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A Review on the Therapeutical Effects of Tea

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ABSTRACT

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. 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. Tea may contain alkaloids (caffeine), flavonoids (catechins), phenolic acids (gallic acid, coumaric acid, caffeic acid and chlorogenic acid) and volatile oils (essences). 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.

Key words: Tea, antioxidant, therapeutical effects, diseases

INTRODUCTION

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 genuses *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 m if left undisturbed but cultivated plants usually have a height around 50-70 cm (Hara, 2001; Moxham, 2009).

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 5th century by Turkish traders (Alkan *et al.*, 2009).

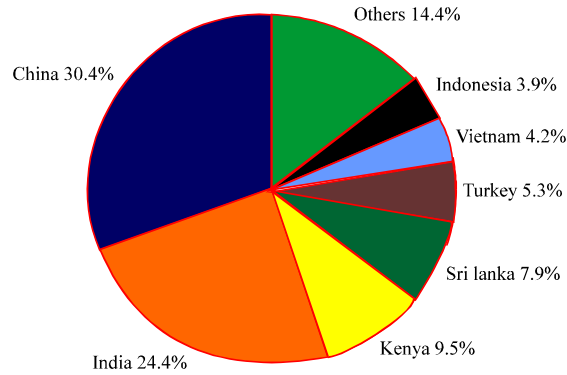


Fig. 1: The tea producing regions in 2007

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 Fig. 1. 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).

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).

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) (Wang *et al.*, 2000; Jayaganesh and Venkatesan, 2010; Venkatesan and Anbu-Sujitha, 2007).

Table 1: The classification of primary and subordinate tea agents

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

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 (Wagner and Blatt, 1996; Hara, 2001).

Polyphenols: Theanine and flavonoids (catechins in particular) are the main polyphenols found in tea constituting 30% of its agents (John *et al.*, 2006a).

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% 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 and Beecher, 1998; Keys, 1976; John *et al.*, 2006b). All catechins have 2 asymmetric carbons, thus there are four isomers of them: Catechin (C)(+), Catechin Gallate (CG)(-), galocatechin (GC) and galocatechin 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 (Fig. 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 (Jayaganesh *et al.*, 2011; Soomro *et al.*, 2008).

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

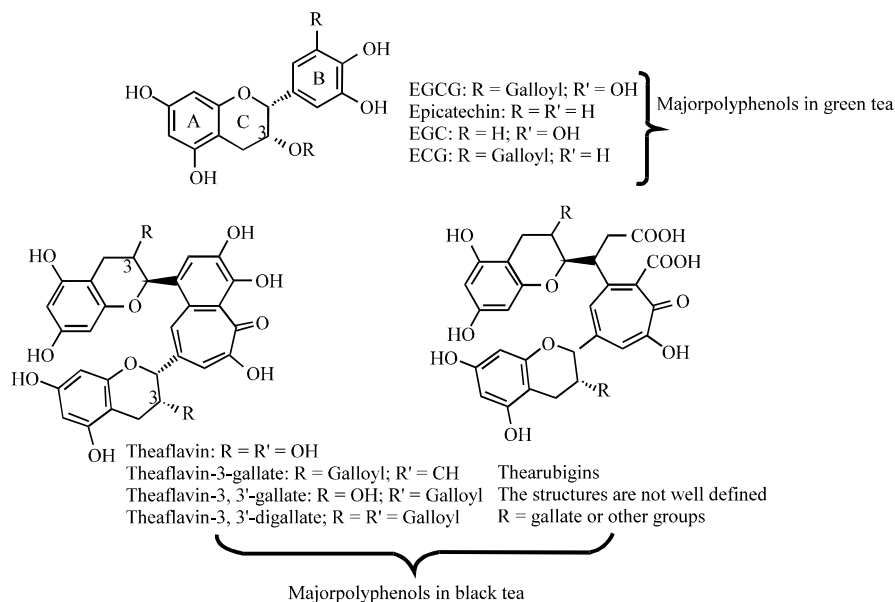


Fig. 2: Major polyphenols in green and black tea

as a result of the quinone appearance, turn into some colorful agents including theaflavin and thearubigin, both of which are plentiful in black tea (Fig. 2) (Hara, 2001; Leung *et al.*, 2001; Cadenas and Packer, 2002; Hemalatha and Venkatesan, 2011).

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 iolido paravinile phenol, hexenol, hexenal, aldehydes, phenyl ethyl alcohols, phenols and geraniols (Hara, 2001).

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 (Fig. 3). The less processed the tea, the greater the polyphenols content will be, which the extent of oxidation accounts for:

- **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
- **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
- **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
- **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

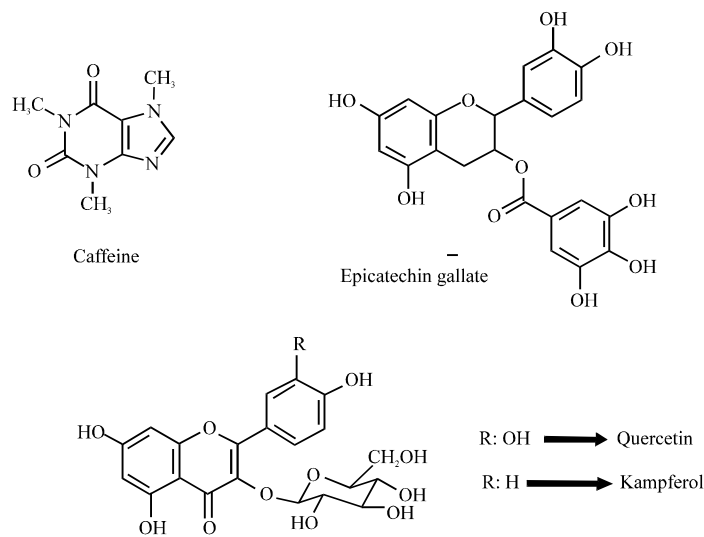


Fig. 3: Major antioxidants in 20% fraction of black tea

- **Black tea:** The manufacturing process for black tea includes withering of fresh leaves, rolling, fermenting and drying. Thorough fermentation is done in black tea
- **Pu-erh:** Pu-erh is applied to old tea with extreme fermentation in it (Hara, 2001; Kuo *et al.*, 2005; Lin and Lin-Shiau, 2006; <http://en.wikipedia.org/wiki/Tea>; <http://www.tea-of-chinese.com>)

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, 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 and Beecher, 1998; Dulluge *et al.*, 1998; IMC, 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; Leung *et al.*, 2001; Alipoor *et al.*, 2008; Obaid *et al.*, 2011). 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 *et al.*, 1991).

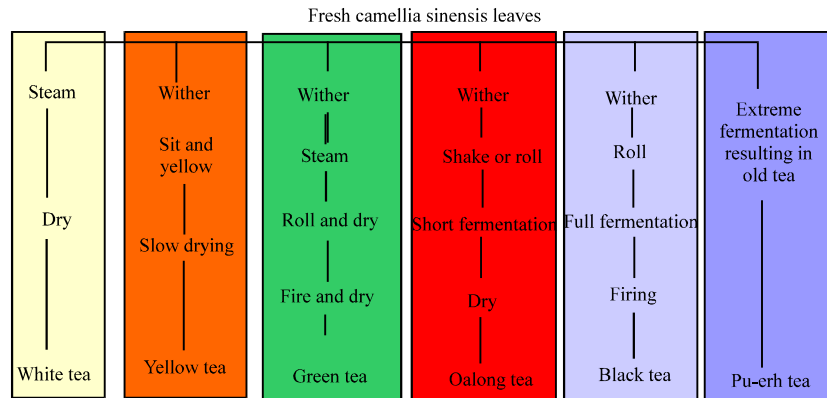


Fig. 4: The production of different types of tea

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). 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; IMC, 2000; Mills and Bone, 2000; McKay and Blumberg, 2002; Wright, 2005; Kao *et al.*, 2006; Sasso *et al.*, 2006; Alipoor *et al.*, 2011).

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 (Fig. 4) (Alipoor *et al.*, 2010).

Caffeine is a strong antioxidant and its activity being equal to that of glutathione and exceeding that of vitamin C (Devasagayam *et al.*, 1996; Kammat *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 β 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).

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 β -cell function. EGCG has also been shown to suppress cytokine-induced β -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; Anandh Babu *et al.*, 2006; Wolfram *et al.*, 2006; Igarashi *et al.*, 2007; Badawoud *et al.*, 2007; Rahimi *et al.*, 2007; Potenza *et al.*, 2007; Chigozie *et al.*, 2008; Balouchzadeh *et al.*, 2011).

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 and Dabbagh, 1998; Miura *et al.*, 2001; Guleria *et al.*, 2002; Kasaoka *et al.*, 2002; Nakagawa and Yokozawa, 2002; Sabu *et al.*, 2002; Skrzydlewska *et al.*, 2002; Anandh 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 and Dabbagh, 1998; Sur-Altiner and Yenic, 2000; Yokozawa *et al.*, 2002; Vinson and Zhang, 2005; Alipoor *et al.*, 2008). Some studies have investigated the effects of purified tea polyphenols and drawn similar results (Quine and Raghu, 2005; Yamabe *et al.*, 2006; Abu Bakar *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; Surmen-Gur *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; Anandh 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; Anandh Babu *et al.*, 2006; Alipoor *et al.*, 2009).

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 and Nakachi, 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; 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; Davies *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; Davies *et al.*, 2003; Henning *et al.*, 2004).

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 and Higdon, 2003; Bajerska *et al.*, 2010).

CONCLUSION

Tea is a great source of antioxidants especially flavonoids. Animal studies have strongly supported the idea of tea being an efficient suppressor of oxidative stress in 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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