

## Green Tea As A Phyto-Therapeutic Agent In Medicine And Dentistry: A Literature Review

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**Abstract:** Over the past decades, focussed interest in drugs obtained from medicinal plants has markedly increased. Since times immemorial, tea has traditionally been the most popular and widely consumed beverages in the world obtained from the extracts of leaves of the plant *Camellia sinensis* by the process of oxidation. It is the oldest non-alcoholic beverage containing caffeine. Amongst the varieties of tea manufactured, green tea is considered of utmost significance since it exerts antimicrobial, anti-cancer, antioxidant, anti-collagenase, anti-diabetic, anti-obesity and anti-hypertensive activities due to rich content of polyphenols, namely catechins, which prevent the pathogenesis of numerous disease processes and play a pivotal role as a scavenger of free radical generation. The present review discusses the botanical description, phyto-chemical constituents and biological activity of green tea with clinical relevance in medicine and dentistry.

**Keywords:** Green tea, *Camellia sinensis*, antimicrobial, anti-cancer, antioxidant, anti-collagenase, anti-diabetic, anti-obesity, anti-hypertensive, polyphenols, phyto-chemicals

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### I. Introduction

Since ancient civilizations, natural plants have been used as traditional medicines for the treatment of various ailments. Alternative medicines are a part of primary health care regimens due to high cost treatment regimens and cross-resistance to chemically manufactured drugs. The affordability and safety issues have drawn the world towards the use of phyto-medicines to treat various human diseases. Tea is the second most widely consumed beverage ever since 3000 B.C.<sup>1</sup> It is obtained from infusion of the extracts of leaves and leaf buds of plant *Camellia sinensis* originally from South West China. It was originally used as a medicine for various illnesses as a bitter concoction since they were rich in polyphenols catechins.<sup>2</sup> According to the different methods of processing, three types of tea are produced including Black Tea (fully oxidized/fermented), Oolong Tea (semi-oxidized/ fermented) and Green Tea (Non-oxidized/non-fermented). Green tea is the most important amongst all since it contains highest amount of polyphenols catechins. Catechins are dietary polyphenolic compounds associated with a wide variety of beneficial health effects proven in-vitro, in-vivo and clinically. Emerging evidence has shown catechins and their metabolites to possess antimicrobial, anti-cancer, antioxidant, anti-collagenase, anti-diabetic, anti-obesity and anti-hypertensive activities anti-oxidant, anti-cancer, anti-diabetic, anti-asthmatic, anti-collagenase, anti-hypertensive and anti-obesity activities preventing pathogenesis of numerous disease processes and playing a pivotal role as a scavenger of free radical generation. In dentistry, green tea has proved to be useful in the prevention of oral cancers, dental caries and periodontal diseases.<sup>3</sup> Use of green tea provides potent antimicrobial activity against pathogens in the oral cavity and also, eliminates the risk of tissue toxicity, emphysema and allergic potential. So, researchers are in the constant look-out for alternatives to the medicines used in the treatment of infections due to their varied adverse effect profiles and development of resistant strains.<sup>4,5</sup> The present review discusses the botanical description, phyto-chemical constituents and biological activity of green tea with clinical relevance in medicine and dentistry.

**Pharmacological Uses of Green Tea in the Field of Medicine:** Green tea has an important role on various molecular targets such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-2 (IL-2), thus, suggesting that a polyphenolic extract of green tea, epigallocatechin-3-gallate (EGCG), could modulate various biochemical pathways involved in the inflammatory responses and joint destruction seen in arthritis. EGCG inhibits interleukin-1 beta (IL-1 beta) induced cartilage proteoglycan degradation and expression of enzymes matrix metalloproteinases-1 and 13 (MMP-1 and 13) in human chondrocytes, thus, suppressing precipitation of cartilage degradation seen in arthritis.<sup>6</sup> EGCG catechin mainly inhibits alpha amylase activity in saliva as well as decreases intestinal amylase activity, thus, lowering the hydrolysis of starch and glycogen to glucose reducing glucose assimilation and hence, decreasing the digestive enzyme activity.

It, also, increases tyrosine phosphorylation of insulin receptor, insulin receptor substrate and reduces gene expression of gluconeogenic enzymes, namely phosphoenolpyruvate carboxykinase, thereby, exerting an anti-diabetic action. Polyphenols in green tea protect the body against oxidative stress associated with late complications of diabetes. Regular consumption of green tea reduces body weight and suppresses the dietary food intake. EGCG has inhibitory effect on enzyme acetyl carboxylase which has an important role in fatty acid biosynthesis. It influences sympathetic nervous system activity, upregulates enzymes involved in hepatic fat oxidation and increases fat oxidation in the body, thus, preventing fat accumulation. Caffeine along with catechins present act synergistically to increase fat oxidation in the body and prolong sympathetic stimulation of thermogenesis.<sup>7,8</sup> It, also, prevents osteoporosis commonly seen in elderly females. L-theanine present in green tea has been proven to lower high arterial blood pressure and is a good anti-hypertensive agent.<sup>9,10</sup> Green tea improves the immune status of the body through antioxidant activity and cytokine gene expression in cases of immuno-compromised patients like heavy smokers. The hepato-protective role of green tea on cadmium-induced hepato-toxicity in liver has been evaluated and it has been shown that green tea shows decreased expression of hepatic enzymes including serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH).<sup>11,12</sup> Green tea constituents like catechins and theanine have neuro-protective activities by minimizing eicosanoid accumulation and oxidative damage in cases of ischemia-induced brain injury. EGCG improves age-related cognitive-deficits and protects against cerebral ischemia. It has, also, been shown to exert protective effect against beta-amyloid-induced neuro-toxicity in cultured hippocampal neurons as observed in the various animal models. Green tea has anti-stress, calming and healing properties due to the presence of L-theanine which is believed to facilitate generation of alpha waves in the brain and reduce cortisol levels during stress to produce relaxed yet alert state of mind. Green tea, also, possesses a potent anti-asthmatic activity via an increased expression of tumour necrosis factor-beta (TNF-beta), interferon-gamma (IFN-gamma) and decreasing anti-asthmatic cytokines in the lungs.<sup>13,14</sup> Consumption of green tea substantially decreases risk of cardiovascular diseases and prevents atherogenesis by protecting low density lipoproteins (LDL) fraction against oxidative injuries. There is activated synthesis of prostaglandins (PGs) and catechins have anti-platelet and metal chelating properties.  $\alpha$ -tocopherol which is the main antioxidant to protect LDL against oxidative injuries is regenerated due to green tea consumption.

EGCG reduces cholesterol and triacylglycerol levels in the blood by interfering with the micellar solubilisation of cholesterol in the digestive tract and its absorption. Green tea extracts have inhibitory effect on cyclo-oxygenase (COX) and lipoxygenase (LOX) pathways of arachidonic acid metabolism. Antioxidants present in green tea neutralize the adverse effects of free radicals in the body and reduces DNA damage, thus, protecting the skin from the harmful UV rays.<sup>15,16</sup> Green tea polyphenols prevent diabetic retinopathy by modulation of genetic pathways such as angiogenesis and by antioxidant defence mechanism. Green tea has shown antimicrobial activity against enteric pathogens like *S. epidermis*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-sensitive *Staphylococcus aureus*, *Helicobacter pylori* (*H. pylori*), *Staphylococcus aureus*, *Streptococcus mutans*, *Salmonella typhi*, *Shigella sp.* and *Vibrio cholera*. EGCG has been found to inhibit Influenza virus A and B, HIV virus enzymes, Hepatitis B, Rota virus and Enteroviruses in monkey cell cultures. EGCG binds to the cell surface CD4 molecules and prevents HIV infection in the body. It has, also, been found to be effective against a wide range of fungi, namely *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida dubliensis*.<sup>17,18</sup>

**Role of Green Tea in the Field of Dentistry:** Various experimental reports have shown green tea to possess antioxidant potential due to rich content of catechins and tannins. Reduced free radical generation, lipid peroxidation and oxidative DNA damage has been reported after green tea consumption in smokers. The order of antioxidant potential of various catechins present in green tea extracts is EGCG>ECG>EGC>EC and that of theaflavins TF<sub>2</sub>>TF<sub>1</sub>>TF. Green tea has anti-cancer effects via modulation of genes involved in cancer initiation, promotion and progression acting in the following manner:<sup>19-21</sup>

1.It acts as an inhibitor of cyclo-oxygenase (COX) and lipoxygenase (LOX) pathways of arachidonic acid metabolism and tumour necrosis factor (TNF) and interleukin (IL) pathways for development and progression of cancer cells;

2.It has preventive effect via activation of tumour suppressor genes such as p53 and pTEN/p21, inhibits angiogenesis by suppressing activation of HIF-1 $\alpha$  and NF- $\kappa$ B pathways, regulates apoptosis and prevents other transcription factors which are involved in the development and progression of cancer cell lines;

3.It has antioxidant potential and neutralises free radicals, thus, preventing progress of the tumour in the body;

4.It modulates the genes involved in the process of carcinogenesis. Green tea polyphenols and EGCG activates p53 gene by increasing its transcriptional activity and acetylation. EGCG inhibits growth and invasion of cancer cells by causing cell cycle arrest and inducing apoptosis in them;

5.It inhibits growth of cancer cells by inhibiting activation of oncogenes such as HER2 and HER3 and epidermal growth factor (EGF) receptors;

6.It causes inhibition of telomerase, AP-1 and IGFIR responsible for carcinogenesis;

7.It activates peroxisome-proliferator receptors inducing apoptosis in various cancer cell lines. EGCG has been shown to suppress the growth of melanoma cells in-vivo and has been found to be effective in chronic lymphatic leukemia (CLL) patients in Phase 1 trials. It is a potent chemotherapeutic agent in the treatment of leukoplakia patients and in oral squamous cell carcinoma (OSCC) causing G1 cell cycle arrest and inducing apoptosis in such patients.<sup>22,23</sup> Anecdotal reports quoted in the literature are suggestive of green tea helping in the prevention of dental caries if taken regularly. EGCG and ECG significantly reduce interleukin-6 and 8 (IL-6 and 8) expression in dental pulp cells exposed to prostaglandins (PGs). Intercellular adhesion molecule-1 and vascular adhesion molecule-1 expression is, also, reduced after treatment with EGCG and ECG suggestive of catechins in prevention of exacerbation of pulpitis.<sup>24</sup> Catechins in green tea, mainly EGCG, ECG, and ECG show potent antimicrobial activity against the gram positive and gram negative oral bacteria, thus, preventing dental caries. Green tea and extracts influence the progression of dental caries at different stages by inhibiting the proliferation of the streptococcus agent, interfering in its adhesion to the tooth structure and/or, by acting as inhibitors of enzymes glucosyl transferase and amylase.<sup>25</sup> A study conducted by Suyama et al<sup>26</sup> showed that consumption of green tea extracts based gum increases the resistance of the enamel to acid attack and hence, reinforces its potential to re-mineralization. A commercial mixture of catechins from green tea, namely Sunphenon prevented attachment of *S. mutans* to the saliva-coated hydroxyapatite crystals upto 91% due to catechin-mediated denaturation of protein ligands like surface fimbriae. EGCG and ECG have, also, been found to prevent the progression of the process of dental caries by getting adsorbed to protein components of salivary pellicles and modifying their physical properties and preventing further development. They, also, significantly inhibit *Streptococcus mutans* and *Lactobacilli* when used as mouth wash in high caries risk patients and as chewing gums by decreasing dental plaque formation. Green tea intake reduces dentin erosion and abrasion due to the inhibition of enzymes matrix metalloproteinases (MMPs).<sup>27</sup> Tannic acid, caffeine and tocopherol present in green tea extracts coagulate the proteins in dentin making it resistant to acid demineralization. EGCG reduces the size of peri-apical lesions by inhibiting the expression of enzyme cysteine in osteoblasts and decreasing the infiltration of macrophages preventing bone resorptions. The polyphenols present in green tea prevent *E. faecalis* biofilm formation onto the root canal walls when used as an endodontic irrigant. Green tea is, also, useful as a storage media for avulsed teeth since it maintains periodontal cell viability upto 90% due to rich content of catechins.<sup>28-31</sup> Green tea based mouth washes reduce halitosis associated with periodontal disease since EGCG deodorizes methyl mercaptan which is the main cause of halitosis in patients with periodontal disease. EGCG, also, has the potential to reduce periodontal breakdown by inhibiting the activity of enzyme proteinases in infections caused by *P. gingivalis*. Matrix metalloproteinases-1, 2, 9 and 13 (MMP-1, 2, 9 and 13) are the main factors involved in carrying-out the resorption of bone collagen by osteoblasts. Green tea polyphenols, also, protect the bone from resorption during periodontal diseases due to inhibition of the enzyme matrix metalloproteinase-9 (MMP-9) in osteoblasts and activation of osteoclasts.<sup>32</sup>

**Green Tea: Not Everything is Positive:** Although green tea has been proven to have therapeutic benefits in the various disease set-ups, excessive intake of green tea can be harmful to the body and is known to cause numerous adverse effects including:<sup>33</sup>

1.Excessive intake of green tea can cause staining of teeth due to interaction of the components with salivary pellicle and the hydroxyapatite crystals of enamel;

2.It blocks the absorption of nutrients like iron and thiamine;

3.It might lead to symptoms of restlessness, irritability, palpitations, loss of appetite, nausea, gastro-intestinal upsets and rashes;

4.It can result in easy and prolonged bleeding tendencies due to increase in bleeding time;

5.EGCG present in green tea extracts is cytotoxic, if consumed, in larger quantities;

6. Caffeine and catechins present in green tea extracts can cause birth defects due to folic acid antagonism;
7. Excessive intake of green tea in pregnant and breast feeding females can cause palpitations due to the presence of vaso-constrictive and stimulative caffeine;
8. Excessive intake of green tea accumulates aluminium in the body resulting in various neurological disorders.

## **II. Discussion**

The present day sedentary lifestyle and dietary habits have increased the risk for a plethora of diseases including various cancers and cardiovascular disorders. Use of phyto-medicine in the treatment of such diseases has considerably increased in the recent years owing to the potential toxic effects of the conventional therapeutic agents used. Tea is considered as a pleasant, economical and socially accepted health beverage proving to be a potent phyto-therapeutic agent in the prevention of chronic diseases in humans. Various epidemiological studies and laboratory investigations have indicated that polyphenols, namely catechins present in the green tea possess strong antimicrobial, anti-cancer, antioxidant, anti-collagenase, anti-diabetic, anti-obesity and anti-hypertensive activities which prevent the pathogenesis of numerous disease processes and play a pivotal role as a scavenger of free radical generation.<sup>4-7</sup> These polyphenols, also, promote other physiological functions including anti-fibrotic and neuro-protective properties and protect skin from the harmful UV radiations. They, also, contribute to increase the bone density and improve body immunity.<sup>8,9,11,13</sup> Several mechanisms have been presented to explain the chemo-preventive effects of EGCG amongst which its effect to target specific cell signaling pathways has received considerable attention for regulating the cellular proliferation and the process of apoptosis. The diversified effects of EGCG include its broad pharmacological effects in modulating the cell signaling pathways. In-vivo studies have proved that green tea catechins increase the total plasma antioxidant activity by decreasing the production of malondialdehyde which is a marker of oxidative stress. Green tea has been proven to have rich antioxidant properties and better free radical scavenging property than Vitamin C and E. In addition to other mechanisms, it is known to activate cell death signals and induce apoptosis in pre-cancerous and cancer cell lines resulting in the inhibition of the development and progression of cancer cells. EGCG modulates the signal transduction pathways involved in cell proliferation, transformation, apoptosis and metastasis. Most importantly, these anti-proliferative and pro-apoptotic effects of EGCG have been shown to be selective for cancer cells only as normal cells are not affected during the treatment procedure. In cancer cells, EGCG, also, causes inhibition of the activity of specific receptor tyrosine kinases and related downstream pathways of signal transduction. Hence, it acts synergistically to enhance the effect of various anti-cancer drugs when used in combination therapy.<sup>22-24</sup> EGCG present in green tea reduces the amount of *S. mutans* and *Lactobacillus* bacteria in saliva and plaque and increases the salivary pH, thus, preventing dental caries. There is increased resistance of enamel to acid induced de-mineralization. In endodontics, it has demonstrated good antimicrobial activity against *E. faecalis* eliminating the risk of adverse effects including tissue toxicity, allergy and emphysema commonly seen with the conventional root canal irrigants like sodium hypochlorite. The antimicrobial action of green tea might be attributed to its flavonoid content by inhibiting the bacterial enzyme gyrase by binding to adenosine triphosphate-B (ATP-B) sub-unit preventing, thereby, the adherence of the bacteria onto the dentinal walls. It, also, maintains the viability of periodontal cells, hence, can be used as a storage media for avulsed teeth. Numerous studies have revealed the antibacterial effect of green tea by the stimulation of protective components such as immunoglobulins, lysosomes, lactoferrin, histatins and mucin. It has, also, been proven to be of clinical significance in the prevention of dental caries and promoting periodontal health by reducing inflammation, preventing bone resorption and limiting the growth of bacteria which are supposed to be associated with the periodontal diseases. Polyphenols present in green tea can, also, prohibit the co-aggregation of periodonto-pathogens seen in biofilms formed on tooth/root surfaces. Polyphenols, also, reinforce to increase the collagen formation and accelerate the soluble-to-insoluble collagen conversion during tissue regeneration. They, also, prohibit the production of PGE2 and can, thus, reduce the progress of periodontitis.<sup>25,26,34</sup> Though with potential advantages and therapeutic benefits, information regarding the bioavailability of catechins and other polyphenols present in green tea extracts is limited in humans studies. Further studies are, therefore, mandated to know the exact details about their absorption, distribution and metabolism in the body. Hence, a careful evaluation of the available data is mandatory to harness the complete therapeutic advantages they can offer for improving the health outcomes without significantly compromising the body systems with the common adverse effects seen with the conventional therapeutic agents.<sup>35,36</sup>

## **III. Conclusion**

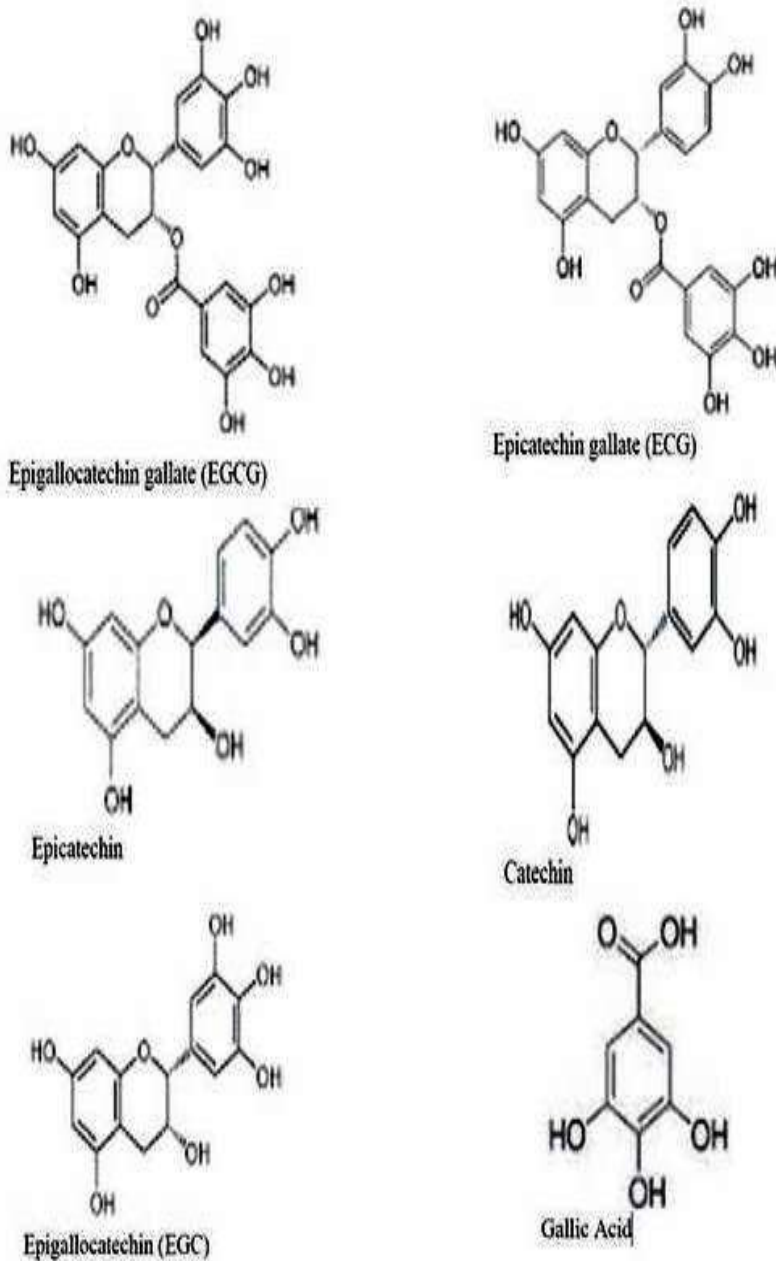
Phyto-medicine has been of increasing interest in the recent years. The major advantages of green tea are its safety, easy availability, cost-effectiveness, increased shelf life and a lack of microbial resistance. According to the substantial evidences available, green tea has been proven to have potential therapeutic properties, however, the literature is scarce with regard to the information on the quality, safety and efficacy of its potential use in various disease set-ups. Hence, further clinical trials are mandated to support its use as

effective alternatives to the synthetically available drugs. Furthermore, research is, also, mandated to investigate into the toxicity and possible drug interactions of their constituents in the various aspects of medicine and dentistry.

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Figure with Legend  
Basic structures of different green tea polyphenols



Chemical structures of various polyphenols present in Green tea.