Medicinal and Pharmaceutical Potentialities of Tea (*Camellia sinensis* L.)

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Summary

Tea is among the most widely consumed beverages in the world. There are three types of tea depending on the level of fermentation, i.e., green (unfermented), oolong (partially fermented) and black (fermented) tea. Many health benefits of various types of tea have been known up to present time. In general, green tea has been found to be superior to black tea in terms of antioxidant activity owing to the higher content of (−)-epigallocatechin gallate. The processes used in the manufacture of black tea are known to decrease levels of the monomeric catechins to a much greater extent than the less severe conditions applied to other teas. In the present review, we have discussed the current state of the science with regard to laboratory studies on various types of tea and some of health disorders including some types of cancer, coronary heart disease, atherosclerosis, metabolic syndrome, diabetes, resistance to insulin hypertension and obesity have been discussed.

Keywords: Tea; Antioxidants; Cardiovascular health; Obesity; Ethno medicine; Human health

Introduction

Tea is one of the most pleasant drinks used widely by people with various tastes all over the world, especially in oriental countries. Although black tea is the most common type of tea, but recently the use of green tea, the unfermented form, is attracting more attention in most of countries. This is due to its higher content of polyphenols, mainly flavanols, as compared to oolong, semi-fermented and black, fermented teas (1). It is known that flavanols can exhibit many pharmaceutical functions, such as antioxidative, antitumor, and anticarcinogenic activities (2). Tea is rich in nutrients and many beneficial phytochemicals including flavenoids and polyphenols. As a source of nutrients, it is, therefore, susceptible to microbial contamination. A suitable method to inactivate microorganisms is needed which does not cause the loss of color, flavor and taste during heat (3). Some researchers have observed that tea polyphenols are sensitive to heat as they are vulnerable to decomposition and isomerization during heat processing, especially for epigallocatechin, EGC and epigallocatechin gallate, EGCG (4).

History

In the 1770s Captain James Cook discovered the *Melaleuca alternifolia* or tea tree, when he witnessed native Australians brewing tea from its leaves (5). Tea tree grows as high as 20 feet it, therefore, is almost a shrub. The essential oil extracted from tea leaves has shown many health benefits such as antioxidant and antibacterial properties. Normally, the tree's leaves are collected twice a year and distilled to expel the oil.

The earliest scientific research examining the properties of tea tree oil was performed by Dr. Arthur Penfold the Australian researcher in 1920. He discovered that *Melaleuca* oil was about 12 times more potent than carbolic acid, the accepted antiseptic at the time. The use of tea tree oil in medical applications was then started and increased rapidly in the following decades. In the late 1940s, the introduction of antibiotics such as penicillin caused a drop in the use of tea tree oil. Once again in 1980, increasing demand for natural products and growth in immunity to antibiotics, led to improved tea tree harvesting procedures (6).

It has been shown that tea tree oil is also effective as an additional treatment for colds, bronchitis, whooping cough and pneumonia. Adding it to a vapourizer and inhaling the fumes helps to reduce microorganisms infecting the sinuses and lungs. Similar to eucalyptus oil, tea tree oil also opens clogged respiratory passages (6). It can also be utilized to reduce the spread of infection in hospitals. Besides sterilizing surgical instruments, washing with soap containing the oil reduces the chances of cross contamination. New detergents made from this oil are stronger antiseptic compared to other disinfectant products. They do not cause bacterial resistance, unlike the antibacterial commercial soaps available. In Australia, dental patients are often instructed to apply tea tree oil to infected teeth a few days before dental work occurs to prevent post-operative infections (7).

Chemistry and Biology of Tea

Brewed tea contains many compounds, especially polyphenols, terpenoids and a group of chemical and biological compounds most of which possess antioxidant and antibacterial activity. In addition to polyphenols, e.g. catechins and flavonoides, other chemical compounds such as alkaloids such as caffeine, theobromine, theophylline, etc., volatile oils, polysaccharides, amino acids, lipids, vitamins, e.g. vitamin C, inorganic elements, e.g. aluminium, fluorine and manganese), are also found in tea. However, the polyphenols are primarily responsible for the beneficial properties of tea. A wide range of several studies have shown that polyphenolic compounds present in tea reduce the risk of a variety of diseases. Polyphenols (Figure 1) are a group of chemicals with many pharmaceutical functions, such as antioxidative, antitumor, and anticarcinogenic activities (8, 9). It has been observed that tea polyphenols, TPs are sensitive to heat as they are vulnerable to decomposition and isomerization during heat processing, especially EGC and EGCG (10).

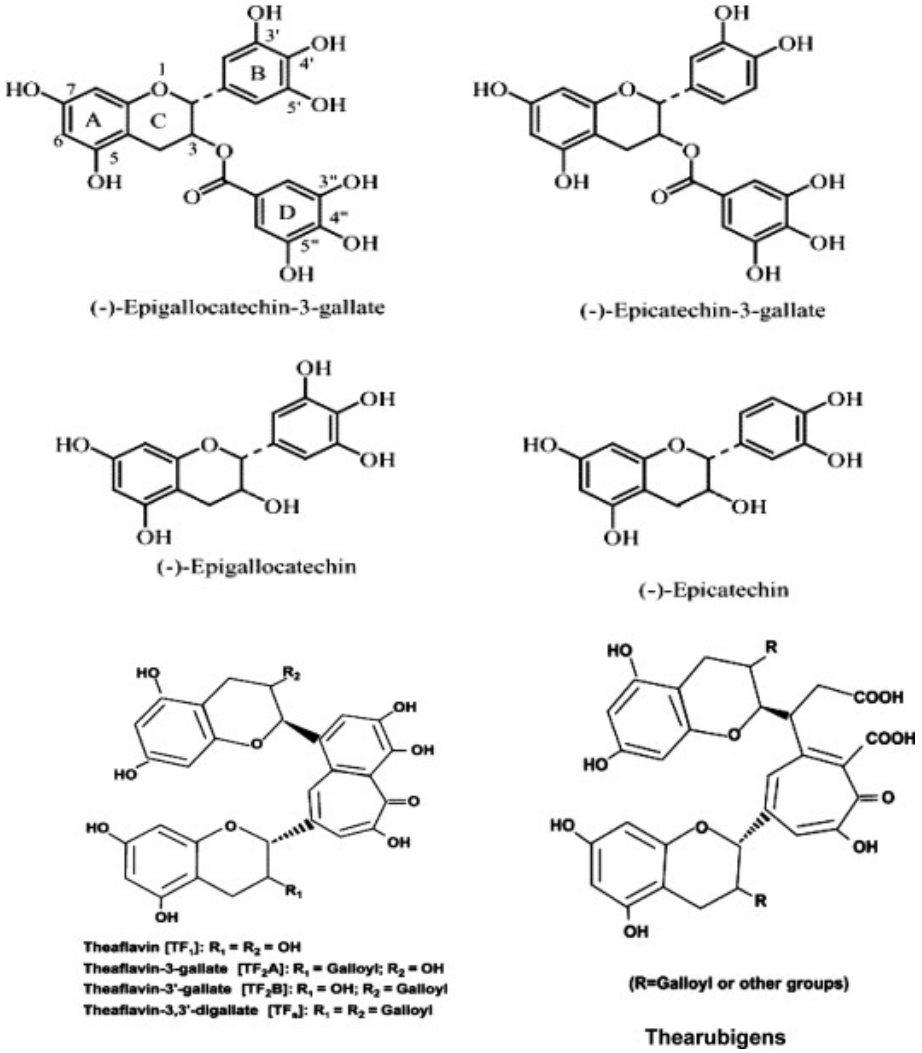

Figure 1. Chemical structures of the major tea polyphenols.

Tea catechins have antioxidants properties comparable and, even higher than important natural antioxidants such as vitamins C and E, tocopherol and β-carotene. The antioxidant activity of tea polyphenols is not only due to their ability to scavenge superoxide but also due to increased activity of some detoxifying enzymes such as glutathione peroxidase, glutathione reductdase, glutathione-S-transferase, catalase and quinine reductase in small intestine, liver and lungs. These strong antioxidant properties of tea may, therefore, be effective in preventing many human disorders including atherosclerosis and coronary artery disease (11).

Types of Tea

More than three billion kilograms of tea plant *Camellia sinensis* is grown, processed and used during one year in the whole world. Processed tea is brewed to produce a beverage acceptable for the taste of many individuals from different parts of the world. Tea beverage is consumed as green, black, Oolong and white tea. About 20% of the total tea used in the whole world is in the form of unfermented (green tea). This form of tea is the unfermented

type and is mostly used in China and Japan. The largest amount of total tea (about 78%) is in the form of black tea that is the fully fermented type of tea which is widely used in Europe. The remaining 2%, i.e. Oolong tea, is produced by partial fermentation and is not as common as the other two types of tea. White tea is produced from the buds and young tea leaves, collected before the buds have fully opened. They are steamed and dried with the minimum amount of processing. White tea retains the greatest levels of antioxidants, in the form of polyphenols (TPs), mainly flavanols and the lowest levels of caffeine than any other tea from the *C. sinensis* plant (green, black or oolong).

Green Tea

As the name applies, this type of tea is unfermented leaves compared to the leaves of oolong tea which are partially fermented and black tea which are fully fermented. In Table 1 some of physical and chemical properties of green and black tea are compared. Green tea is a great source of beneficial chemicals with maximum positive effects on human beings. Since thermal pasteurization may affect the antioxidant activity of green tea, pulsed electric fields have been applied as potential complements or replacements to thermal pasteurization (12). It has been demonstrated that while the process led to inactivation of *Escherichia coli* and *Staphylococus aureus* in green tea beverage, it did not considerably affect the color, polyphenols content, and total free amino acids in green tea extracts. Green tea may also reduce the risk of coronary heart disease related to lipoprotein composition in patient's plasma. Ingestion of 300 mL green tea on plasma total antioxidant capacity in healthy volunteers has been studied (13). It has been found that white tea possesses the highest content of phenolics compounds followed by green and black tea. Green tea is highly efficient in protecting low density lipoprotein from oxidation driven by peroxyl and ferril radicals. Although phenol-rich compounds are a natural source of antioxidants, but the phenolic content alone is not an index of their in vivo antioxidant activity.

Table 1. Selected physical and chemical properties of green and black tea.

Type of Tea	**Black**	**Green**
Fermentation time	More than 5 hours	No fermentation
Color of brewed	Cinnamon red	Yellowish green
Taste	Distinct flavor	Bitter
Antioxidants	High Flavonoid content	High polyphenol content
Caffeine	High	Lower
Health effects	Cardiovascular system	Irritate to empty stomach
pH	7.0 ± 02	6.0 ± 02

It should be emphasized that about 35% of constituents of green tea by the dry weight, are the polyphenols, including flavonols, flavones, and flavan-3-ols (Table 2). Aproximately 60–80% of these compounds are a group of chemically related substances called the flavan-3-ols also known as catechins. On the other hand, the other two types of tea, i.e., oolong and black teas which are produced from partially fermented or completely fermented *C. sinensis* leaves, respectively, contain approximately half the catechin content of green tea (10, 13).

Table 2. Flavonoid composition of brewed green tea.

Components	**Amount mg/100 g (100 ml)**
Epigallocatechin 3-gallate	77.8±7.0
Epicatechin 3-gallate	19.7±2.8
Epigallocatechin	16.7±1.4
Epicatechin	8.3±0.5
Quercetin	2.7±0.3
Catechin	2.6±1.5
Gallocatechin	1.5±0.0
Thiarubigins	1.1±1.1
Theaflavin	0.1±0.0
Total Flavonoids[a]	130.5

[a]Total flavonoid content is estimated as the sum of the following five subclasses: flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins.

White tea

This type of tea is a combination of tea blossoms and very young tea leaves. The buds and young tea leaves are collected before the buds have fully opened. They are then steamed and dried with the minimum amount of processing. Therefore, white tea retains the greatest levels of antioxidants and the lowest levels of caffeine than any other tea from the *C. sinensis* plant. This type of tea is very rare in commercial market having the highest price. However, we have found that besides it highest antioxidant properties, white tea possesses strong antibacterial effect on a broad range of gram positive and gram negative bacteria, even those resistant to all antibiotics [unpublished results]. Due to its high price, it is suggested that white tea is more suitable for pharmaceutical and research applications

Black tea

About 72% of the world's total tea production is in the form of black tea. While most of the EGCG antioxidants are oxidized during the fermenting process, there is comparatively high number of the polyphenols such as flavonoids in black tea (Fig. 2). The main effect of tea flavonoids on human health is to reduce the harmful effects of toxins. They have antioxidant properties and, similar to many synthetic antioxidants, they are able to scavenge free radicals. In general, flavonoids can be divided into various classes on the basis of their molecular structure (3). The molecular structure of each group of flavonoids is given in Figure 2. It should be noted that flavonoids belonging to the catechins are mainly found in green and black tea (14), whereas anthocyanins are found in strawberries and other berries and grapes.

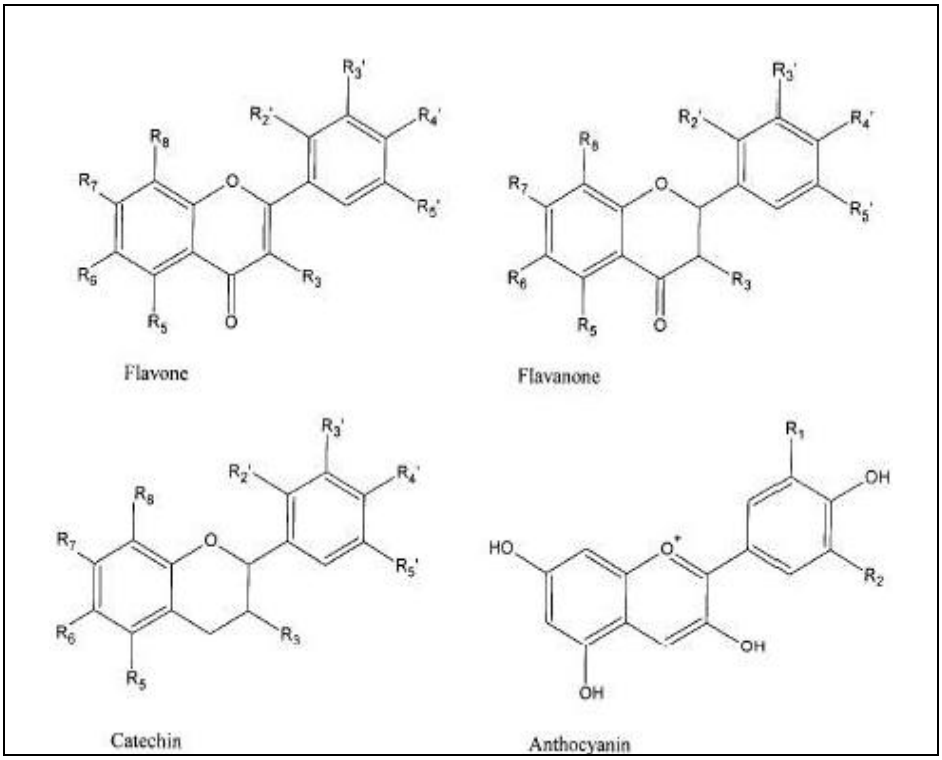

Figure 2. The molecular structure of different flavonoids.

Oolong tea

Oolong tea is a partially fermented tea and has the flavor and health characteristics of both green and black teas. It contains a high number of antioxidants, beneficial to human health and increase the rate of survival of many important disorders. This type of tea is less common in Western world, but is used in Far East countries. In general, tea extracts are powerful antioxidants, mainly owing to the presence of (+)-catechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epigallocatechin gallate and (−)-epicatechin gallate (Salah et al., 1995).

In general, it is suggested that the type and duration of tea processing during its manufacture could highly affect its physical and chemical properties. It is known that polyphenols are key non-volatile components having important role in tea. They provides a lot of beneficial effects of tea in terms of free radical scavenging ability, i.e. its powerful antioxidant activity (15). Most polyphenols such as catechins, monomeric flavonols, and (−)-epigallocatechin gallate (EGCG) are detected in fresh tea leaves at a high level (16). It has been found that fermentation process can seriously affect polyphenols content of tea. Flavanols, flavandiols and phenolic acids like gallic acid, cumaric acid and caffeic acid are predominant in non-fermented green tea, whilst some polyphenols are oxidised, degraded and polymerised enzymatically to theaflavins and thearubigens in black tea during the full fermentation (17). It has been reported that the degree of antioxidant effectiveness depends on variety and the content of EGCG [Katalinic et al., 2006]. High content of EGCG and (−)-epigallocatechin (EGC) was detected in non-fermented and semi-fermented tea, i.e. green and Oolong types.

Whereas the content of both of these beneficial components are significantly decreased in fully fermented black tea (18).

Health benefits and Medicinal Usage

Antioxidant Properties

Reactive oxygen species (ROS) and free radicals are responsible for the pathogenesis of various human diseases, including cancer, aging and chronic arterial disease (11). The effect of ROS on human health has been studied for decades. It has been found that they increase the risk of cancer, arthritis, degenerative eye and neurological disorders, and general aging (19). More recent research has focused on the effect of free radicals on cardiovascular disease and related disorders; atherosclerosis, hypertension, hypercholesterolemia, type 2 diabetes, and heart failure (20).

Various extracts of tea have been studied for their effect as antioxidants and their potential benefits studied. It has been found that hot water extract of green tea leaves could be potential sources of antioxidants (21). It is believed that interesting benefits of tea is related to its high antioxidant properties played partly by polyphenolic compounds. The most abundant and biologically active polyphenols found in green tea is EGCG. It has been shown that EGCG have a great effect on several types of cancer cells in culture (22). The beneficial effect of tea polyphenols is also extended to prevent diabetes. It has been shown that drinking large volume of green tea (>6 cups per day) per week could highly reduce the risk of developing type 2 diabetes (23). The type of solvent used could highly alter the extraction yield as well as the antioxidant activity of extracts. It has been reported that the extraction conditions has altered the content of active antioxidant components from green tea leaves (14).

Cardiovascular Diseases

Regular use of tea could be beneficial in reducing the risk of cardiovascular disease (24). The cardiovascular health effects of drinking tea are thought to be largely due to flavonoids. It is found that most flavonoids of tea are associated with reduced risk of cardiovascular disease (24). Most European and American observations about association between tea consumption and reduced risk of cardiovascular disease are not specific to green or black tea. However, a number of Asian studies have suggested a higher cardioprotective effect of green tea compared other types of tea (25). A more recent study has demonstrated that daily consumption of either green or black tea 3 cups/day, was associated with reduced risk of ischemic stroke (26). The relationship between tea intake and atheroslerosis, a chronic vascular disorder that can increase the risk of heart attack, have investigated. The results have revealed that carotid plaques are less frequent in women who drank a few cups of tea per day (27). A population study has also shown that using high concentration of isolated flavonoids is associated with decreased carotid atherosclerosis in middle-aged men (28, 29).

It is known that any increase in platelet activation can results in an increased susceptibility to aggregation and clotting. This can contribute to thrombosis, myocardial infarction and stroke. A randomized controlled study in humans has revealed the effects of flavonoid-rich foods

and beverages on platelet function (30). It has been shown that regular ingestion of tea for 4 weeks can reduce the concentration of circulating p-selectin, a marker of platelet activation (31).

Effect on Various Types of Cancer

The chemopreventive effect of various types of tea, especially green, on carcinogenesis has been studied by many scientists. They have revealed that the presence of tea catechins can cause this type of effect through different possible mechanisms including, inhibition on cell proliferation (32), cell cycle arrest (33), blockade of growth factor receptors, reduction in cytokines release (34), inhibition of angiogenesis by interfering with the activities of metalloproteinases, serine proteinases and vascular endothelial growth factor (35), prevention of nuclear factor kappa B and activator protein 1 activation (36), inactivation of topoisomerase I (37) and telomerase (38) resulting in apoptosis. Studies on the preventive effect of green tea in esophageal cancer have produced inconsistent results.

Lung cancer is one of the most common types of cancer among men and women in the world. In 2002 the death incidences were reported to be about 1.18 million (39). In few last decades many new improvements are made for treatment of all types of cancer including surgery, radiation, and medical therapies. However, the 5-year survival rates have remained under 20% for patients with lung cancer (40). Therefore, prevention in addition to early detection is still the main aim of many scientists working in this area. Many population-based studies have shown that various types of tea possess cancer protective effects (41). It is believed that polyphenols found in tea leaves are powerful antioxidants. They may, therefore, play an important role in the prevention of cancer by reducing damage of DNA in the cell and activation of cancer leading to malignancy. It has been found that EGCG present in green tea is potent inducible nitric oxide synthase and cyclooxygenase-2 inhibitor (41, 42). In suppressing the release of nitric oxide and prostaglandins, which are important mediators for inflammation and tumorogenesis, green tea can limit inflammatory reactions and promotion of cancer. It has also been shown that EGCG can bind to a specific metastasis associated 67-kDa laminin receptor that is expressed on a variety of tumor cells (43). Green tea may then interfere with the promotion of cancer by preventing metastasis of the tumour. Other factors that are related to metastasis, e.g., urokinase plasminogen activator (44), urokinase (45) and matrix metalloproteinases (46) were also reported to be inhibited by green tea (Figure 3).

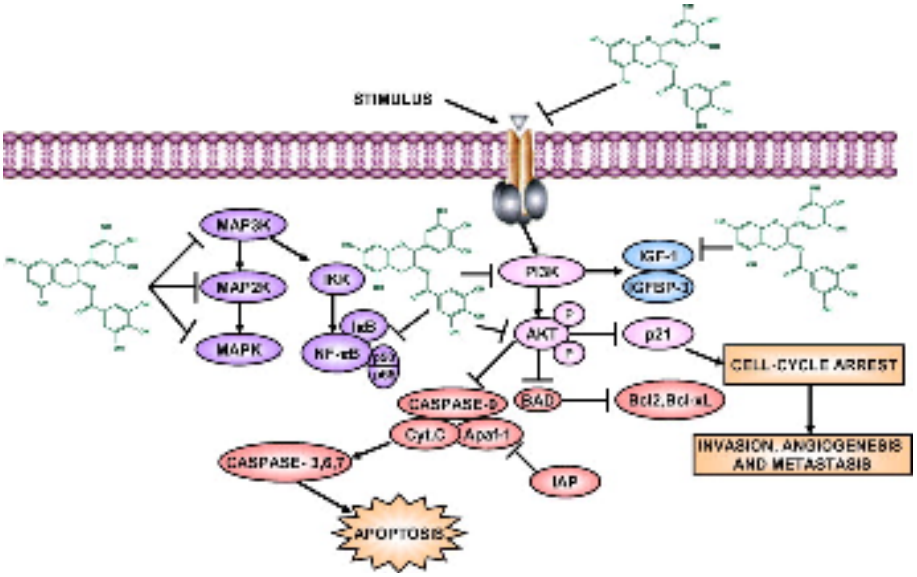

Fig. 3. Effect of EGCG on the modulation of various signal transduction pathways.

Effect on Respiratory Diseases

Theophylline is a chemical compound found in tea having structural similarity to tea caffeine. This important tea component is used as a licensed medicine for the treatment of some respiratory diseases such as asthma. For many years, theophylline in tea has been used to prevent respiratory diseases like wheezing, shortness of breath, and difficulty breathing caused by asthma, chronic bronchitis, emphysema, and other lung diseases. The compound acts through relaxation and opening of air passages in the lungs. Therefore, it can ease breathing (47).

Effect on Digestion

It has been shown that tea catechins are well absorbed after oral administration (48, 49). Among all tea catechins, (−)-epigallocatechin gallate is the most stable form in the stomach and small intestine. After absorbtion, tea catechins are biotransformed in the liver to conjugated metabolites, i.e., glucuronidated, methylated, sulfated derivatives. It has been found that green tea can activate intracellular antioxidants, inhibit procarcinogen formation, suppress angiogenesis and cancer cell proliferation while digested in gastrointestinal tract. It could be suggested that tea consumption can reduced the incidents of cancers in the stomach and colon. As tea catechins are well absorbed in the gastrointestinal tract and they interact synergistically in their disease-modifying actions, thus drinking unfractionated green tea is the most simple and beneficial way to prevent gastrointestinal disorders.

Weight Control and Prevention of Metabolic Syndrome

Many investigations have been conducted to show the effect of various types of tea on control of weight. It has been revealed that consumption of GTC with a dose of 270 mg to 1200 mg/day could reduce body weight and fat. Several mechanisms have been proposed by which GTC may influence body weight and composition. The predominating hypothesis is that GTC influences sympathetic nervous system (SNS) activity. This action increases the

energy expenditure and promotes fat oxidation. Caffeine is one of the compounds naturally present in green tea. It can influence the activity of SNS and, therefore, act synergistically with GTC to increase energy expenditure and fat oxidation. Other potential mechanisms by which tea could help reduce weight include modifications in appetite, up-regulation of enzymes involved in hepatic fat oxidation, and decreased nutrient absorption (50).

One of the potential mechanisms explaining the antiobesity effects of GTC is suggested to be through decreased nutrient absorption in the gastrointestinal tract. Some data obtained from in vitro studies have suggested that GTC could reduce glucose absorption by inhibiting gastrointestinal enzymes involved in nutrient digestion, in particular, α-amylase and α-glucosidase activity (51). Studies about cellular mechanism have also shown that GTC decreases glucose uptake in intestinal cells and inhibits the sodium-dependent glucose transporter (52).

The important point is that the effect of green tea catechin on the absorption and metabolism of glucose is highly depended on the time of its consumption (53). It has been reported that when EGCG and ECG were administered one hour prior to eating glucose, it may cause circulating glucose levels actually exceeded those of the water control (53). They postulated that GTC, and in particular, the gallated catechins, inhibit circulating glucose uptake via competitive inhibition of glucose transporters located throughout the body. The increase in glucose was accompanied by an increase in insulin levels.

Indirect evidence from intervention trials has suggested that GTC may alter fat metabolism through promoting lipolysis from specific fat depots. The fat depots of the abdomen are more responsive to NE-induced lipolysis than those in other depots (54). Abdominal fat is more lipolytically active than lower body adipose depots, altering fatty acid uptake and release in a way that selectively reduces abdominal adipose tissue more so than peripheral fat depots. The effects of a brewed green tea beverage having about 75 mg caffeine with added GTC has been evaluated and compared to a caffeine-matched control beverage for men and women undergoing treatment for diabetes (55). It is known that this type of population has a high prevalence of increased abdominal adiposity. It was shown that at the end of the 12 week intervention period, body weight did not differ between the GTC and control groups. On the other hand, their waist circumference was significantly reduced among those consuming the GTC.

One of the most successful and interesting results of green tea consumption is its effect on metabolic syndrome, MetS. This is a complex condition defined by the presence of elevated waist circumference, dysglycemia, elevated blood pressure, decrease serum high-density lipoprotein-associated cholesterol, and increased serum triglycerides. Both *in vitro* and *in vivo* studies have examined the effects of green tea and EGCG against the symptoms of MetS. The results of these studies have demonstrated that green tea and EGCG have preventive effects in both genetic and dietary models of obesity, insulin resistance, hypertension, and hypercholesterolemia. Various mechanisms have been proposed based on these studies and include: modulation of dietary fat absorption and metabolism, increased glucose utilization, decreased *de novo* lipogenesis, enhanced vascular responsiveness, and antioxidative effects. Some of the studies on various aspects of MetS have been reviewed and presented in following sections showing the appropriate references.

Prevention of insulin resistance and diabetes

Insulin resistance is an early marker of type 2 diabetes (T2D) and development of insulin resistance is associated with obesity (56). It has been suggested that a major contributor to the development of insulin resistance is an overabundance of free fatty acids in the plasma (57). Hyperinsulinemia which may ultimately end to T2D is a syndrome resulting from resistance to insulin and, therefore, interruption of insulin signaling in responsive tissues. As a result, in a long period the body will not produce enough insulin to overcome insulin resistance and the pancreas may reduce or stop insulin production (58). On the other hand, resistance to insulin may cause decreased levels of lipoprotein lipase in peripheral tissues. It is worth to recall that type I diabetes (T1D) begins early in life and is normally the result of autoimmune destruction of pancreatic β-cells causing insulin deficiency (59).

Prevention of hypertension and modulation of plasma cholesterol

High blood pressure or hypertension is another important condition related to metabolic syndrome. Drnking tea could result in reduction of blood pressure leading to improve of endothelial function in animal studies (60). Endothelial dysfunction is an alteration of endothelial cells, resulting from oxidative stress and impaired vasodilatory response (60). It is known that both hypertension and perturbed homeostasis of the ratio of HDL-cholesterol and low-density lipoprotein-associated (LDL)-cholesterol are risk factors for cardiovascular disease. The effect of green tea extract on arterial hypertension in Sprague–Dawley rats has been investigated (61). The result of this *in vivo* study showed that green tea treatment also reduced Ang II-induced increases in plasma hydroperoxides and aortic endothelial expression of hemeoxygenase I and superoxide dismutase, SOD. The increase in expression of hemeoxygenase I and superoxide dismutase is indicative of a decrease in vascular oxidative stress. It has also been found that 0.6% green tea extract as the sole source of drinking fluid reduced final systolic and diastolic blood pressure by 20% and 24%, respectively in Ang II-treated rats after 14 days (62).

Prevention of obesity-related fatty liver disease

The term nonalcoholic fatty liverdisease NAFLD is referred to a group of fatty liver diseases including hepatic steatosis and nonalcoholic steatohepatitis, NASH. This group of liver abnormality is often associated with obesity and show almost no other symptoms. It is clear that when hepatic fatty acid oxidation is low and there is a concomitant decrease in ATP levels, leads to an increase in one's appetite. Consumption of medium-chain fatty acids and 1,3-diacylglyceride oil ingredients that increase hepatic fatty acid oxidation, have been shown to reduce food intake in human subjects (63). The entire mechanisms leading to NASH is not well known, but at least two possible pathways have been proposed to describe the events contributing to the development NASH (64). The first one refered to as hepatic steatosis, is characterized by obesity and dysregulated lipid metabolism i.e. higher *de novo* lipogenesis (DNL) and adipose lipolysis leading to excess accumulation of hepatic lipid (65). Secondly, due to vulnerability of steatotic livers to oxidative stress, they may induce the progression of NASH (64). Furthermore, it triggers hepatic mitochondrial dysfunction and oxidative stress inducing serious injury to the liver (66). Up to now, there is no medical recommendation or treatment for NAFLD except the control of food intake in order to reduce weight (67). However, it is generally observed that weight loss has a poor long-term success

rate. Therefore, there is a serious need to reduce the development and progression of hepatic steatosis, oxidative stress, and inflammation in association with NAFLD (68). Epidemiological studies have suggested that consumption of green tea as a habitual drink could not only decrease mortality from cardiovascular disease (69), it may also provide reasonable protection against liver disorders (70). It is well known today that most of the health benefits of green tea are due to the action of its catechins. It has been shown that this group of compounds exhibit hypolipidemic (71) and antioxidant (11) properties that may ease multiple causes of NAFLD. Considering that green tea catechins (GTC) may increase hepatic fat oxidation, it could be postulated that GTC may also reduce the appetite and, therefore, cause a slight weight loss too.

Arthritis

Osteoarthritis (OA) and rheumatoid arthritis (RA) are a group of inflammatory diseases with a similar outcome, i.e. joint destruction. OA involves the erosion of articular cartilage, inflammation of synovial membrane, and resorption of the underlying sub-chondral bone (72). It has been demonstrated that extracts of green tea and its polyphenols can inhibit the inflammatory responses in different cell types *in vitro* and the development of arthritis *in vivo* (20). There are some evidences that (−)-epigallocatechin-3-gallate (EGCG), the predominant green tea polyphenol, inhibits enzyme activities and signal transduction pathways important in inflammation and joint destruction in arthritis (20). It can be explained that after oral consumption of EGCG become bioavailable. It may then interact directly with a set of protein targets and alter the physiological response of the cells leading to possible inhibition of arthritis. It has been shown that tea extract could also significantly inhibit acute inflammation observed following sodium urate administration, thus exhibiting possible anti gout activity (73). However, despite the large number of pharmacological studies on tea carried out worldwide, search of published articles reveal that there is still a need to investigate its anti-inflammatory activity. A number of factors including inflammation and oxidative stress are believed to play a role in the development of chronic joint diseases. Arthritis is a major inflammatory problem which has affected about 46 million people in the USA and is estimated that the number of people with arthritis rise to 67 million by 2030 (73). It is now well known that cycloxygenase (COX) and lipoxygenase (LO) enzymes are associated with the generation of the lipid mediators, which exert proinflammatory acitivity (74). Studies with different anti-inflammatory agents have revealed that over expression of such enzymes (75) increased levels of lipid mediators (76) and generation of damaging free radicals (77) could occur during the inflammatory process. It has been suggested that tea extract probably interfere with: (i) the expression of COX and/or LO; (ii) enzyme (COX/LO)-catalysed reactions; (iii) functioning of the mediators (probable occupation of the receptors); and (iv) generation of free radicals (78).

Conclusions

Tea is a common, pleasant, popular, economical and healthy drink that has rapidly found a commercial and industrial place as a potential and pharmaceutical plant material. Among all types of tea, the unfermented green form is now becoming very popular and accepted in all parts of the world. The benefits of green tea include very low caffeine content, mild nature and no adverse side effects. The incredible advantages of this ancient wonder have now been

discovered by many scientists. It is also strongly recommended as an advantageous drink by health specialists. In this review we presented a part of considerable data available, in an attempt to reveal the primary mechanism(s) of action, the dose-response relationships involved, and the best way to translate the results to human intervention studies. As mentioned here, various types of catechin in tea leaves play multi-targets and multi-functions with very low to non-toxic effects. This uniqueness makes it possible for tea catechin, as a new class of chemical chaperones, to induce preventive activity in various organs in humans. The action is mediated through the property of chemical chaperone leading to cancer preventation.

Studies have demonstrated that epigallocatechin gallate, the major catechin in green tea, can significantly induce apoptosis and cell cycle arrest in human carcinoma cells (79). Therefore, the protective effect of tea consumption on lung cancer is biologically plausible. Tea catechins can effectively scavenge relevant reactive oxygen and nitrogen species (49, 80).

Metabolic syndrome (MetS) and obesity are significant public health problems worldwide. Although effective surgical and pharmacological methods have been developed to treat symptoms related to metabolic syndrome, these treatments can be costly and are not without potential adverse effects (81, 82). A large number of valuable research works have demonstrate the efficacy of green tea as a preventive agent for MetS and have tried to understand the underlying mechanisms of its action. As discussed in this review, the green tea catechins appear to have activity against MetS, but caffeine may also play a role.

It has been estimated that about 5.5 million dollars of green tea based dietary supplements were marketed in 2008 (83). Although green tea beverage has a long history of safe use in the diet, a more limited number of controlled animal and human studies have been conducted to determine the maximum tolerated dose of green tea components given in alternative formulations such as pills and capsules. No large scale controlled human intervention studies have reported serious adverse effects to date, however a number of observational case reports, as well as laboratory studies have suggested that high doses of green tea polyphenols can cause hepatotoxicity (84). The therapeutic index of these agents must be established, not only when the compounds are delivered via the diet, but also when converted to formulations such as pills and capsules. Only with such a complete understanding can the potential benefits of green tea for the prevention of MetS be realized.

On the other hand, increased levels of systemic oxidative stress after smoking cigarette may play an important role in the induction of lung damage. Considering the high number of people smoking cigarette all through the world, dinking tea, especially green tea may have the ability to slow down the cigarette smoke-induced disease progression through prevention of airspace enlargement and goblet cell hyperplasia after suppression of oxidative stress.

In the case of hepatoprotective role of tea beverages, it should be noted that tea extracts can mitigate hepatic injury through inhibiting hepatic lipid accumulation and reducing oxidative damage and inflammation. The effects of tea extracts as a medication is dose-dependent and are likely mediated via alterations in adipose lipid metabolism and improvements in hepatic anti-inflammatory responses and antioxidant defenses.

Green tea is regarded as one of the most promising dietary agents for the prevention and treatment of many chronic diseases. EGCG is the predominant polyphenol in green tea and is regarded as the most active catechin of green tea. *In vitro* and *in vivo* studies have demonstrated that EGCG possesses potent antioxidant and anti-inflammatory activity. The anti-inflammatory effects of green tea may be mediated via different pathways associated

with adjunct inflammatory response. However, any single, several, or all the reported biological pathways may yield benefit to reduce the risk of inflammation in OA and RA (85-87). Pharmaceutical preparations of EGCG may deliver the in vivo dose equivalent to the concentration used in vitro and may be effective in suppressing inflammation and the catabolic response in arthritic joints. The use of green tea as a habitual drink may provide inhibiting disease progression in OA and RA.

In conclusion, tea is increasingly moving from a traditional beverage to a healthy drink, a source of pharmacologically active materials, an important member of the antioxidant food group, and a functional food endowed with beneficial health properties (88, 89). The number experimental evidence showing the properties of tea is still increasing. Numerous studies in a variety of experimental animal models have demonstrated that green tea consituents play antioxidant, antimutagenic, antidiabetic, anti-inflammatory, antibacterial and anticancer properties. Better understanding of the fundamental mechanism(s) of action of these molecules and their bioavailability is also needed in order to determine the potential tea as an anti-cancer agent. A fundamental understanding in this area is important for the design of future human intervention trials to reveal the relationship between tea consumption and cancer (90).

References

1. Terada S, Maeda Y, Masui T, Suzuki T, Ina K. Comparison of caffeine and catechin components in infusion of various green (green, oolong, and black tea) and tea drinks. Nippon Shokuhin Kogyo Gakkaishi 1987; 34(1): 20-27.
2. Yang CS, Sang S, Lambert JD, Hou Z, Ju J, Lu G. Possible mechanisms of the cancer-preventive activities of green tea. Molecular Nutrition and Food Research (2006); 50(2):170-175.
3. Wang LF, Kim DM, Chang LY. Effects of heat processing and storage on flavanols and sensory qualities of green tea beverage. Journal of Agriculture and Food Chemistry 2000; 48: 4227-4232.
4. Chen AP, Schell JB, HO CT, Chen KY. Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett. 1998; 129:173-179.
5. Gale Encyclopedia of Alternative Medicine, Volume 4"; Jacqueline L. Longe; 2005.
6. http://www.associatedcontent.com/article/94032/health_benefits_of_tea_tree_oil.html
7. http://aromatherapy4u.wordpress.com/2006/09/18/the-healing-properties-of-tea-tree-essential-oil.
8. Chung K, Wei C, Johnson MC. Are tannins a double-edged sword in biology and health? Food Science and Technology 1998; 9: 168-175.
9. Conney AH, Wang ZY, Ho C, Yan CS, Huang M. Inhibitory effect of green tea on tumorigenesis and tumor growth in mouse skin. In: Phenolic compounds in food and their effects on health II 1992.
10. Zhu GY. Stability of green tea catechins. Journal of Agriculture and Food Chemistry 1997; 45: 4624-4628.
11. Miura Y, Chiba T, Tomita I. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. Journal of Nutrition 2001; 131:27-32.

12. Min S, Jin ZT, Min SK, Yeom H, Zhang, QH. Commercial-scale pulsed electric field processing of orange juice. Journal of Food Science 2003; 68:1265-1271.
13. Serafini M, Laranjinha João AN, Leonor M, Almeida J, Maiani G. Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. The Journal of Nutritional Biochemistry 2000; 11(11-12):585-590.
14. Sakanaka S, TachibanaY, Okada Y. Preparation and antioxidant properties of extracts of Japanese persimmon leaf tea (kakinoha-cha). Food Chemistry 2005; 89:569-575.
15. Frei B, Higdon JV. Antioxidant activity of tea polyphenols in vivo: Evidence from animal studies. Journal of Nutrition 2003; 133(10): 3275S-3284S.
16. Almajano MP, Carbó R, Jiménez JAL, Gordon MH. Antioxidant and antimicrobial activities of tea infusions. Food Chemistry 2008; 108:55-63.
17. Liebert M, Licht U, Böhm V, Bitsch R. Antioxidant properties and total phenolics content of green and black tea under different brewing conditions. Zeitschrift für Lebensmitteluntersuchung und -Forschung A 1999; 208: 217-220.
18. Pripdeevech P, Machan T. Fingerprint of volatile flavour constituents and antioxidant activities of teas from Thailand, Food Chemistry 2011; 125(2):797-802.
19. Aruoma OI. Free radicals, oxidative stress, and antioxidants in human health and disease. Journal of the American Oil Chemists' Society 1998; 75(2):199-212.
20. Hamilton CA, Miller WH, Al-Benna S, Brosnan MJ, Drummond RD, McBride MW et al. Strategies to reduce oxidative stress in cardiovascular disease. Clinical Science 2004; 106(3):219-234.
21. Farhoosh R, Golmovahhed GA, Khodaparast MHH. Antioxidant activity of various extracts of old tea leaves and black tea wastes (*Camellia sinensis L.*). Food Chemistry 2007; 100(1):231-236.
22. Katiyar S, Elmets CA, Katiyar SK. Green tea and skin cancer: Photoimmunology, angiogenesis and DNA repair. Journal of Nutritional Biochemistry 2007; 18(5):287-296.
23. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A. The relationship between green tea and total Caffeine Intake and risk for self-reported type 2 diabetes among Japanese adults. Annals of Internal Medicine 2006; 144:554-562.
24. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. Am J Epidemiol 2001; 154:495-503.
25. Kuriyama S. The relation between green tea consumption and cardiovascular disease as evidenced by epidemiological studies. J Nutr 2008; 138:1548S-1553S.
26. Arab L, Liu W, Elashoff D. Green and black tea consumption and risk of stroke: a meta-analysis. Stroke 2009; 40:1786-1792.
27. Debette D, Courbon N, Leone J, Gariepy C, Tzourio JF Dartigues P, Barberger-Gateau K, Ritchie A, Alperovitch P, Amouyel P, Ducimetiere M. Tea consumption is inversely associated with carotid plaques in women. Arterioscler Thromb Vasc Biol 2008; 28:353-359.
28. Mursu J, Nurmi T, Tuomainen TP, Ruusunen A, Salonen JT, Voutilainen S. The intake of flavonoids and carotid atherosclerosis: the Kuopio ischaemic heart disease risk factor study Br J Nutr 2007; 28:814-818.
29. Hodgson JM, Devine A, Puddey IB, Beilby J, Prince RL. Drinking tea is associated with lower plasma total homocysteine in older women. Asia Pacific J Clin Nutr 2006; 15:253-258.

30. Holt RR, Actis-Goretta L, Momma TY, Keen CL. Dietary flavanols and platelet reactivity. J Cardiovasc Pharmacol 2006; 47:S187-S196.
31. Lee W, Min WK, Chun S, Lee YW, Park H, Lee DH, Lee YK, Son JE. Long-term effects of green tea ingestion on atherosclerotic biological markers in smokers. Clin. Biochem. 2005; 38:84-87.
32. Chen ZY. Stabilizing effect of ascorbic acid on green tea catechins, Journal of Agriculture and Food Chemistry 1998; 46: 2512-2516.
33. Liang YC, LinShiau SY, Chen CF, Lin JK. Inhibition of cyclin-dependent kinases 2 and 4 activities as well as induction of cdk inhibitors p21 and p27 during growth arrest of human breast carcinoma cells by (−)-epigallocatechin-3-gallate. J Cell Biochem 1999; 75:1-12.
34. Fujiki H. Two stages of cancer prevention with greentea. J Cancer Res Clin Oncol 1999; 125:589-597.
35. Jung YD Ellis LM. Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. Int J Exp Pathol 2001; 82(6):309-316.
36. Ahmad N, Gupta S, Mukhtar H. Green tea polyphenol epigallocatechin-3-gallate differentially modulates nuclear factor kappa B in cancer cells versus normal cells. Arch. Biochem. Biophys. 2000; 376: 338-346.
37. Berger SJ, Gupta S, Belfi CA, Gosky DM, Mukhtar H. Green tea constituent (−)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells. Biochem Biophys Res Commun 2001; 228:101-105.
38. Naasani I, Seimiya H, Tsuruo T. Telomerase inhibition, telomerase shortening, and senescence of cancer cells by tea catechins. Biochem Biophys Res Commun 1988; 249:391-396.
39. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. 2002, CA Cancer J Clin. 2005; 55:74-108.
40. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T et al., Cancer statistics 2008 CA Cancer J Clin 2008; 58:71-96.
41. Muto S, Fujita KI, Yamazaki Y, Kamataki T. Inhibition by green tea catechins of metabolic activation of procarcinogens by human cytochrome P450. Mutat Res 2001; 479:197-206.
42. Raso GM, Mcli R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.I. Life Sci 2001; 68:921-931.
43. Tachibana H, Koga K, Fujimura Y, Yamada K. A receptor for green tea polyphenol EGCG. Nat. Struct Mol Bio 2004: 1-2.
44. Kim MH, Jung MA, Hwang YS, Jeong M, Kim SM, Ahn SJ, Shin BA, Bong WA Jung YD. Regulation of urokinase plasminogen activator by epigallocatechin-3-gallate in human fibrosarcoma cells. Eur J Pharmacol 2004; 487:1-6.
45. Jankun J, Selman SH, Swiercz R, Skrzypczak-Jankun E. Why drinking green tea could prevent cancer. Nature 1997; 387:561-568. 47. Huerta C, Lanes SF, García Rodríguez LA. Respiratory medications and the risk of cardiac arrhythmias. Epidemiology 2005; 16(3):360-366.
46. Sazuka M, Imazawa H, Shoji Y, Mita T, Hara Y Isemura M. Inhibition of collagenases from mouse lung carcinoma cells by green tea catechins and black tea theaflavins. Biosci Biotechnol Biochem 1997; 61:1514-1516.

47. Cooper R, Morré DJ, Morré DM. Medicinal benefits of green tea: Part I. Review of non-cancer health benefits. J Altern Complement Med 2005:; 11:521–528.
48. Nakagawa K, Okuda S, Miyazawa T. Dose-dependent incorporation of tea catechins (−)-epigallocatechin-3-gallate and (−)-epigallocatechin, into human plasma Biosci Biotechnol Biochem 1997; 61:1981-1985.
49. Yang CS, Wang ZY. Tea and cancer. J Natl Cancer Inst. 1993; 85:1038-1049.
50. Rains TM, Agarwal S, Maki. Kevin C. Antiobesity effects of green tea catechins: a mechanistic review. The Journal of Nutritional Biochemistry 2011; 22(1):1-7.
51. Matsui T, Yoshimoto C, Osajima K, Oki T, Osajima Y. In vitro survey of alpha-glucosidase inhibitory food components. Biosci Biotechnol Biochem 1996; 60:2019-2022.
52. Johnston K, Sharp P, Clifford M, Morgan L. Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. FEBS Lett 2005; 579:1653-1657.
53. Park JH, Jin JY, Baek WK, Park SH, Sung HY, Kim YK et al.. Ambivalent role of gallated catechins in glucose tolerance in humans: a novel insight into non-absorbable gallated catechin-derived inhibitors of glucose absorption. J Phyisiol Pharmacol 2009; 60:101-109.
54. Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. An N Y Acad Sci 2006; 1083:129-152.
55. Nagao T, Meguro S, Hase T, Otsuka K, Komikado M, Tokimitsu I et al. A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes, Obesity (Silver Spring) 2009; 17:310-317.
56. Fonseca V, Inzucchi SE, Ferrannini E. Redefining the diagnosis of diabetes using glycated hemoglobin. Diabetes Care 2009; 32:1344-1345.
57. Eckel RH, Grundy SM,. Zimmet PZ. The metabolic syndrome. Lancet 2005; 356:1415-1428.
58. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008; 88:1254-1264.
59. Sherwood L. Human physiology: from cells to systems (3rd ed.) Wadsworth Publishing Co. Belmont CA 1997; 753.
60. Ferroni P, Basili S, Paoletti V, Davi G. Endothelial dysfunction and oxidative stress in arterial hypertension. Nutr Metab Cardiovasc Dis 2006; 16:222-233.
61. Antonello M, Montemurro D, Bolognesi M, Di Pascoli M, Piva A, Grego F, et al., Prevention of hypertension, cardiovascular damage and endothelial dysfunction with green tea extracts. Am J Hypertens 2007; 20:1321-1328.
62. Papparella I, Ceolotto G, Montemurro D, Antonello M, Garbisa S, Rossi G, et al. Green tea attenuates angiotensin II-induced cardiac hypertrophy in rats by modulating reactive oxygen species production and the src/epidermal growth factor receptor/akt signaling pathway. J Nutr 2008; 138:1596-1601.
63. Kamphuis MMJW, Mela JD, Westerterp-Plantenga MS. Diacylglycerols affect substrate oxidation and appetite in humans. Am J Clin Nutr 2003; 77:1133-1139.
64. Day CP. Pathogenesis of steatohepatitis. Best Pract Res Clin Gastroenterol 2002; 16:663-678.

65. Postic C, Girard J. The role of the lipogenic pathway in the development of hepatic steatosis. Diabetes Metab 2008; 34:643-648.
66. Carter-Kent C, Zein NN, Feldstein AE. Cytokines in the pathogenesis of fatty liver and disease progression to steatohepatitis: implications for treatment. Am J Gastroenterol 2008; 103:1036-1042.
67. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 364:1221-1231.
68. Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 2000; 1:113-119.
69. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al.. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006; 296:1255-1265.
70. Imai K, Nakachi K. Cross sectional study of effects of drinking green tea on cardiovascular and liver disease BMJ 1995; 310:693-696.
71. Arden N Nevitt MC. Osteoarthritis: Epidemiology. Best Practice & Research: Clinical Rheumatology 2006; 20(1):3-25.
72. Babu PV, Liu D. Green tea catechins and cardiovascular health: an update. Curr Med Chem 2008; 15:1840-1850.
73. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis & Rheumatism 2007; 58(1): 15-25.
74. Seihut K, Zang Y, Leahy K. Pharmacological and biochemical demonstration of the role of cycloxygenase-2 in inflammation and pain. Proc Natl Acad Sci USA 1994; 91:12013-12017.
75. Amit SK Zhiyang Z. Discovery and design of selective cycloxygenase-2 inhibitors as non-ulcerogenic, antiinflammatory drugs with potential activity as anticancer agents. Curr Drug Targets 2001; 2:79-106.
76. Sen T, Ghosh TK, Bhattacharjee S, Nag Chaudhuri AK. Action of Pluchea indica methanolic extract as a dual inhibitor on PAF-induced paw oedema and gastric damage. Phytother Res 1996; 10:74-76.
77. Sen T, Dhara AK, Bhattachacharjee S, Pal S, Nag Chaudhuri AK. Antioxidant activity of the methanolic fraction of Pluchea indica-root extract. Phytother. Res. 2002; 16:331-335.
78. Chaudhuri N, Karmakar S, Roy D, Pal S, Pal M, Sen T. Anti-inflammatory activity of Indian black tea (Sikkim variety) Pharmacological Research 2005; 51(2): 169-175.
79. Moskovitz J, Yim MB, Chock PB. Free radicals and disease, Archives of Biochemistry and Biophysics 2002; 397(2):354-359.
80. Nakagawa T, Yokozawa T. Direct scavenging of nitric oxide and superoxide by green tea. Food Chem Toxicol 2002; 40:1745-1750.

81. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley Cm Worrall C. et al., Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304:411-418.

82. Pories WJ. Bariatric surgery: risks and rewards. J Clin Endocrinol Metab 2008; 93:S89-S96.
83. Cavaliere C, Rea P, Lynch ME, Blumenthal M. Herbal supplement sales experience slight increase in 2008. HerbalGram 2009; 82:58-61.

84. Lambert JD, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (−)-epigallocatechin-3-gallate in mice. Food Chem Toxicol 2010; 48:409-416.
85. Singh R Akhtar N and Haqqi TM. Green tea polyphenol epigallocatechi3-gallate: Inflammation and arthritis. Life Sciences 2010; 86(25-26):907-918.
86. Lee DM and Weinblatt ME. Rheumatoid arthritis. Lancet 2001; 358:903-911.
87. vander-Kraan WB vanden-Berg PM. Anabolic and destructive mediators in osteoarthritis. Current Opinion in Clinical Nutrition & Metabolic Care 2000; 3(3):205-211.
88. Cooper R, Morré DJ, Morré DM. Medicinal benefits of green tea: Part I. Review of non-cancer health benefits. J Altern Complement Med 2005:; 11:521–528.
89. Vasisht K, Sharma PD, Karan M, Rakesh D, Vyas S, Sethi S, et al. Study to promote the Industrial Exploitation of Green Tea Polyphenols in India. ICS-UNIDO Italy 2003;15-22.
90. Park HK, Han DW, Park YH, Park JC. Differential biological responses of green tea polyphenol in normal cells vs. cancer cells. Current Applied Physics 2005; 5(5):449-452.

List of abbreviations

COX	Cycloxygenase
DNL	D*e novo* lipogenesis
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
GTC	Green tea catechins
HDL	High density lipoprotein
LDL	Low density lipoprotein
LO	Lipoxygenase
MetS	Metabolic syndrome
NAFLD	Nonalcoholic fatty liverdisease
NASH	Nonalcoholic steatohepatitis
SNS	Sympathetic nervous system
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TPs	Tea polyphenols