damages inflicted by oxidative stress; since they are low in free radical quenching enzymes such as catalase, glutathione peroxidase and superoxide dismutase.  $\beta$ -cells are responsible for the sensing glucose and secreting appropriate amount of insulin in response to glucose boots. This process is pretty complex, but the critical significance of mitochondrial glucose metabolism in linking stimulus to secretion is well established. This is one reason that oxidative stress can blunt insulin secretion due to its ability to damage mitochondria (Evans *et al.*, 2003; Robertson *et al.*, 2004).

Chronic oxidative stress can also affect insulin gene expression. At least two critical proteins that activate the insulin promoter are involved in defects in insulin gene expression. One is PDX-1 and the other is RIPE-3b1 activator recently identified as MafA. Glucose toxicity and lipotoxicity both of which lead to increased oxidative stress have been shown to leave deleterious effects on islet cells (Robertson, 2004).



Apoptosis is one other way through which oxidative stress can cause beta-cell dysfunction. There is some evidence that NF- $\kappa$ B is in part responsible for the induction of apoptosis in  $\beta$  cells; NF- $\kappa$ B production is stimulated by oxidative stress (Evans *et al.*, 2002; Robertson, 2004).

Uncoupling proteins (UCP) are carriers expressed in the mitochondrial inner membrane that uncouple oxygen consumption by the respiratory chain from ATP synthesis and can play a significant role in diabetes. These proteins can control ROS production in the mitochondria. UCP2 and UCP3 are expressed in adipose tissue and skeletal muscles, the tissues important for thermogenesis and substrate oxidation. Elevated expression of UCP2 has been shown to exert negative regulation of  $\beta$ -cell insulin secretion and contribute to the impairment of  $\beta$ -cell function. UCP3 level has been reported to be decreased in diabetic patients and is assumed to facilitate fatty acid oxidation and minimize ROS production (Maiese *et al.*, 2007).

As mentioned previously, hyperglycemia increases peroxide generation in mitochondria which then through many different routes results in endothelial dysfunction and other diabetic complications in the end. Figure 2 illustrates how oxidative stress induced by hyperglycemia leads to the downstream events.

Superoxide overproduction decreases eNOS activity, but increases iNOS expression through NF- $\kappa$ B and protein kinase C (PKC); the final effect is greater NO generation and strong oxidant peroxynitrite which in turn produces in iNOS and eNOS, an uncoupled state resulting in the production of superoxide rather than NO, and damages DNA. DNA damage is necessary for the activation of the nuclear enzyme poly (ADP-ribose) polymerase (PARP). This reduces the intracellular concentration of NAD<sup>+</sup> which it uses as a substrate. The rate of glycolysis, electron transport and ATP formation reduces as a result of decreased NAD<sup>+</sup> and an ADP-ribosylation of the GAPDH (glyceraldehydes 3-phosphate dehydrogenase) occurs. This process results in acute endothelial dysfunction in diabetic blood vessels, which contributes to the development of diabetic complications. NF- $\kappa$ B activation also induces a proinflammatory conditions and overexpression of the adhesion molecules overexpression. All these alterations end in the diabetic complications, and cardiovascular disorders.

NF- $\kappa$ B, one major intracellular target of hyperglycemia and oxidative stress which can be activated by a number of stimuli including hyperglycemia, elevated FFA, ROS, TNF- $\alpha$ , IL-1 $\beta$ , and other proinflammatory cytokines, AGE (advanced glycation end product)-binding to RAGE (receptor for AGE), DNA damage, viral infection and UV irradiation, regulates the expression of a large number of genes, including growth factors (vascular endothelial growth factor (VEGF), proinflammatory cytokines like TNF- $\alpha$  and IL-1 $\beta$ , RAGE, adhesion molecules like vascular cell adhesion molecule-1, and many others).

VEGF has been identified as a primary initiator of proliferative diabetic retinopathy and as a potential mediator of nonproliferative retinopathy. It is also involved in the development of nephropathy and neuropathy. Thus VEGF seems to play an important role in the etiology of several complications of diabetes (Ishii *et al.*, 2001; Evans *et al.*, 2002; Esposito *et al.*, 2002; Ceriello, 2003; Ceriello, 2006; Negrean *et al.*, 2007)

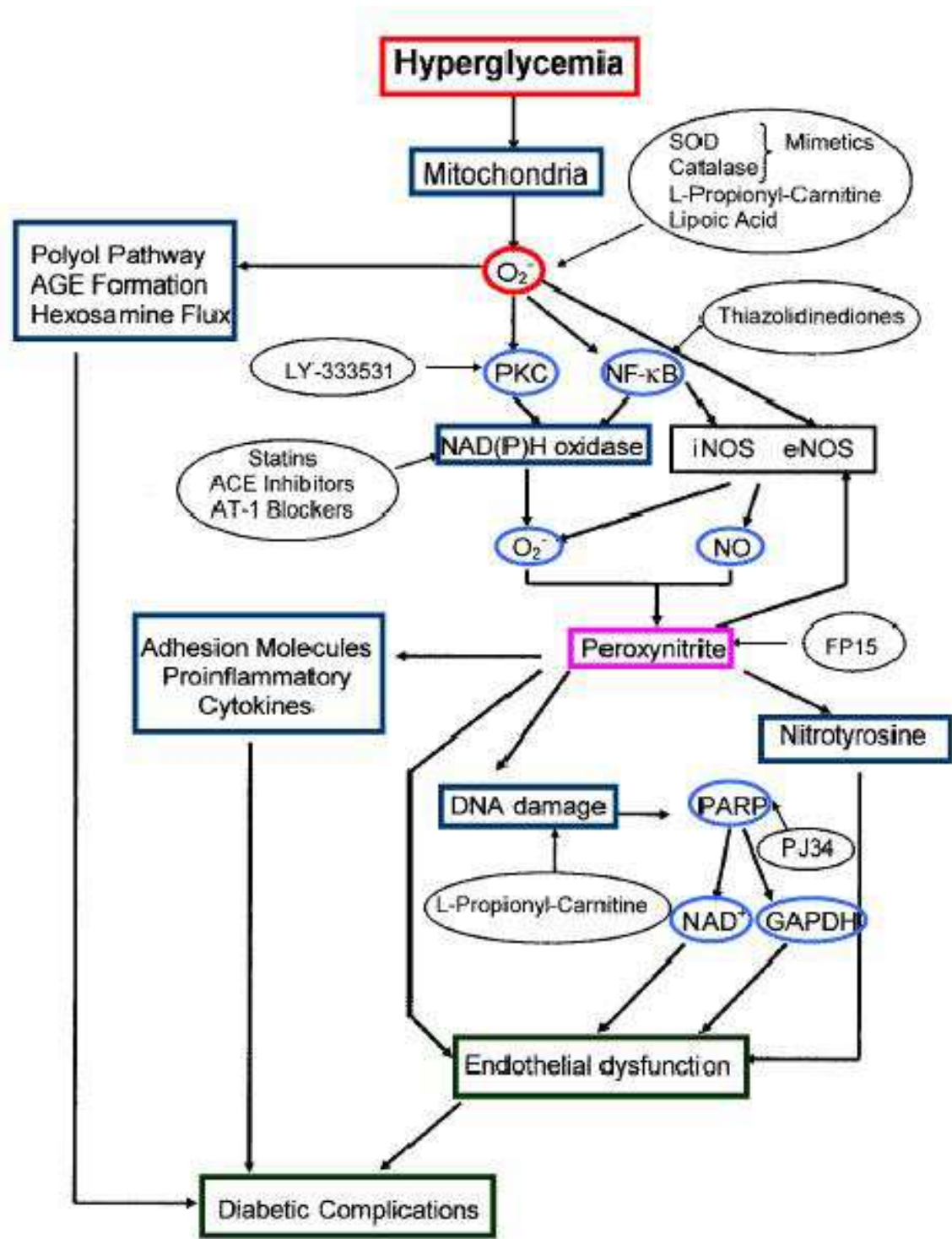


Fig. 2. Hyperglycemia results in endothelial dysfunction and diabetic complications through causing oxidative stress

3.5 Oxidative stress and antioxidants

Several free radical species are normally produced in the body to perform specific functions. O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub> and NO are three free radical reactive oxygen species (ROS) that are essential for

normal physiology, but are also believed to accelerate the process of aging and to mediate cellular degeneration in disease states. These agents together produce highly active singlet oxygen, hydroxyl radicals, and peroxynitrite that can attack proteins, lipids, and DNA. Antioxidants are defined as any compound that can donate at least one hydrogen atom to a free radical, resulting in the termination of radical chain reactions. An alternative type of antioxidant is defined by its ability to prevent the initiation of a free radical chain reaction rather than to terminate them. This latter type of antioxidant is usually dependent upon the ability to bind metal ions and includes ceruloplasmin, transferrin and albumin. Cells must maintain the levels of antioxidants, often defined as antioxidant potential, through dietary uptake or *de novo* synthesis. Excess production of free radicals can reduce the intracellular antioxidants, resulting in oxidative stress. In brief, acute hyperglycemic episodes such as an oral glucose tolerance test or a meal can decrease the antioxidant capacity of plasma in both normal and diabetic subjects and increase oxidative stress in diabetic patients. As a type 2 diabetic patient ages, increased basal levels of free radical production and decreased antioxidants are even further intensified by elevated plasma glucose. Analysis of individual vitamin and enzyme components of the antioxidant system in man reveals significant changes in diabetes. The levels of vitamins A and E and catalase activity are decreased in both type 1 and 2 patients compared with controls. Whereas GSH-metabolizing enzymes are decreased in type 1 but not type 2 patients, SOD activity is lower in type 2 but not type 1 (Vincent *et al.*, 2004).

#### 4. Tea

The scientific name given to tea, in the first volume of the book "Species Plantarum" by Carl Linnaeus, was "Thea Sinensis"; but in the second volume of the very book, the tea tree is addressed as "Camelia". Later in 1762, Linnaeus assuming black and green tea to be obtained from two different shrubs, chose the names "Thea bohea" and "Thea vividis" for black and green tea respectively. Now it is revealed that it is "Thea bohea" from which, both black and green tea are attained. Also the scientists have merged the two genres "Camelia" and "Thea". Today the international scientific expression for tea is "*Camelia Sinensis* (L) O.kuntze", *Camelia* and *Sinensis* indicating the genus and the variety respectively, (L) regarding Linnaeus, the first botanist to give tea a scientific name and O.kuntze being the one who combined the names used for black and green tea. *Camelia Sinensis* is an evergreen plant which can grow into a tree of up to 30 meters if left undisturbed; but cultivated plants usually have a height around 50-70 centimeters (Hara, 2001; Moxham, 2009).

##### 4.1 Historical background

It may always remain in mist, when tea first stepped into man's life. General consensus attributes the birth of the tea bush to the area we now call eastern China. But the discovery of a tea bush deep in Assam, India with leaves much larger than the Chinese one, caused controversy, as far as it concerns the birthplace of *Camelia Sinensis*. Today it is assumed that the tea bush was first found in the southwestern China, centered in the Yunnan district (Hara, 2001). Tea was first carried westwards during 5<sup>th</sup> century by Turkish traders (Alkan *et al.*, 2009).

The question as to when the man first consumed tea is unanswered as well. According to Chinese mythology, it was the emperor Shen Nung who discovered tea for the first time in 2737 B.C.; but this is not in consistence with the first credible documentary reference on tea which was made in 59 B.C. (Hara, 2001; Gupta *et al.*, 2002).

It is probable that our forbears used tea in response to their instinctive seek for a material to calm them; because tea is rich in an alkaloid called caffeine which acts as an opioid in the nervous system, relaxing the consumer.

On tropical and subtropical climates and regions on which precipitation is coordinate according to months and where summers and winters are lukewarm, tea production is realized. Sour and humid land structure is crucial to growing tea as well (Alkan *et al.*, 2009). Based on the data generated by the food and agriculture organization (FAO) of the united nations as of January 2010, China was the leading country in tea production in 2006, 2007 and 2008, followed by India, Kenya, Sri Lanka, Turkey, Vietnam and Indonesia. Other main tea producing countries are Japan, Argentina, Iran, Bangladesh, Malawi and Uganda Figure (3). The global tea production growth rate in 2006 extended more than 3% to reach an estimated 3.6 million tons, China, Viet Nam and India being the main counties to have contributed to this rise. It is predicted that world black tea production rate decreases in the current century, due to slowing down of production growth in Africa. India followed by Kenya and Sri Lanka are projected to be the main contributors to black tea production by 2017 which is estimated to reach 3.1 million tons (<http://en.wikipedia.org/wiki/Tea>; Hicks, 2009).

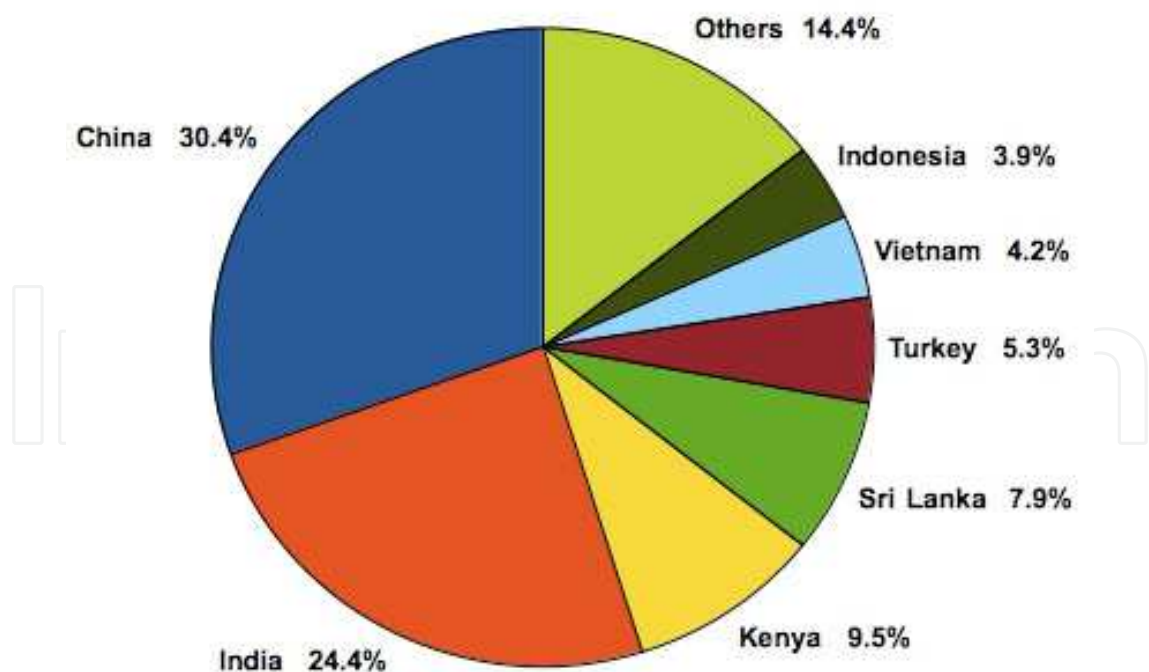


Fig. 3. The tea producing regions in 2007



4.2 Chemical compounds in tea

In contrast to the history of tea drinking which is ancient, the chemical components of tea have quite recently been investigated. Teas acquired from different regions may have different chemical components in different amounts. The agents found in tea are classified as primary or subordinate (Table 1):

Primary components	subordinate components
Alkaloids (xanthines)	Mineral acids
Polyphenols	Organic acids
Vitamins	Proteins
Enzymes	Pectin
Volatile oils (essence)	Lignans
	Amino acids

Table 1. The classification of primary and subordinate tea agents

The quality of a tea is related to its content of alkaloids (caffeine), flavonoids (catechins), phenolic acids (gallic acid, coumaric acid, caffeic acid and chlorogenic acid) and volatile oils (essences) (Table 1) (Bendini *et al.*, 1998; Wang *et al.*, 2000).

*Alkaloids:* In 1827, caffeine which is present in a few other plants was discovered in tea. By then it was given the name "Theine" which was dropped as its structure was proven to be exactly the same as that of caffeine, in 1820. The mean content of caffeine in tea ranges between 1.9 and 4.5 and is negatively correlated with the age of the leaves (Wanger *et al.*, 1996; Hara, 2001).

*Polyphenols:* Theanine and flavonoids (catechins in particular) are the main polyphenols found in tea constituting 30% of its agents.

*Theanine:* A unique substance in tea is theanine which is a kind of amino acid comprising more than half of the amino acids present in tea. It has an "umami" or sweet taste and constitutes 2% of tea (Hara, 2001).

*Flavonoids:* Flavanols and their derivatives including flavan-3-ols (catechins and epicatechins) and flavonols are the chief flavonoids in tea. Under mild oxidation, flavan 3-4 diol derivatives of flavonoids are converted to catechins and its isomers. Green tea is a great source of catechins and thus exerts antioxidant properties. These catechins change into oligomeric quinones under the fermentation process of black tea which reduces its antioxidant capacity by 2-6 times in comparison to the green tea (Hara, 2001). Each gram of green tea contains 123.8- 206.3 milligrams of catechins which is 10-30 percent of the dry weight of the green leaves. In black tea, 79.3 milligrams of catechins is found in one gram (Wang *et al.*, 2000; Bronner *et al.*, 1998; Keys, 1976). All catechins have 2 asymmetric carbons, thus there are four isomers of them: catechin (C)(+), catechin gallate (CG)(-), gallocatechin (GC) and gallocatechin gallate (GCG) (-). The number of hydroxyl group on the B ring differs for the derivatives of catechins. Like catechins, epicatechins are the monomers of the condensed thanines, are derived from flavan 3-4 diols and have two asymmetric carbons in their structure resulting in four isomers. These isomers include: epicatechin (EC)(-), epigallocatechin (EGC)(-), Epicatechin gallate (ECG)(-) and epigallocatechin gallate (EGCG)(-). Catechins and epicatechins are the major polyphenols found particularly in green tea (Figure 4).



Epigallocatechin gallate (EGCG), being the greatest in amount in tea compared to the other catechins, makes up to 50% of its catechins. EGCG is more abundant in green tea and its quantity is negatively correlated with the age of the leaves (Hara, 2001; Leung *et al.*, 2001).

**Vitamins and minerals:** Vitamin C was discovered in 1924 in fresh tea leaves. Tea is a great source of fluoride too (Hara, 2001). Other vitamins and minerals may be present in tea at little amounts as well.

**Enzymes:** The enzymes in tea which catalyze the oxidation processes are called Thease. During fermentation in which tea pectins are demethylated, polyphenolic compounds are decomposed which as a result of the quinone appearance, turn into some colorful agents including theaflavin and thearubigin, both of which are plentiful in black tea (Figure 4) (Hara, 2001; Leung *et al.*, 2001; Cadenas, 2002).

**Volatile oils:** More than 600 volatile agents have been established in tea, most of which have a yellow color and a characteristic scent. Linalool is the main essence in tea, other of lesser importance ones being dihydroactinide iodido paravinile phenol, hexenol, hexenal, aldehydes, phenyl ethyl alcohols, phenols and geraniols (Hara, 2001).

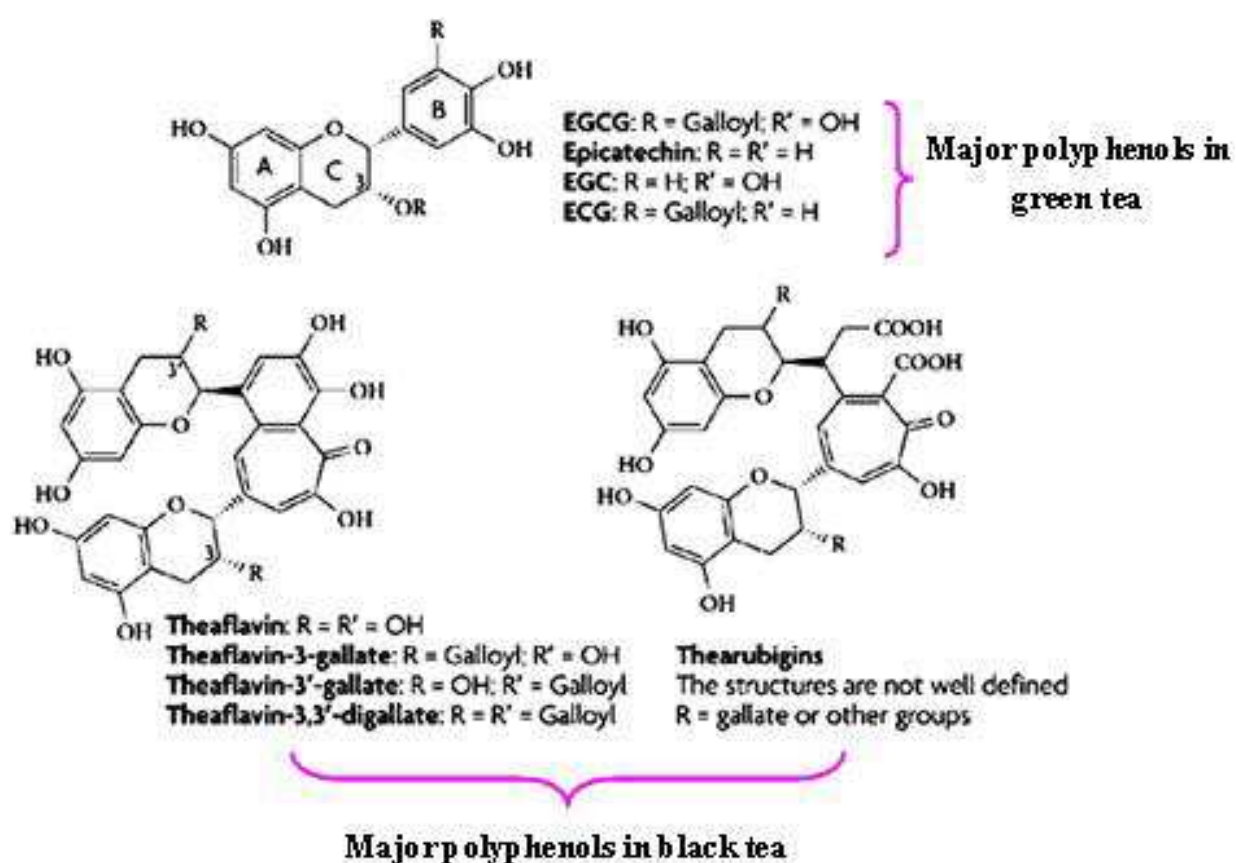


Fig. 4. Major polyphenols in green and black tea

Based upon the preparation method, the degree to which it is fermented and the steps it goes under during the production, different types of tea consumed all over the world are classified into at least six categories (Figure 5). The less processed the tea, the greater the polyphenols content will be, which the extent of oxidation accounts for (Santana-Rios *et al.*, 2001).

1. White tea: White tea is manufactured only from the buds or first leaves of *C.sinensis*. It is the least processed type of tea and is simply steamed and dried without a prior withering stage; therefore the concentrations of EGCG and also methylxanthines (like caffeine) are enriched in white tea compared with green and black tea.
2. Yellow tea: It usually implies a special tea processed in a similar way to green tea; but the drying process takes place at a slower rate. The damp tea leaves are allowed to sit and yellow. Its taste resembles that of green and white teas.
3. Green tea: To manufacture green tea, first the fresh leaves are steamed, then primary drying-rolling, rolling, secondary drying-rolling, final drying-rolling and at last drying are performed. No fermentation takes place in this type of tea.
4. Oolong tea: Fresh leaves undergo solar withering at the first step, indoor withering and rolling, pan firing, rolling, mass breaking and drying are the steps to be taken, to produce oolong tea. In this kind of tea, partial fermentation occurs after the rolling.
5. Black tea: The manufacturing process for black tea includes withering of fresh leaves, rolling, fermenting and drying. Thorough fermentation is done in black tea.
6. Pu-erh: Pu-erh is applied to old tea with extreme fermentation in it (Hara, 2001; Santana-Rios *et al.*, 2001; Kuo *et al.*, 2005; Lin *et al.*, 2006; Sohle *et al.* 2009; Wang *et al.*, 2008; <http://en.wikipedia.org/wiki/Tea>; <http://www.tea-of-chinese.com>).

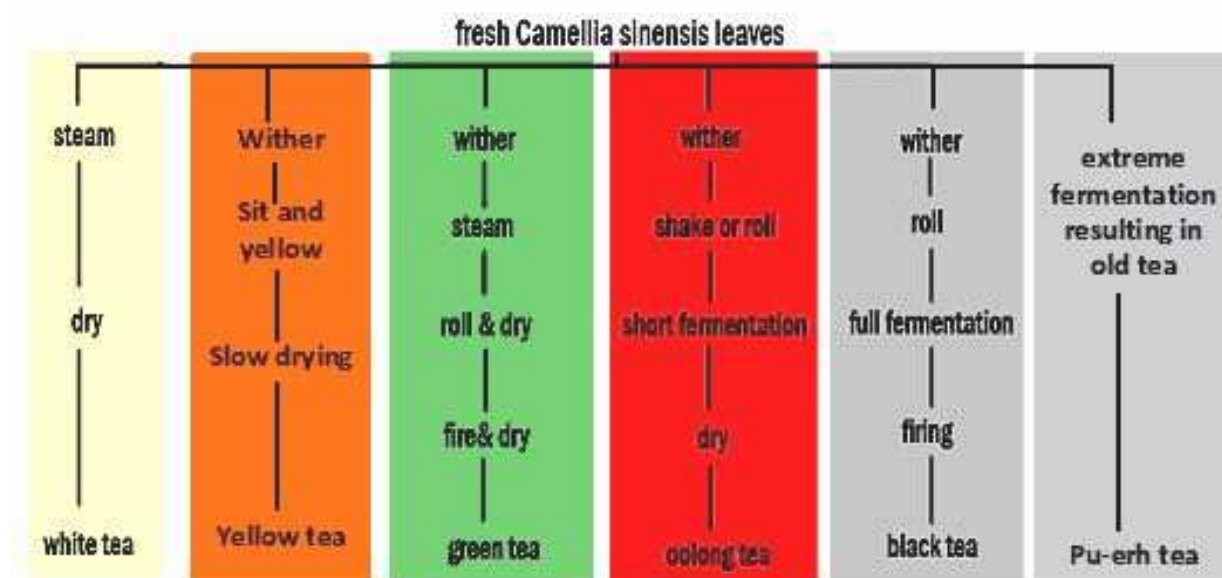


Fig. 5. The production of different types of tea

#### 4.3 Tea and diseases

Tea being a great source of phytoestrogens and fluoride, both of which play a major role in bone health, is reported to prevent osteoporosis and the lower prevalence of the very disease in Japanese postmenopausal women in comparison with American and European ones, is attributed to greater amounts of tea consumed by Japanese (Adlercreutz *et al.*, 1991; Adlercreutz *et al.*, 1992; Johnell *et al.*, 1995; Kanis *et al.*, 1999).

Tea due to its content of polyphenols has been found to be effective in preventing many types of cancer including liver, small intestine and lung. Polyphenols increase the catalytic

activity of enzymes involved in glutathione and quinone synthesis and remove the free radicals of hydrogen peroxide and superoxide anions. Tea consumption also inhibits metastasis of human lymphoid leukemia cells through stimulation of apoptosis and hindrance of platelet aggregation (Bronner *et al.*, 1998; Dulluge *et al.*, 1998; Integrative Medicine, 2000; Springhouse, 2001).

Studies have shown that tea is beneficial in delaying cardiovascular disorders. Some mechanisms described are: inhibiting the progression of atherosclerosis and thrombosis, preventing hypertension by either exerting effects similar to those of beta-blockers or stimulating diuresis, decreasing postprandial blood cholesterol and triglycerides, inhibition of LDL oxidation and improvement of endothelial function. Also, decreasing the activity of lipoxygenase enzymes and stimulating central nervous system, tea can improve heart muscle function, circulation in coronary vessels and respiration (Yamamoto, 1997; Robbers *et al.*, 1999; Leung *et al.*, 2001; Alipoor *et al.*, 2008). Hypertension is another disorder which can be corrected by tea and its polyphenols. This has been attributed to its role in regulating renin-angiotensin system (RAS) and improving endothelial function (Adlercreutz, 1991).

Since tea and its polyphenols have been observed to reduce digestion and absorption of fats and carbohydrates, and due to their role in controlling food intake, increasing energy expenditure, modifying the activity of liver, muscle, gastrointestinal tract and fat cells, weight loss and prevention of diabetes mellitus could be one advantage of drinking appropriate amounts of tea (Watanabe *et al.*, 1998; Kuo *et al.*, 2005; Ynng *et al.*, 2006). How tea can play a major role in prevention and treatment of many complications of diabetes mellitus will be presented more precisely in the next section.

Other disorders which tea can play a role in prevention or treatment of, includes inflammation, migraine, nausea, diarrhea, maldigestion, sore throat, depression, prostatitis, hemochromatosis, neurodegenerative diseases like Parkinson and Alzheimer, cataract, dental carries and some viral and bacterial infections including influenza, polio, herpes simplex and AIDS (Duke, 1985; Robertson *et al.*, 1991; Hertog *et al.*, 1993; Cummings *et al.*, 1995; Tavani *et al.*, 1996; Van Het Hof *et al.*, 1997; Integrative Medicine, 2000; Mills *et al.*, 2000; McKay *et al.*, 2002; Wright, 2005; Kao *et al.*, 2006; Sasso *et al.*, 2006; Alipoor *et al.*, 2011).

#### 4.4 Tea antioxidants and oxidative stress

There is a considerable amount of evidence indicating the benefits of tea consumption to prevent diabetes and reducing its resulting complications. The less processed the tea, the more its antioxidant content; which may explain why most studies have been conducted using green tea as the supplement. Recently, white tea which is not fermented either, has been studied for its impact on diabetes too. Some ways through which tea and its bioactive compounds affect diabetes are not related to the antioxidant properties of tea, thus not within the scope of this chapter; and won't be discussed here.

Many studies have shown that different types of tea are potentially effective in reducing oxidative stress and related diseases. Attempts have been made to manufacture products containing tea bioactive compounds for prevention and treatment of mentioned diseases. In order to design such product, the effective compounds of tea and the safe dose of them must be first identified. For instance, EGCG has been shown to act as a prooxidant when administered in high doses and lead to apoptosis. Furthermore compounds other than

catechins may exert the desired effects as well (Liao *et al.*, 2001; Mandel *et al.*, 2004; Kao *et al.*, 2006). To determine the very compounds acting as antioxidants in black tea, Alipoor *et al.*, (2009) performed a study in which diabetic rats were supplemented total extract of black tea and its fractions. Total extract and fractions were attained by hydromethanol method and solid phase extraction using Sep-Pak respectively. Results of this study showed that injection of total extract and 20% fraction of black tea decreased malondialdehyde (MDA) and increased total antioxidant, Super oxide Dismutase (SOD), Glutathione Peroxides (GPX) and Glutathione in diabetic rats. To find out the major substances in the 20% fraction, Analytical HPLC, Preparative HPLC (High Performance Liquid Chromatography) and NMR (Nuclear Magnetic Resonance) (CNMR and HNMR) were employed. Caffeine, Epicatechin Gallate, Quercetin and Kampferol were the main compounds capable of combating oxidative stress, to be determined in 20% fraction of tea (Figure 6) (Alipoor *et al.*, 2010).

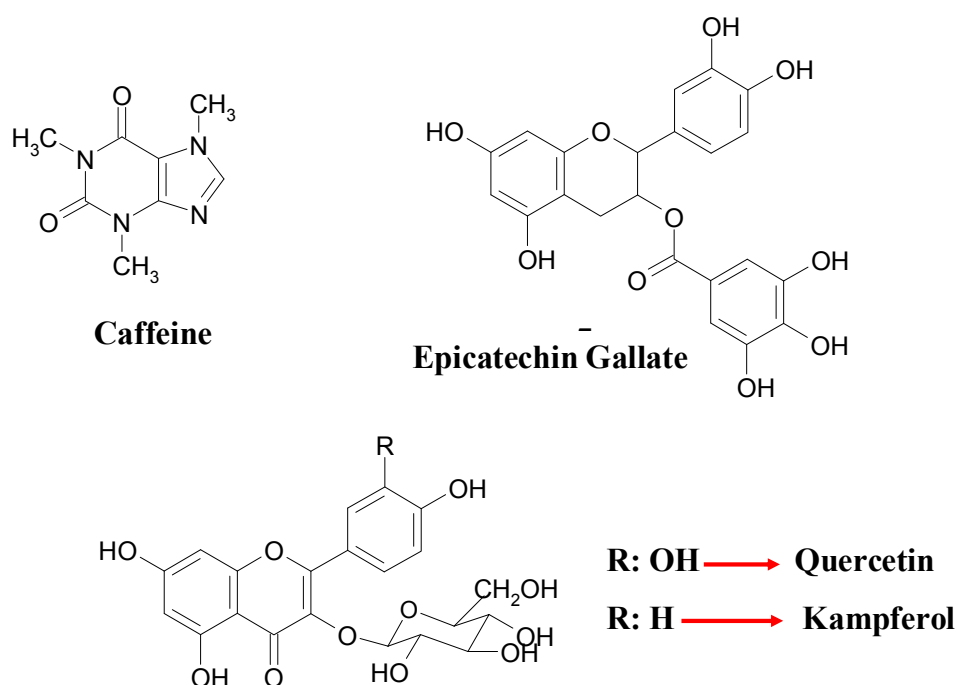


Fig. 6. Major antioxidants in 20% fraction of black tea

Caffeine is a strong antioxidant and its activity being equal to that of glutathione and exceeding that of vitamin C (Devasagayam *et al.*, 1996; Kamat *et al.*, 2000; Nikolic *et al.*, 2003). The free radical scavenging capacity of flavonoids is due to the 3', 4' dihydroxyl and 3' hydroxy in the  $\beta$  ring (Amic *et al.*, 2003). The 20% fraction of black tea has been shown to be more effective than the other fractions which may be explained by the high concentration of the aforementioned compounds in it and absence of polyphenol antagonists in the very extract prepared (Alipoor *et al.*, 2009).

Tea polyphenols have been found to induce expression of phase II enzymes and endogenous antioxidants that defend cells from oxidative stress. The promoter regions of the phase II genes contain specific DNA sequences, termed the antioxidant response elements (AREs) or the electrophile response elements (EREs) that are required for induction by chemopreventive compounds, oxidative stress or electrophiles. In an attempt to find the



transcription factors that bind to ARE, NF-E2-related factor 2 (Nrf2) was identified (Zhang, 2006). Nrf2 binds to Kelch-like ECH-associated protein 1 (Keap1) under nonstressed conditions. Keap1 in complex with cullin3, Roc1 and E2 proteins provides ubiquitination followed by proteasomal degradation. When oxidative stress occurs, oxidation of Keap1 leads to inability to bind Nrf2 protein by forming intramolecular disulfide bonds. Then Nrf2 migrates into the nucleus and binds a protein of Maf family (like sMaf) and CBP/p. This complex is formed on ARE promoter region of certain genes leading to transcription activation. Phosphorylation of by protein kinases which may be activated by oxidants is one way to provide Nrf2 migration in nucleus (Lushchak, 2011).

#### 4.4.1 Evidence from animal studies

Tea polyphenols have been demonstrated to improve lipid profile in diabetic and nondiabetic models. In this section, we follow the antioxidant properties of tea. Improved glucose tolerance and increased plasma insulin concentrations by tea, have been found in some studies which may be, in part, explained by the effect of tea antioxidants on insulin resistance and  $\beta$ -cell function. EGCG has also been shown to suppress cytokine-induced  $\beta$ -cell damage; this may also contribute to glucose lowering effect of tea (Gomes *et al.*, 1995; Han *et al.*, 1999; Kao *et al.*, 2000; Sabu *et al.*, 2002; Wu *et al.*, 2004; Tsuneki *et al.*, 2004; Babu *et al.*, 2006; Wolfram *et al.*, 2006; Igarashi *et al.*, 2007; Badawoud *et al.*, 2007; Ostad Rahimi *et al.*, 2007; Potenza *et al.*, 2007).

Lipid peroxidation is an indicator of oxidative stress and plays major role in development of some complications of diabetes. Animal studies have shown that green tea administration can reduce lipid peroxidation in diabetic animals (Yamaguchi *et al.*, 1991; Tijburg *et al.*, 1997; Vinson *et al.*, 1998; Miura *et al.*, 2001; Guleria *et al.*, 2002; Kasaoka *et al.*, 2002; Nakagawa *et al.*, 2002; Liuji *et al.*, 2002; Sabu *et al.*, 2002; Skrzydlewska *et al.*, 2002; Babu *et al.*, 2006). Black tea has been reported to be an efficient reducer of peroxidation of lipoproteins as well (Tijburg *et al.*, 1997; Vinson *et al.*, 1998; Sur-Altiner *et al.*, 2000; Yokozawa *et al.*, 2002; Vinson *et al.*, 2005; Alipoor *et al.*, 2008). Some studies have investigated the effects of purified tea polyphenols and drawn similar results (Quine *et al.*, 2005; Yamabe *et al.*, 2006).

MDA is another important indicator of oxidative stress that is usually measured in diabetics. Based on the results of studies, tea seems to affect this factor too and reduce its plasma concentration (Durate *et al.*, 2001; Skrzydlewska *et al.*, 2002; Chander *et al.*, 2003; Sürmen-Gür *et al.*, 2006; Alipoor *et al.*, 2009).

The activity of antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase and glutathione peroxidase has been shown to increase by supplementation of tea or its polyphenols as well. Actually some enzymes showed greater activity after the very supplementation in one study but not the other which seems to be due to different doses of supplementation, design and duration of the study (Khan *et al.*, 1992; Lin *et al.*, 1998; Durate *et al.*, 2001; Sabu *et al.*, 2002; Skrzydlewska *et al.*, 2002; Chander *et al.*, 2003; Kuo *et al.*, 2005; Babu *et al.*, 2006; Alipoor *et al.*, 2009).

Glutathione is another parameter which has been measured in some studies and seems to increase in diabetics receiving tea intervention (Sohn *et al.*, 1994; Lin *et al.*, 1998; Durate *et al.*, 2001; Sabu *et al.*, 2002; Skrzydlewska *et al.*, 2002; Babu *et al.*, 2006; Alipoor *et al.*, 2009).



#### 4.4.2 Evidence from human studies

Human studies are not as conclusive as animal ones. There is some evidence that in countries with higher tea consumption like Japan, diabetes is less prevalent (Iso *et al.*, 2006). Some studies have shown a negative correlation between tea consumption and heart disorders and its consequent death (Stensvold *et al.*, 1992; Imai *et al.*, 1995; Duffy *et al.*, 2001; Geleijnse *et al.*, 2002; Hodgson *et al.*, 2002; Hakim *et al.*, 2003) which can be, in large part, attributed to the effects of tea on endothelial function through reducing oxidative stress; but there have been studies in which no relation was observed (Brown *et al.*, 1993; Sesso *et al.*, 2003).

Tea consumption decreased lipid peroxidation in some clinical trials (Klaunig *et al.*, 1999), but was not as effective in the others (Van Het Hof *et al.*, 1999; Hodgson *et al.*, 2000; Rumpler *et al.*, 2001; Hodgson *et al.*, 2002).

Results for malondialdehyde were inconsistent as well: some investigations indicating a negative relation between tea and MDA (Freese *et al.*, 1999; Hirano-Ohmori *et al.*, 2005; Nagao *et al.*, 2005), others showing no significant relationship (Rumpler *et al.*, 2001; Davis *et al.*, 2003).

The activity of antioxidant enzymes or oxidative status of the serum were improved by tea intervention in some studies (Serafini *et al.*, 1996; Nakagawa *et al.*, 1999; Leenen *et al.*, 2000; Sung *et al.*, 2000; Young *et al.*, 2002), but remained unchanged in the others (Van Het Hof *et al.*, 1997; Princen *et al.*, 1998; Freese *et al.*, 1999; Miura *et al.*, 2000; Davis *et al.*, 2003; Henning *et al.*, 2004; Davis *et al.*, 2005).

As reviewed above there is some evidence that tea and its fractions can act against development of diabetes and its complications but some studies have shown insignificant results. More detailed and precise clinical trials are essential to better understanding of tea's role in diabetes through its capacity to reduce oxidative stress.

Although animal studies provide great deal of evidence on usefulness of tea and its polyphenols against oxidative stress and its consequences in diabetes, human studies are not conclusive and limited research has not generally revealed significant decreases in biomarkers of *in vivo* oxidative damage. Far wider genetic variations in the response of humans to oxidative stress in comparison with animals may be one important factor obscuring small changes in biomarkers induced by tea and its polyphenols. Another reason may be that, though the dose of tea and its effective compounds used in animal and human studies do not differ much. Much higher doses relative to body weight is used in animal studies (Frei *et al.*, 2003).

#### 5. Conclusion and future trends

Oxidative stress has been showed to play an important role in initiation and progression of diabetes and its accompanying complications. Thus to prevent the very consequences of oxidative stress, it seems logical to take the necessary steps to reduce it. Antioxidants have been reported to be effective in fulfilling this goal. Tea is a great source of a group of antioxidants so called flavonoids. Animal studies have been done to detect which compounds in tea are responsible for its effects on oxidative stress but human studies are lacking.

Animal studies have strongly supported the idea of tea being an efficient suppressor of oxidative stress in diabetic animals but human studies have faced inconsistency which may be rooted in factors like the design and time course of the study, the dose supplemented, the oxidative status of the subjects at baseline, the type of the tea studied, the stage of the disease, confounding factors not considered in some studies. It is recommended that well designed controlled clinical trials be done taking into account all the factors affecting the oxidative status of the patients and using sensitive and specific indicators of oxidative stress.

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## **Oxidative Stress - Environmental Induction and Dietary Antioxidants**

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This book focuses on the numerous applications of oxidative stress theory in effects of environmental factors on biological systems. The topics reviewed cover induction of oxidative stress by physical, chemical, and biological factors in humans, animals, plants and fungi. The physical factors include temperature, light and exercise. Chemical induction is related to metal ions and pesticides, whereas the biological one highlights host-pathogen interaction and stress effects on secretory systems. Antioxidants, represented by a large range of individual compounds and their mixtures of natural origin and those chemically synthesized to prevent or fix negative effects of reactive species are also described in the book. This volume will be a useful source of information on induction and effects of oxidative stress on living organisms for graduate and postgraduate students, researchers, physicians, and environmentalists.

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