

Probable benefits of green tea with genetic implications

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Abstract

Tea is produced from the *Camellia sinensis* plant and can generally be divided into categories based on how they are processed. In general, green tea that is unfermented *C. sinensis* has been considered superior to black tea in health benefits. It contains a unique set of catechins that possess biological activity as antioxidant, anti-inflammatory and antiproliferative, which is potentially significant to the prevention and treatment of various forms of diseases. Oral cavity oxidative stress and inflammation, consequent cigarettes due to nicotine and acrolein, may be reduced in the presence of green tea polyphenols. In addition, green tea polyphenols can close down halitosis through modification of odorant sulfur components. Usually, green tea defends healthy cells from malignant transformation and locally has the ability to induce apoptosis in oral cancer cells. In unison, there is an increasing implication in the health benefits of green tea in the field of oral health. This review will cover recent findings on the therapeutic properties and anticancer health benefits of green tea.

Keywords: Antioxidants, *Camellia sinensis*, cancer, tea

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INTRODUCTION

Tea is made from the leaves of *Camellia sinensis* and is one of the most widely consumed beverages in the world.^[1] The tea plant is believed to have originated in the landmass encompassing Tibet, Western China and Northern India. Drinking the beverage tea has been considered a health-promoting habit since ancient times. The modern medicinal research is providing a scientific basis for this belief. The evidence supporting the health benefits of tea drinking grows stronger with each new study that is published in the scientific literature. In the last couple of years, green tea has gained popularity in the Western countries due to scientific findings that show the health potentials of the beverage. *C. sinensis* is a plant which yields a variety of tea

which can be categorized into four types, depending on the level of fermentation.^[2-4] The preparation of four different types of tea is illustrated in Figure 1.^[5,6]

1. Green tea (unfermented) - It is prepared in such a way to preclude the oxidation of green leaf polyphenols
2. Black tea (fermented) or red tea (Pu-Erh) - During its production, oxidation is promoted so that most of these substance are oxidized
3. Oolong (partially fermented) - It is partially oxidized
4. White tea - it is made from new growth buds and young leaves that have been steamed to inactivate polyphenol oxidation and then dried.

The 78% of the tea consumed worldwide is black, only about 20% is green and <2% is oolong tea.^[7] Usually, black

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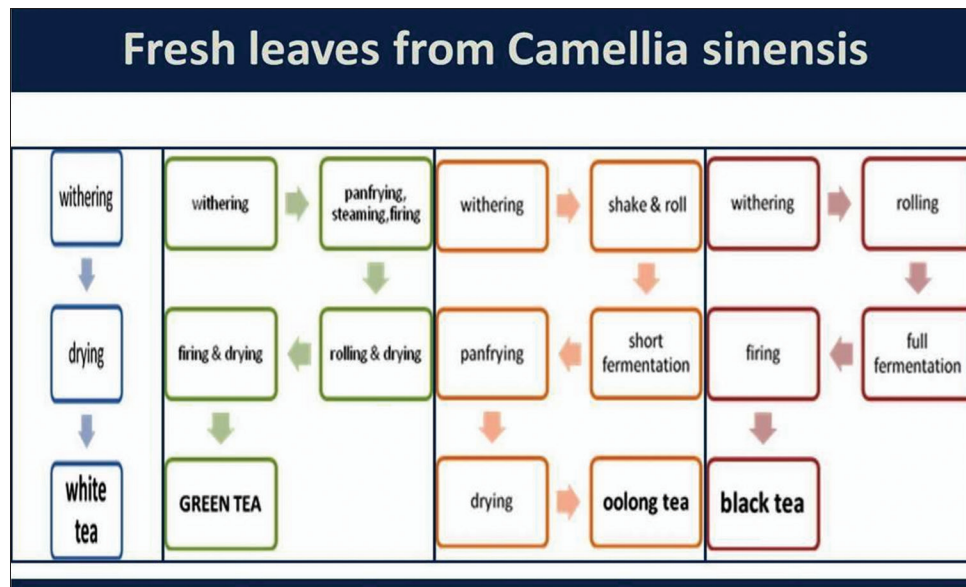


Figure 1: Processing of tea

tea is consumed in the United States, oolong tea is most popular in China and Taiwan and green tea is most popular in China, Japan and Korea.^[6] Among the health benefits that have been studied using green tea are as an antioxidant, anti-inflammatory, anticarcinogenic, in cardiovascular health, oral health and as an antimicrobial. This article provides a critical review of oral benefits of green tea, discusses the possible common mechanisms involved and evaluates the human relevance of the published health effects.

Chemical composition of green tea

Green tea is a complex mixture of precious compounds including polyphenols, flavonoids, flavonols and other constituents such as amino acids, organic acids, lipids, vitamins, polysaccharides and thiamine [Table 1]. The major components of green tea are the polyphenols, and the major polyphenols (called catechins) are flavonoids.^[8] Green tea also contains garlic acid, quercetin, kaempferol, myricetin and chlorogenic acid along with some amount of caffeine although half of that found in coffee [Table 2].^[9-11] One cup of green tea usually contains about 300–400 mg of polyphenols and between 50 and 100 mg of caffeine. Green tea commercially is available as bottled and sweetened with sugar or an artificial sweetener, in single tea bags, loose-leaf and in instant-powder. Green tea supplements are sold in capsule form or liquid extracts.

Mechanism of action

Green tea is rich in polyphenolic compounds, with catechins as its major component. Studies have shown that catechins possess diverse pharmacological properties that include antioxidative, anti-inflammatory, anticarcinogenic,

Table 1: Constituents of green tea with percentage of catechin in green tea

Compounds	Percentage of dry weight
Polyphenols (%)	37
EC (6.4)	
EGC (19)	
ECG (13.6)	
EGCG (59)	
Protein	15-20
Amino acids	1-4
Fiber	26
Carbohydrate	7
Lipids	7
Lignin	6.5
Pigments	2
Minerals	5
Oxidized phenolic compound	0
Caffeine	3.5
Chlorophyll	0.5
Ash	5

EC: Catechin epicatechin, EGC: Epigallocatechin, ECG: Epicatechin gallate, EGCG: Epigallocatechin gallate

Table 2: The average amount of caffeine found in coffee and tea

Products	Caffeine (mg/serving)
Tea	
Green (different variety)	20-45 mg/8 oz serving ^[12]
Black tea	47 mg/8 oz serving ^[13]
Green, black, oolong	50 mg/190 ml serving ^[14]
Coffee	
Instant	75 mg/190 ml serving ^[14]
Brewed (filtered or percolated)	100-115 mg/190 ml serving ^[14]

antiarteriosclerotic and antibacterial effects. The primary pharmacologic action center around the antioxidant effects of green tea is polyphenols. Green tea inhibits reactive oxygen species (ROS) in the body which restrict the damage of DNA, RNA, oxidize protein, oxidize lipids and activation of cell suicide. Intake of green tea can stop

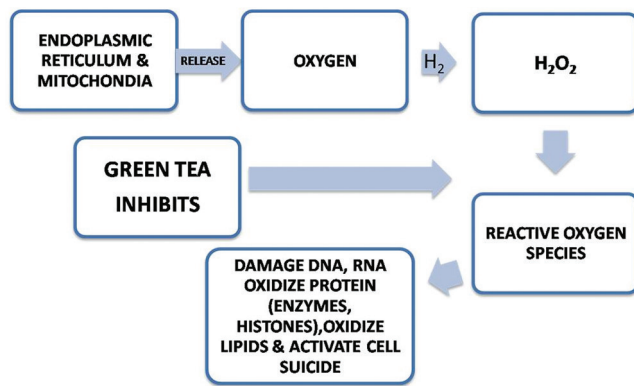


Figure 2: Mechanism of action of green tea

all these degenerative changes by inhibiting the action of the ROS molecule [Figure 2].

Therapeutic application

The health benefits of green tea (*C. sinensis*) catechins are becoming increasingly recognized day by day. In ancient times, green tea has been considered by the traditional Chinese medicine as a healthful beverage. Recent human studies suggest that green tea may contribute to maintenance of endothelial function and vascular homeostasis and an associated reduction in atherogenesis and cardiovascular disease risk reduction and some forms of cancer^[12] as well as to the promotion of oral health and other physiological functions such as antihypertensive effect, solar ultraviolet protection, bone mineral density, antifibrotic properties, antioxidative,^[13] antibacterial^[14] and antiviral activity^[15] and neuroprotective power.^[16] Other uses are listed in Table 3.^[17-35] 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. In the gastrointestinal tract, green tea was found to activate intracellular antioxidants, inhibit procarcinogen formation, suppress angiogenesis and cancer cell proliferation. Studies on the preventive effect of green tea in esophageal cancer have produced inconsistent results; however, inverse relationships of tea consumption with cancers of the stomach and colon have been widely reported.^[24]

Green tea and oral health

Prevention of dental caries and plaque

Oral pathologies such as dental caries, periodontal diseases and teeth loss can greatly influence human health. Among those, dental caries is caused as a result of infectious diseases caused by numerous reasons related to nutrition and bacterial infections. Green tea protects against bacterial induced dental caries and plaque scores. It controls bacteria

Table 3: Various uses of green tea

Role
Weight loss ^[17]
Antiaging ^[18]
Immunity ^[19]
Liver disease ^[20,21]
Cardiovascular disease ^[12,22]
Cancer ^[12,23,24]
Arthritis ^[25,26]
Diabetes ^[27]
Alzheimer's ^[28]
Parkinson's ^[29]
Cold N Flu ^[30]
Asthma ^[31]
Stress ^[32]
Food poisoning ^[18]
HIV ^[18]
Control blood cholesterol level ^[33]
Anti-inflammatory ^[34]
Antiarthritic ^[26]
Genital warts ^[35]

and lowers the acidity of saliva and dental plaque, which is nowadays considered to be useful tool in preventing cavities.^[24,36-38] In recent researches, it has been shown that green tea prevents gathering of bacteria and therefore results in the formation of plaques on teeth which leads to decreasing construction of human amylase excretion, preventing glucosyltransferase and finally limiting glucan biosynthesis which gets stuck on teeth. In addition, it was specified that the routine consumption of green tea in human studies could reduce the intensity of teeth caries.^[39-42] Many researchers showed that tea extract reduced α -amylase activity in human saliva. Therefore, tea consumption is likely to be an anticariogenic agent which lessens the cariogenic potential of starch-containing foods such as crackers and cakes.

Prevent halitosis

Bad breath, i.e., halitosis is basically due to volatile sulfide compounds, especially hydrogen sulfide, methyl mercaptan and dimethyl sulfide which are formed due to the proteolytic breakdown of various sulfur-containing substrates by anaerobic Gram-negative oral pathogens. Oral microorganisms degrade proteinaceous substrates to cysteine and methionine, which are then converted to volatile sulfide compounds. Green tea polyphenols, catechins, especially EGCG deodorizes methyl mercaptan can abolish halitosis through modification of odorant sulfur components.^[43,44] Epigallocatechin gallate (EGCG) (active at 250–500 $\mu\text{g/ml}$) inhibited growth and adhesion of *Porphyromonas gingivalis* to buccal epithelial cells. Catechins are found to be inhibitory against *Streptococcus mutans* and *Streptococcus sobrinus* at minimum inhibitory concentration (MIC) ranging between 50-1000 $\mu\text{g/ml}$.^[45]

Protection from oral oxidative stress and cigarette smoke-induced inflammation

Cigarette smoking contains more than 4000 identified chemical compounds including sixty known carcinogens.^[46] Cigarette smoke encompasses and creates various ROS and reactive nitrogen species, such as superoxide radical, hydrogen peroxide, hydroxyl radical and peroxyxynitrite.^[47] Highly reactive radicals can damage the cell membrane and also induce DNA fragmentation, tissues damage and alter the cellular antioxidant defense system.^[48,49] Cigarette smoke destroys oral cavity homeostasis. It decreases salivary antioxidant status, initiates oral inflammatory diseases and promotes oral malignancies.^[16] Oral cavity oxidative stress and inflammation, consequent to cigarette smoking and cigarettes' deleterious compounds nicotine and acrolein, may be reduced in the presence of green tea polyphenols.^[50] The protective role of green tea against cigarette smoke-induced oxidative stress may be explained by the large amounts of catechins, including EGCG that accounts for more than 80% of all active ingredients in green tea and has been shown to have the greatest antioxidant activity among several compounds. The content of EGCG in green tea is 10-fold higher than that in black tea. Unlike black tea, green tea also contains ascorbic acid. These results suggest that green tea may act as a potent antioxidant.^[51] The natural production of polyphenols, the tea plant converts theanine into catechins. This means that tea leaves harvested during one part of the growing season may be high catechins (good for antioxidant benefits) while leaves harvested during another time of year may be higher in theanine. L-theanine has been linked to the feelings of relaxation reported by those who drink green tea. Green tea shows calming and curative properties due to the presence of L-theanine; an amino acid found primarily in green and black teas that produce tranquilizing effects in the brain. Experimental studies have also shown that L-theanine appears to negate some of the effects of caffeine, and theanine in green tea may play a role in reducing stress.^[52]

Fluorosis

Intakes of high amounts (≥ 51 /week) of certain tea may result in excess risks of dental or skeletal fluorosis. In general, the level of fluoride in tea is inversely related to the EGCG contents.^[53] The tea plant takes up fluoride from the soil and accumulates it in its leaves where it becomes a major source of fluoride.^[54] In countries where regular tea consumption is culturally determined, tea plays an important role in triggering fluoride undesirable effects on tooth formation. In some Chinese villages, where dental fluorosis is endemic, fluoride intake from tea has been strongly correlated to this condition.^[55,56] However, fluoride intake from these beverages is so high that daily

consumption of one unit exceeds the upper limit in terms of risk to esthetically acceptable dental fluorosis.^[57]

Pulpitis

The antimicrobial activity is due to inhibition of bacterial enzyme gyrase by binding to ATP B subunit.^[58] Green tea exhibits antibacterial activity on *E-faecalis* planktonic cells. It is also found to be a good chelating agent. Green tea catechins may prevent the exacerbation of pulpitis.^[8,59] Catechins (bioactive polyphenols in green tea) are known to exhibit potent anti-inflammatory properties. However, the anti-inflammatory effects of catechins on inflamed dental pulp tissue are not known. The presence of EGCG and electrocardiogram (ECG) significantly reduced, in a concentration-dependent manner, the expression of interleukin (IL)-6 and IL-8 in dental pulp cells exposed to lipopolysaccharide (LPS) or peptidoglycan (PG). Increased expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on the dental pulp cells in response to bacterial components was also decreased by treatment with EGCG and ECG. These findings suggest that green tea catechins may prevent the exacerbation of pulpitis.^[60]

Potentially oral malignant lesions

Li et al.^[61] in 1999 concluded oral and topical administration of a tea preparation significantly reduced the size of oral lesions and the incidence of micronucleated oral mucosa cells in leukoplakia, and Chow and Hakim^[62] in 2011 showed significant decrease in the number and total volume of the silver-stained nucleolar organizer regions, and the proliferation cell nuclear antigen in oral mucosa of the treated group compared to the control group.

Periodontium

The antioxidant, antimicrobial, anticollagenase, antimutagenic and chemopreventive properties of these catechins proved to be helpful in the treatment of chronic diseases such as periodontal disease [Table 4].^[11,27,59-63] Studies have shown that daily intake of green tea was

Table 4: Role of catechin in periodontal tissue

Polyphenol	Action	Oral microflora
Catechin	Inhibits	Growth of <i>P. gingivalis</i> , <i>P. intermedia</i> and <i>P. nigrescens</i> and adherence of <i>P. gingivalis</i> on buccal epithelial cells ^[59]
Catechin	Inhibits	Production of toxic end metabolites of <i>P. gingivalis</i> ^[60]
Catechin	Bactericidal	Against black-pigmented, Gram-negative anaerobic rods, <i>P. gingivalis</i> and <i>Prevotella</i> species ^[61]
EGCG	Inhibits	Osteoclasts formation thus prevent bone resorption ^[13]

P. gingivalis: *Porphyromonas gingivalis*, EGCG: Epigallocatechin gallate, *P. nigrescens*: *Prevotella nigrescens*, *P. intermedia*: *Prevotella intermedia*

Table 5: Effect of green tea on periodontium

Authors	Year	Results
Makimura <i>et al.</i> ^[67]	1993	Inhibits collagenous activity
Kaneko <i>et al.</i> ^[68]	1993	Reduce halitosis associated with periodontal disease
Yasuda and Arakawa ^[44]	1995	Reduce halitosis by deodorizing methyl mercaptan
Sakanaka <i>et al.</i> ^[63]	1996	Inhibition of growth and adherence of <i>P. gingivalis</i> to epithelial cells
Hirasawa <i>et al.</i> ^[65]	2002	Reduction of marker of gingivitis by the use of slow-release devices Bactericidal activity of green tea catechins against <i>P. gingivalis</i> and <i>Prevotella</i>
Okamoto <i>et al.</i> ^[69] and Sakanaka and Okada ^[64]	2004	Neutralize etiological agents such as gingipains, protein tyrosine phosphate
Yun <i>et al.</i> ^[70]	2004	Inhibits bone resorption by preventing the expression of MMP-9 from osteoblasts induced by <i>P. gingivalis</i> extracts
Nakamura <i>et al.</i> ^[71]	2009	Inhibition of bone resorption by inducing apoptotic cell death of osteoclasts through caspase Inhibition of nuclear translocation of NF-kappa beta activated by lipopolysaccharide Inhibits IL-1 β production, directly inhibits osteoclastogenesis, inhibit oncostatin M Induce CXCL-10 production in human fibroblasts Inhibits IL-17A, induce CCL-20 production, in human gingival fibroblasts

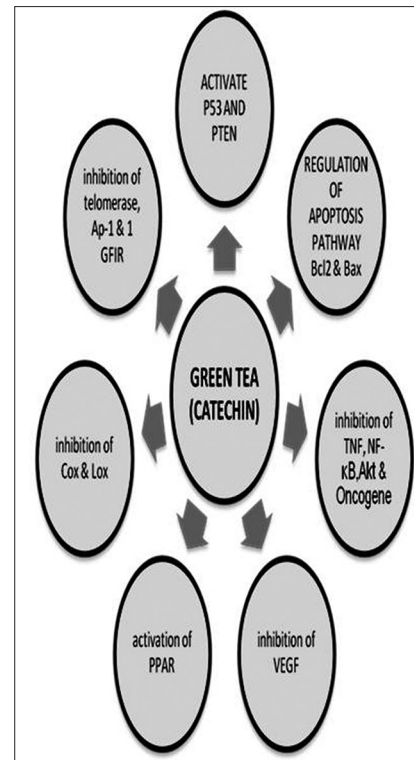
MMP: Matrix metalloproteinases, NF: Nuclear factor, IL: Interleukin, *P. gingivalis*: *Porphyromonas gingivalis*, CXCL: Cxc chemokine ligand, CCL: Chemokine ligand

significantly associated with probing depth (PD), bleeding on probing (BOP) and clinical attachment loss (CAL), such that the more frequently person drank green tea, better was their periodontal condition and concluded that the intake of green tea was inversely correlated with the mean PD, mean CAL and BOP [Table 5].^[44,63-70]

Oral cancer chemoprevention

The cancer promotion stage is a reversible and a long-term process, in which some intracellular signaling pathways and proteins associated with cell cycle are involved. Oncogene mutation and ROS play important roles in the initiation of cancer. Oncogene mutation leads to procarcinogen activation by activating some phase I enzymes such as the cytochrome P450s. ROS actively participate in the metabolic activation of procarcinogens. EGCG can neutralize these procarcinogens by inhibiting the activity of cytochrome P450 enzymes and modulating ROS. EGCG exerts its anticancer effect by interfering with many signaling pathways and modulating cell cycle [Figure 3].^[72]

Polyphenols may inhibit carcinogenesis in the stage of initiation, promotion or progression. In particular, dietary

**Figure 3:** Signaling pathway in cancer modulated by green tea

polyphenols decrease incidence of carcinomas and exert protection against oral cancer by induction of cell death and inhibition of tumor growth, invasion and metastasis.

The consumption of green tea is associated with a lower risk of several types of cancer, including stomach, esophagus and lung. The cancer chemopreventive effect of tea has been attributed to its major phytopolyphenols. The tea polyphenols comprise about one-third of the weight of the dried leaf, and they show profound biochemical and pharmacological activities including antioxidant activities, inhibition of cell proliferation, modulation of carcinogen metabolism, induction of cell apoptosis and cell cycle arrest. They intervene in the biochemical and molecular processes of multistep carcinogenesis. Recently, studies have found that the major tea polyphenol EGCG suppresses extracellular signals and cell proliferation through epidermal growth factor receptor (EGFR) binding in human A431 epidermoid carcinoma cells; EGCG also blocks the induction of nitric oxide synthase by downregulating lipopolysaccharide-induced activity of the transcription factor nuclear factor-kB (NF-kB) in macrophages. Furthermore, EGCG blocks the cell cycle at the G1 phase in MCF-7 cells. Lin JK in 1999 studied the EGCG inhibits the activities of cyclin-dependent kinases (cdks) 2 and 4; meanwhile, EGCG induces the expression of the Cdk inhibitors p21 and p27 and concluded that the tumor promotion can be enhanced

by ROS and oxidative mitotic signal transduction, and this enhancement can be suppressed by EGCG or other tea polyphenols.^[73] Ho HC in 2007 concluded that EGCG could inhibit the invasion and migration of human oral cancer cells and that the effects may partially be because of the decreased productions of matrix metalloproteinase-2 (MMP-2), MMP-9 and urokinase-type plasminogen activator (uPA).^[74] EGCG suppressed androgen receptor expression and signaling through several growth factor receptors. Cell cycle arrest or apoptosis involved caspase activation and altered Bcl-2 family member expression. EGCG inhibited telomerase activity and led to telomere fragmentation. At high concentrations, polyphenols had pro-oxidative activities, and at much lower levels, antioxidative effects occurred. EGCG reduces nitric oxide production and black tea theaflavins by suppressing inducible nitric oxide synthase through blocking nuclear translocation of the transcription factor NF- κ B as a result of decreased kappa B kinase activity. Polyphenols up- or downregulated activity of a number of key enzymes, including mitogen-activated protein kinases and protein kinase C and increased or decreased protein/mRNA levels, including that of cyclins, oncogenes and tumor suppressor genes. Metastasis was inhibited through effects on urokinase and MMPs. Polyphenols reduced angiogenesis, in part by decreasing vascular endothelial growth factor (VEGF) production and receptor phosphorylation.^[75]

Specifically, EGCG regulates expression of VEGF, insulin-like growth factor 1, EGFR, MMPs, uPA cell cycle regulatory proteins and inhibits NF- κ B, PI3-K/Akt, Ras/Raf/MAPK and AP-1 signaling pathways, thereby causing strong cancer chemopreventive effects.^[76] EGCG appears to have an immunosuppressive effect on the proliferation of peripheral blood mononuclear cells, indicating that EGCG also acts for immunomodulatory effects in autoimmune diseases and tissue transplantation.^[18]

SIDE EFFECTS

The risks associated with a high dose of green tea are:

- Drinking a large amount may cause neural tube birth defect in infants due to folic acid antagonism because of the presence of caffeine, catechins and tannic acids in green tea
- Drinking tea or coffee stains or discolors the dental plaque but not the teeth itself
- Increased bleeding time
- Increased risk of bladder cancer^[8]
- Stain esthetic restorative material in oral cavity
- Insomnia, anxiety, irritability, nausea and headaches
- Stomach upset and diuresis
- Heart irregularities, tremor and restlessness.

PRECAUTIONS

Patients such as pregnant or breast-feeding women, those with heart problems or increase blood pressure, stomach ulcers, kidney or liver problems or anxiety disorders, thyroid hyperfunction, elevated susceptibility to spasm and certain psychic disorders (e.g., panicky states of anxiety), should not take green tea supplements or extracts or should drink no more than one or two cups per day only because of the presence of caffeine in extracts.

CONCLUSION

Tea is most widely consumed beverage in the world because of its cooling, slightly bitter and astringent flavor that people enjoy. Tea can generally be divided into categories based on how they processed. Green tea nowadays becoming more pronounced among population in world due to its beneficial effects on human beings. In this modern world, dietary habits influence the risk of developing a variety of diseases, so drinking green tea is a relatively an easy and cheap habit to maintain a healthy life. It lowers the risk of diabetes, cardiovascular problems, obese and dental caries, etc.

As the human clinical evidence is still limited, future research needs to define the actual magnitude of health benefits. The development of various biomarkers as well as molecular markers for green tea consumption will facilitate future research in this area.

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Conflicts of interest

There are no conflicts of interest.

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