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Tea (*Camellia sinensis*) and its multifactorial health benefits

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Abstract: Tea, a daily beverage for time immemorial, has already attracted very wide interest for its ability to control inflammation, improve immune function, suppress autoimmune disease and prevent cancer. The active components of tea responsible for such biological effects are known to be Catechins (known as Polyphenols), Theanines and Polysaccharides. Polyphenols constitute seven forms including Epigalocatechingallate (EGCG). Anti-inflammatory, analgesic and immunomodulatory activities of green and black tea have been getting more clinical importance in this frame of time. Whether we can perform preliminary studies with normal healthy human volunteers is going to be the talk of the town in next decade.

Keywords: *Tea; Black; Green; Benefit; Clinical trial*

Introduction

Tea (*Camellia sinensis*) is a widely consumed beverage for several thousand years since its introduction in China. Anti-inflammatory, peripheral analgesic and immunomodulatory activities of green tea and black tea had been depicted in different literature.[1,2] Tea is grown in about 30 countries but is consumed worldwide, although at greatly varying levels.[3] It is the most widely consumed beverage besides water with a per capita worldwide consumption of approximately 0.12 liter per year.[3] Green tea is consumed primarily in China, Japan, and a few countries in North Africa and the Middle East. Traditionally, tea has been known to have potentially beneficial effects, but these effects were not documented by well-controlled laboratory studies until 1970s.[4] However, current studies have revealed the biological effects of tea such as anti-tumor as well as antimicrobial effects, even at a molecular level.

Components of Tea

The tea plant, *Camellia sinensis*, is a member of the Theaceae family, and black, oolong, and green tea are produced from its leaves. It is an evergreen shrub or tree and can grow to heights of 30 feet, but is usually pruned to 2–5 feet for cultivation. The leaves are dark green, alternate and oval, with serrated edges, and the blossoms are white, fragrant, and appear in clusters or singly. Tea is manufactured in three basic forms – Green, Oolong, and Black. Green tea is prepared in such a way as to preclude the oxidation of green leaf polyphenols. During black tea production, oxidation is promoted so that most of these substances are oxidized. Oolong tea is a partially oxidized product. Of the approximately 2.5 million metric tons of dried tea manufactured, only 20% is green tea and less than 2% is oolong tea. Fresh tea leaf is unusually rich in the flavanol group of polyphenols known as Catechins, which may constitute up to 30% of the dry leaf weight. Other polyphenols include flavanols and their glycosides, and depsides such as chlorogenic acid, coumarylquinic acid, and one unique to tea, theogallin (3-galloylquinic acid).[5] Caffeine is present at an average level of 3% along with very small amounts of the other common methylxanthines, theobromine and theophylline. The amino acid theanine (5-N-ethylglutamine) is also unique to tea. Tea accumulates aluminum (Al) and manganese (Mg). In addition to the normal complement of plant cell enzymes, tea leaf contains an active polyphenol oxidase which catalyzes the aerobic oxidation of the catechins when the leaf cell structure is disrupted during manufacturing of black tea.[3] The various quinones produced by the enzymatic oxidations undergo condensation reactions, which result in a series of compounds, including bisflavanols, theaflavins, epitheaflavic acids, and thearubigens, which impart the characteristic taste and colour properties of black tea.[3] Most of these compounds readily form complexes with caffeine. There is no tannic acid in tea. Thearubigens constitute the largest mass of the extractable matter in black tea, but their composition is not well known. Proanthocyanidins make up part of the complex. Tea peroxidase may be involved in their generation. The catechin quinones also initiate the formation of many of the hundreds of volatile com-

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pounds found in the black tea aroma fraction. New volatile substances are produced during the drying stage.

Green tea, black tea and Chinese oolong tea are all made from leaves of the same plant: *Camellia sinensis*. Black tea is fermented. Chinese oolong tea is semi-fermented. Green tea is not fermented, and thus it has not lost many healthful components such as tea-polyphenols, flavonoids, amino acids, and vitamins A, C, and E. There are three main water-soluble components of green tea that are responsible for its taste. One is L-theanine, which has a mild sweet taste. It remains unaltered only in non-fermented tea. L-theanine promotes the formation of the neurotransmitter dopamin, and increases the α-waves in the brain. It can also relax people and improve memory and sleep quality too. Other benefits of L-theanine include cranial vascular system repair (preventing dementia), and it assists the immune system by being an antigen, which increases interferon formation.[4] Oolong tea is intermediate in composition between green and black teas. Green tea is produced from steaming fresh leaves at high temperatures, thereby inactivating the oxidizing enzymes and leaving the polyphenol content intact. The main catechins in green tea are epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCg), with the latter being the highest in concentration.[3]

Immunomodulatory Activity of Tea

The active components of tea responsible for such biological effects are known to be Catechins (known as Polyphenols), which constitute seven forms including epigalocatechingallate (EGCG). EGCG is a major catechin compound present in tea extracts and is also the most active form in a variety of biological activities. The immunomodulatory effect of EGCG is slowly being recognized as it is now known that EGCG stimulates the production of Interleukin 1α, IL1β, TNF-α in cultured human peripheral blood mononuclear cells.[5] It protects against UV radiation-induced immunosuppression and tolerance induction by reducing IL10 production and increasing IL12 production in epidermal and dermal cells.[5] Black tea (*Camellia sinensis*) decoction shows immunomodulatory properties on an experimental animal model and in human peripheral mononuclear cells.[2] In this study, black tea showed its effect in *in-vivo* experimental acute and chronic (immunoregulatory) anti-inflammatory model as well as in *in-vitro* model of human peripheral T-lymphocytes.

The immunity enhancers in tea are polysaccharides and theanine. There are several reports on them including clinical trials. It is always better to perform clinical trial by separating active principle rather than using the crude product to pinpoint the exact mechanism.

Anti-inflammatory Activity of Tea

For the treatment of inflammatory diseases, steroidal or non-steroidal anti-inflammatory drugs (NSAID) are used. Besides controlling the inflammation, almost all these agents also produce analgesia. But, they have mild to moderate and even severe adverse drug reactions. Therefore, research is going on all over the world to find out effective, but less toxic drugs for the treatment of inflammatory diseases.

The importance and utility of medicinal plants in the treatment of any chronic disease is well known as they have got the additional advantage of being cheap, and may be used for prolonged period. In 1958, Chopra pioneered the usefulness of many indigenous drugs in inflammatory conditions.[6] Since then, various medicinal plants have been selected for scientific testing and screening for anti-inflammatory and analgesic activity.

Considering these favourable points, tea has been used for its anti-inflammatory activity in various experimental *in vitro* and animal models to substantiate the claim. Gallic acid, epigallocatechin and epigallocatechin gallate are the major tea catechin found to inhibit inducible NOS and down regulate Cox-2.[7] Green and black tea are potent anti-tumour agents that prevent peroxinitrite and nitrite generation from NO. Phenolic components of tea has shown inhibitory effect on the production of IL-1β and enhanced the production of IL-10 (but no effect on IL-6) and TNF-α. Although these effects suggest anti inflammatory properties of tea derived catechin, they were occurred in a concentrations unlikely to be achievable in plasma *in vivo* and are therefore unlikely to contribute to the protective effects of tea-derived flavonoids in anti-inflammatory diseases.[8]

Tea extracts also showed anti-inflammatory activity in the carrageenan-induced paw edema model in rat.[9] It is well known that tumour promoters recruit inflammatory cells to the application site, and cancer development may also act by aggravating inflammation in the tissue and *vice versa*.[10] It is also reported that inflammatory cells are capable of inducing genotoxic effects. Several studies have documented a relation between inflammation and cancer for decades.[11] Analgesic activity of tea has been screened as well, as an extension of the proposed work. As pain is a cardinal feature of inflammation, most of the anti-inflammatory agents also possess analgesic activity. And reversibly, the observation by Vogel *et al.*[12] also suggests that most of the so-called peripheral analgesics

possess anti-inflammatory property.

Anti-oxident Properties of Tea

Green tea polyphenols have demonstrated significant antioxidant, anti-carcinogenic, anti-inflammatory, thermogenic, and antimicrobial properties in numerous human, animal, and *in vitro* studies. The antioxidative activity was studied in 25 kinds of tea and catechins by a new evaluation method using an oxygen electrode. The concentration of catechins in 6 types of green tea was analysed by HPLC.[13] The results indicate that the antioxidative activity of green tea depends to some extent on the amount of catechins present. Black tea and catechins, the major flavonols of tea-leaf, fight against damage by oxidative stress.[14,15] Black tea extract in comparison to free catechins seemed to be a better protecting agent against various types of oxidative stress. Apparently, the conversion of catechins occurs to partially polymerized products such as theaflavin or thearubigin during "fermentation" process[14] for making black tea has no deleterious effect on its scavenging properties. The antioxidant activities of three different green tea extracts were investigated and compared by two different methods. All extracts revealed a strong antioxidant activity, and a particular effectiveness was demonstrated by the extracts having higher amounts of (–)-epigallocathechin-3-gallate and (–)-epigallocathechin, as analysed by reverse-phase HPLC analysis.[13]

Protective Role of Tea in Cardiovascular Diseases

Epidemiological studies suggest that antioxidant flavonoids in tea may reduce the risk of cardiovascular disease, possibly via protection of low-density lipoproteins (LDL) against oxidation.[16] However, the extent of absorption of tea flavonoids and their accumulation in LDL during regular consumption of tea may have some beneficial effects. Although present in LDL, the concentration of catechins in LDL was not sufficient to enhance the resistance of LDL to oxidation *ex vivo*.[13] Hypertriglyceridemia and hypercholesterolemia has also been shown to be normalized by green and black teas, respectively, in rat models.[17] Plasma HDL–cholesterol concentrations were not affected by any tea extract. Although green and oolong tea extracts contained similar composition of catechin, green tea exerted a greater anti-hyperlipidemic effect than oolong tea. The flavonoid components of tea have been associated in epidemiological studies with a decreased risk of cardiovascular disease. Flavonoids have been shown to have antioxidant and vasodilator effects *in vitro*.[18] However, any acute effects of tea on blood pressure did not translate into significant alterations in ambulatory blood pressure during regular tea consumption. Green tea contains polyphenols, chemicals that act as powerful antioxidants. Epidemiological and human studies have shown varying results and a positive association.[18-20]

Anti-Cancer Activity of Tea

In recent years, the concept of cancer chemoprevention has matured greatly. Significant reversal of suppression of pre-malignancy in several sites by chemopreventive agents appears achievable. Tea polyphenols acts in different tumour bioassay systems and show variable chemo-preventive effects. But the anti-mutagenic and anti-carcinogenic effects of tea have been conducted with green tea decoction or a polyphenolic fraction isolated from green tea. Mostly studies have been conducted in a mouse skin tumour model system.[21] Green tea has been shown to exhibit antimutagenic activity *in vitro* and inhibit carcinogen as well as UV-induced skin carcinogenesis *in vivo*. Tea consumption has also been shown to afford protection against carcinogen-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast and colon carcinogenesis in specific bioassay models.[21] Several epicatechin derivatives (polyphenols) present in green tea have been shown to possess anti-carcinogenic activity. Epigallocatechin-3 gallate which is also the major constituent of Green tea and theaflavin-3,3′-digallate,[22] a major component of Black tea are the two most important anticancer factors found in tea.

The mechanism of cancer preventive effects of tea is not completely understood. Several theories have been put forward including inhibition of UV and tumour promoter induced ornithine decarboxylase, cyclooxygenase, lipooxygenase activities, antioxidant and free radical scavenging activity; enhancement of antioxidant (Glutathione peroxidase and catalase) and phase II (Glutathione S transferase) enzyme activities,[21] inhibition of lipid peroxidation and anti-inflammatory activities. These properties of tea polyphenols make them effective chemopreventive agents against the initiation, promotion and progression stages of multistage carcinogenesis.

Anti-Microbial Activity of Tea

Antibacterial activity of tea has shown remarkable achievements in the present decade. EGCG has anti-carcinogenic, anti-oxidant, anti-inflammatory as well

as anti-microbial activities, but the mechanism of anti-microbial activities of EGCG has been studied, it remains unclear. Tea lotion has been reported to have antibacterial activity against *Staphylococcal aureus* and *Staphylococcal pyogenes* and seems to be effective in patients with impetigo contagiosa.[23] Tea has also been reported to have bactericidal activity against *Vibrio cholerae*, *Salmonella typhimurium* and *Salmonella typhi*.[24] It has shown protective activity against *B. pertussis* probably due to the presence of epigallocatechin-3 gallate in Green tea and Theaflavin digallate in black tea. Thus, we can understand that tea is gaining immense biomedical importance in the coming future.

Clinical Trials

Green tea polyphenolic compounds have significant antioxidant and anti-inflammatory activities, and studies suggest that these extract help to prevent ultraviolet radiation damage.[25,26] Chronic intake of green tea increased the reward learning and prevented the depressive symptoms. These results also raised the possibility that supplementary administration of green tea might reverse the development of depression through normalization of the reward function.[27] Black tea is known to be a potent inhibitor of intestinal absorption of non-haem iron, at least in healthy subjects. Regular tea drinking with meals reduces the frequency of phlebotomies required in the management of patients with haemochromatosis.[28] Another Randomized, Double-Blind, Placebo-Controlled Trial of Polyphenon E – an active component of tea in Prostate Cancer Patients before Prostatectomy – demonstrated its role in chemopreventive role in prostate cancer. All trials except Ref. 26 are double blind placebo controlled studies which indicates its necessity in clinical practice in different situations in coming years.[29]

Conclusions

However, such studies would be difficult to undertake in humans as the majority of the population are "tea consumers". Hence, we propose that after a "wash out" period of 2 weeks, preliminary studies can be undertaken with normal healthy human volunteers.

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