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A Review on the Beneficial Effects of Tea Polyphenols on Human Health

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Abstract: The aim of this review is to focus some light on the beneficial effects of the tea polyphenols on human health, based on various laboratory, epidemiological and clinical studies carried out on tea and tea polyphenols in the last few years. Tea is second only to water as the most consumed beverage in the world. Tea has been consumed worldwide since ancient times to maintain and improve health. The health benefits associated with tea consumption have resulted in the wide inclusion of green tea extracts in botanical dietary supplements, which are widely consumed as adjuvants for complementary and alternative medicines. Depending upon the level of fermentation, tea can be categorized into three types: green (unfermented), oolong (partially fermented) and black (highly to fully fermented). Black tea represents approximately 78% of total consumed tea in the world, whereas green tea accounts for approximately 20% of tea consumed. Tea is particularly rich in polyphenols, including catechins, theaflavins and thearubigins, which are thought to contribute to the health benefits of tea. Tea polyphenols comprise about one-third of the weight of the dried leaf and they exhibit biochemical and pharmacological activities including antioxidant activities, inhibition of cell proliferation, induction of apoptosis, cell cycle arrest and modulation of carcinogen metabolism. Several studies demonstrate that most tea polyphenols exert their effects by scavenging Reactive Oxygen Species (ROS) since excessive production of ROS has been implicated in the development of a variety of ailments including cancer of the prostate gland (CaP). Tea catechins include (-)-epicatechin (EC),(-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG) and (-)-epigallocatechin gallate (EGCG). These catechins have been shown to be epimerized to (-)-catechin (C), (-)-gallocatechin (GC), (-)-catechin gallate (CG) and (-)-gallocatechin gallate (GCG), respectively, during heat treatment. Tea polyphenols act as antioxidants *in vitro* by scavenging reactive oxygen and nitrogen species and chelating redox-active transition metal ions. Among the health-promoting effects of tea and tea polyphenols, the cancer-chemopreventive effects in various animal model systems have been intensively investigated; meanwhile, the hypolipidemic and antiobesity effects in animals and humans have also become a hot issue for molecular nutrition and food research. In vitro and animal studies provide strong evidence that tea polyphenols may possess the bioactivity to affect the pathogenesis of several chronic diseases, especially cardiovascular disease and cancer. Research conducted in recent years reveals that both black and green tea have very similar beneficial attributes in lowering the risk of many human diseases, including several types of cancer and heart diseases.

Key words: Polyphenols, catechins, epigallocatechin gallate, biological effects

INTRODUCTION

Plants are the essential source of medicines. Through the advances in pharmacology and synthetic organic chemistry, the dependence on natural products, remain unchanged (Roopashree *et al*., 2008). In India, the majority of populations use traditional natural preparation derived from the plant material for the treatment of various diseases (Siddique *et al*., 2006a) and for that reason it has become necessary to assess their antimutagenic potential or mutagenic potential for modulating the action of plant extract when associated with other substances. The genotoxicity testing provides human a risk assessment. The earlier studies have shown that various plant extracts and natural plant products possess protective role against the genotoxic effects of certain estrogens, synthetic progestins and anticancerous drugs in cultured human lymphocytes (Siddique and Afzal, 2004; Siddique and Afzal, 2005a, b; Beg *et al*., 2007a, b; Siddique and Afzal, 2005, 2006a-c, 2007a-c, 2008a,b) and mice bone marrow cells (Siddique *et al*., 2006d, 2008c). Since the plant extracts have compounds that may either

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enhance or reduce the genotoxic effect of a particular compound, the knowledge of particular plant extract will contribute for us to form the basis of herbal medicine (Roncada *et al*., 2004). The antigeotoxic potential of the plant extracts have been attributed to their total phenolic content (Maurich *et al*., 2004). Medicinal herbs contain complex mixtures of thousands of compounds that can exert their antioxidant and free radical scavenging effect either separately or in synergistic ways (Romero-Jimenez *et al*., 2005).

Plant flavanoids and antimutagenicity: One or the other kind of chemical is being used for almost every activity in our daily life. A large number of substances such as drugs, cosmetics, pesticides and petroleum products have been established as mutagens (Marshall *et al*., 1976; Hahn *et al*., 1991) Ames Test confirmed that several components of the human diet contains a great variety of natural mutagens or 'nature's pesticides'(Kawai *et al*., 2006). The main danger of such wide spread and inadvertant exposure lies in the danger of their potential of enhancing genetic load. The environmental mutagens are attributed to several human ills like cancer, atherosclerosis and ageing (Jensen *et al*., 1990). Thus, the increasing wide use of these mutagens in almost every sphere of human life, requires an urgent need for studies on the possibility of intervention through antimutagenic action. A large number of natural substances are capable of inactivating environmental mutagens. The characterization of these substances is also important for the possibility of intervention using them as chemotherapeutic or prophylactic agents against human ill healths attributable to mutations. These substances are termed as antimutagens (Yamamoto and Gaynor, 2006). They are found in various food items in variable quantities. The chemicals present in plants like Flavanoids, Vitamins A, C, E, Beta- carotenes etc. are some of the important antimutagens. Ames Test has been used generally to identify and characterise antimutagenic potentials of natural plant extracts (Azizan and Blevins, 1995). Flavonoids are widely distributed in plants fulfilling many functions including producing yellow or red/blue pigmentation in flowers and protection against attack by microbes and insects. These flavanoids have been found to possess antitumor properties in animal models (Kandaswami *et al*., 2005). The term Flavonoids according to IUPAC Compendium of Chemical Terminology refers to a class of plant secondary metabolites. They can be classified into:

- Flavonoids, derived from 2-phenylchromen-4-one (2-phenyl-1,4-benzopyrone) structure
- Isoflavonoids, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure
- Neoflavonoids, derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone) structure

Plant polyphenols like quercetin, rutin, catechins, chlorogenic acid, pyrocatechol etc. exhibit antimuagenicity against N- Methyl N-Nitrosoguanidine, Benzo (α) pyrene and UV- induced mutations in Ames Test. Dietary research on the impact of foods and beverages on human health has been globally dominant in the last decade. Flavonoids, a group of phenolic compounds occurring abundantly in vegetables, fruits and green plants, attracted special attention as they showed high antioxidant property. The antioxidants are known to prevent cellular damage caused by reactive oxygen species. Catechins are highly potent flavonoids present in tea and serve perhaps as the best dietary source of natural antioxidants. The tea shrub (genus *Camellia*, family Theaceae) [chromosome number (2n = 30)] is a perennial evergreen with its natural habitat in the tropical and sub tropical forests of the world. Cultivated varieties are grown widely in its home countries of South and South East Asia, as well as in parts of Africa and the Middle East. Based on differences in morphology between *Camellia sinensis* var. *assamica* and *Camellia sinensis* var. *sinensis*, botanists have long asserted a dual botanical origin for tea (Yamamoto *et al*., 1994). *Camellia sinensis* var. *assamica* is native to the area from Yunnan province, China to the northern region of Myanmar and the state of Assam in India. *Camellia sinensis* var. *sinensis* is native to eastern and southeastern China (Yamamoto *et al*., 1994). Historical references to tea date back to 5,000 years. Tea was consumed even earlier by the indigenous peoples of China. Tea recorded as having medicinal value in a Chinese medical book (Maciocia, 2005). In Chinese and Indian traditional medicine, tea has been used for: treatment of insomnia, calming effects, mental and visual clarity, thirst quenching, detoxification of poisons, improving digestion, prevention of indigestion, breaking down oils, fats, body temperature regulation improving urination, speeding bowel evacuation, treatment of dysentery, loosening of phlegm, strengthening of teeth, treatment of epigastric pain, treatment of skin fungus, reducing hunger and longevity.

Tea processing: Leaves of *Camellia sinensis* soon begin to wilt and oxidize if not dried quickly after picking. The leaves turn progressively darker because chlorophyll breaks down and tannins are released. This process, enzymatic oxidation, is called fermentation. Tannins, a group of simple and complex phenol, polyphenols and

flavonoid compounds produced by plants, are relatively resistant to digestion or fermentation (Abe *et al*., 2008). The next step in processing is to stop the oxidation process at a predetermined stage by heating, which deactivates the enzymes responsible. Processing involves following steps (Werkhoven, 1978):

- Withering (the process of letting leaves lose moisture content after plucking; often the first step in the processing of tea)
- Rolling (ruptures cell walls allowing the polyphenols to become oxidized).s
- Fermenting (the process of the polyphenols becoming oxidized)
- Firing (Halts the fermentation process and begins desiccation)
- Drying (reduces moisture content to make the final product more stable)

The various types of tea are made by different combinations of these processes.

The young shoots or flushes are plucked and processed into green (unfermented), black (fermented), oolong (red, partially fermented) or yellow (partially fermented) teas. In fermented teas, the action of leaf oxidizing enzymes, convert the tannins and catechins in tea leaves into brown/red colored products.

Tea is a rich source of polyphenols called flavonoids, the effective antioxidants found throughout the plant kingdom. The slight astringent, bitter taste of green tea is attributed to polyphenols. A group of flavonoids in green tea are known as catechins, which are quickly absorbed into the body and are thought to contribute to some of the potential health benefits of tea. The fresh tea leaves contain four major catechins as colourless water soluble compounds: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG) (Zhu *et al*., 2000) (Fig. 1). EGCG makes up about 10-50% of the total catechin content and appears to be the most powerful of the catechins. In a fresh tea leaf, catechins can be up to 30% of the dry weight. Catechins are highest in concentration in white and green teas, while black tea has substantially less content due to its oxidative preparation. Catechin levels reported for black teas ranged from 5.6-47.5 mg g^{-1}. In green teas catechin levels ranged from 51.5-84.3 mg g^{-1}, with epigallocatechin gallate (EGCG) being the main catechin in Chinese and Indian green teas. Tea contains theanine and the stimulant caffeine at about 3% of its dry weight, translating to between 30 and 90 mg per 0.25 L cup depending on type and brand and brewing method. Tea also contains small amounts of theobromine and theophylline. Tea also contains fluoride, with certain types of brick tea made from old leaves and stems having the highest levels. The health benefits of tea ranging from a lower risk of certain cancers to weight loss and protection against Alzheimer's, have been linked to the polyphenol content of the tea. Green tea contains between 30 and 40% of water-extractable polyphenols, while black tea (green tea that has been oxidized by fermentation) contains between 3 and 10%. Oolong tea is semi-fermented tea and is somewhere between green and black tea. Dried green tea

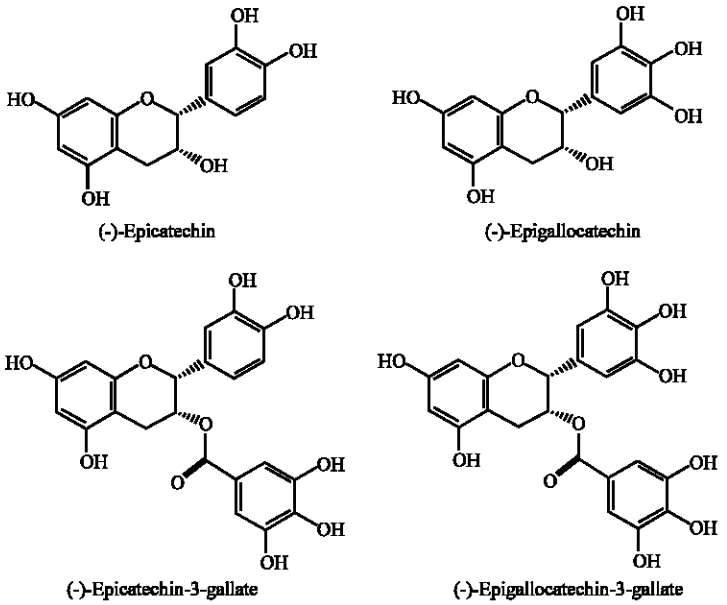
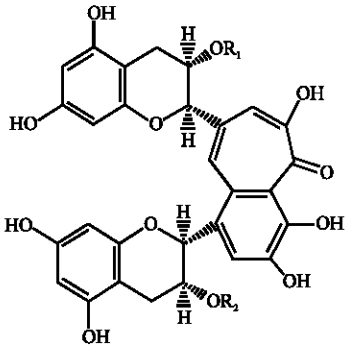


Fig. 1: Main catechin components of green tea polyhenols



1. Theaflavin-1 $R_1 = R_2 = H$
2. Theaflavin-3-gallate-A R_1 = galloyl $R_2 = H$
3. Theaflavin-3'-gallate-B $R_1 = H$ R_2 = galloyl
4. Theaflavin-3, 3'-digallate-B $R_1 = R_2$ = galloyl

Fig. 2: Main polyphenols found in black and oolong tea

leaves contain about 30-40% Catechins, 3-6% Caffeine, ~310 mg polyphenols per 6 ounces, while black tea (Crushed tea leaves → Polyphenol oxidase → Oxidation? Polymerization) contains 3-10% Catechins, 2-6% Theaflavins, > 20% Thearubigins, 3-6% Caffeine, ~340 mg polyphenols per 6 ounces. (According to Nutritional Science Research Group, Division of Cancer Prevention). Both catechins and theaflavins have recently received much attention as protective agents against cardiovascular disease and cancer. (Imai and Nakachi, 1985; Buschman, 1998; Yang, 1999). They are also believed to have a wide range of other pharmaceutical benefits, including antihypertensive (Henry and Srepens-Larson, 1984; Hara *et al*., 1987), antioxidative (Zhang *et al*., 1997; Halder and Bhaduri, 1998) hypolipidemic (Chan *et al*., 1999; Kono *et al*., 1992) activities.

Most of the green tea catechins, during the manufacture of black tea, are oxidized and converted into orange or brown products known as theaflavins (TF) and thearubigins (TR). These compounds retain the basic C6-C3-C6 structure and are thus still classified as flavonoids. Theaflavins consist of two catechin molecules joined together and account for about 10% of the converted catechins, whereas the thearubigins are more complex flavonoid molecules, whose structural chemistry are still unknown and may account for up to 70% of flavonoids in black tea. The major TF in black and oolong tea are theaflavin (TF_1), theaflavin-3-gallate (TF_2A), theaflavin-3'-gallate (TF_2B) and theaflavin-3,3'-digallate (TF_3) (Zhu *et al*., 2000) (Fig. 2). Theaflavins and Thearubigins are responsible for the characteristic color and flavor of black tea. Hence it is rightly quoted by Bernard-Paul Heroux, a Basque Philosopher that There is no trouble so great or grave that cannot be much diminished by a nice cup of tea.

The health benefits of tea ranging from a lower risk of certain cancers to weight loss and protection against Alzheimer's, have been linked to the polyphenol content of the tea (Table 1-4). It is generally believed that possible beneficial health effects of tea polyphenols are due to their anti-oxidant activity, wrote lead author Hui Cheng Lee from the National University of Singapore.

METHODS

Studies on tea polyphenols were done through computerized literature searches using the following databases: Medline, Abstract (Pubmed), Embase, Amed, Google Advanced Search. Only studies indicating the type of tea polyphenols and biological effects of tea and tea polyphenols were included. No language restrictions were imposed. Various studies on tea polyphenols have been summarized in tabular form as follows.

RESULTS AND DISCUSSION

Thus we have seen that all of the above findings clearly report the important biological effects of tea polyphenols. Green tea, being a rich source of polyphenols, contributes to various beneficial health effects (Cabrera *et al*., 2006).

Tea and cancer: As interpreted from the above data, it follows that (EGCG) epigallocatechin gallate, a major catechin of found in green tea, has possible role in chemoprevention and chemotherapy of various types of cancers mainly prostate cancer (Siddiqui *et al*., 2006a, 2007e; Lyn-Cook *et al*., 1999) and colon cancer (Xiao *et al*., 2008; Yuan *et al*., 2007) (Table 1, 2). EGCG inhibits the growth of gastric cancer by reducing VEGF production and angiogenesis and is a promising candidate for anti-angiogenic treatment of gastric cancer (Zhu *et al*., 2007). Green tea extracts contain a unique set of catechins that possess biologic activity in antioxidant, antiangiogenesis and antiproliferative assays that are potentially relevant to the prevention and treatment of various forms of cancer (Cooper *et al*., 2005a,b). Green tea and (-)-epigallocatechin gallate (EGCG) are now acknowledged cancer preventives in Japan and has made it possible for us to establish the concept of a cancer preventive beverage (Fujiki *et al*., 2002). Green tea polyphenols inhibit angiogenesis and metastasis (Isemura *et al*., 2000; Ju *et al*., 2007) and induce growth arrest and apoptosis through regulation of multiple signaling pathways. Catechins are involved in cellular thiol-dependent activation of mitogenic-activated protein kinases (Opare Kennedy *et al*., 2001). Specifically, EGCG regulates expression of VEGF, matrix metalloproteinases,

Table 1: Studies carried out on catechins, green tea polyphenols

S. No.	Properties	Model used	References
1	Inhibit 17 α-Hydroxylase/C(17,20)- Lyase (CYP17)	Rat testis	Kimura *et al.* (2007)
2	Digestive recovery of Catechins modulated	Liver extracts (*in vitro* digestion profiling using HPCL)	Green *et al.* (2007)
3	Increase cellular lipid antioxidant activity of Vitamin C and E.	Human intestinal $CaCO_2$ cells	Intra and Kuo (2007)
4	Act against Octratoxin A-induced cell damage	Pig kidney cell line LLC-PK-1	Costa *et al.* (2007)
5	Protects reactive oxygen species induced degradation of lipids, proteins and 2-deoxyribose	Isolated cell fractions from Rat liver.	Raza and John (2007)
6	Upregulates Superoxide dismutase (SOD), Reversing fat-induced mortality.	*Drosophila melanogaster*	Li and John (2007)
7	Prevents development of spontaneous stroke.	Male Malignant stroke prone spontaneously hypersensitive rats	Ikeda *et al.* (2007)
8	Inhibits bacterial DNA gyrase by interacting with its ATP binding site	Bacteria	Gradisar *et al.* (2007)
9	Reduces blood glucose level by α-glucosidase inhibition	Rat	Matsui *et al.* (2007)
10	Supplements in reducing body fat, as well as other biomarkers of cardiovascular disease risks.	Epidemiological observations in humans of Southeast Asian countries	Basu and Lucas (2007)
11	Green tea has potentials for the prevention as well as treatment of Pca.	Prostate cancer (PCa) cell lines.	Siddiqui *et al.* (2007e)
12	Has medicinal properties with special reference to cancer and cardiovascular diseases.	Animal models of carcinogenesis	Khan and Mukhtar (2007)
13	Regulates expression of VEGF, matrix metalloproteinases, uPA, IGF-1, EGFR, cell cycle regulatory proteins and inhibits Nfk B, PI3-K/Akt, Ras/Raf/MAPK and AP-1 signaling pathways, thereby causing strong cancer chemopreventive effects.	Human epidemiological studies	Shankar *et al.* (2007a)
14	Interfere with the emulsification, digestion and micellar solubilization of lipids, critical steps involved in the intestinal absorption of dietary fat, cholesterol and other lipids.	Human epidemiological studies	Koo and Noh (2007)
15	Strongly inhibit *Plasmodium falciparum* growth *in vitro*. Thus green tea has antimalarial properties.	*Plasmodium falciparum* (*in vitro*)	Saunella *et al.* (2007)
16	Decrease the total number of ACF and the total number of aberrant crypt per rat.	Azoxymethane (AOM)-induced rat colon cancer used as model and aberrant crypt foci (ACF) as an endpoint.	Xiao *et al.* (2008)
17	Act as brain permeable iron chelator, hence has potential for treatment of neurodegenerative diseases	*in vitro* and *in vivo* animal studies	Mandel *et al.* (2006)
18	A small reduction in cytochrome P450 (CYP3A4) activity	Epidemiological studies of human beings.	Chow *et al.* (2006)
19	Have positive inotropic effect and protective role in myocardial ischemia-reperfusion induced injury	Guinea pig heart (NO electrode and fluorometry)	Hotta *et al.* (2006)
20	Have antioxidant activities.	Trolox equivalent antioxidant capacity {TEAC} and Oxygen radical antioxidant capacity assay {ORAC}.	Seeram *et al.* (2006)
21	Cytotoxicity and cytoprotective mechanism evaluated.	Isolated rat hepatocytes (Mitochondrial membrane potential collapse and ROS formation)	Galati *et al.* (2006)
22	Exhibit antioxidant activities, inhibition of cell proliferation, induction of apoptosis, cell cycle arrest and modulation of carcinogen metabolism.	Cell culture and animal model systems of cancer including cancer of the prostate gland (CaP).	Siddiqui *et al.* (2006a)
23	Chemoprevention of lung cancer by tea.	Epidemiological studies on human cancer.	Clark and You (2006)
24	Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer.	A population-based, prospective cohort study in Japanese adults, with over 11 years of follow-up.	Kuriyama *et al.* (2006)
25.	Growth of certain pathogenic bacteria was significantly repressed by tea phenolics and their derivatives,	Different strains of intestinal bacteria	Lee *et al.* (2006)
26	Production of IL-8 after stimulation by proinflammatory cytokines in both nasal fibroblasts and bronchial epithelial cells was significantly blocked by pretreatment with green tea polyphenols.	Nasal mucosal fibroblasts and A549 bronchial epithelial cells were analyzed for the production of IL-8.	Kim *et al.* (2006)

Table 1: Continued

S. No.	Properties	Model used	References
27	Have hypolipidemic and anti-obesity effects.	Various animal model systems.	Lin and Lin-Shiau (2006)
28	Peroxidation of LDL is markedly prevented by green tea extract	LDL of human blood serum	Ostrowska and Skrzydlewska (2006)
29	Decrease the extent of lipid peroxidation and enhance the levels of GSH, GSH/GSSG ratio and activities of GSH-dependent enzymes.	7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis	Chandra Mohan *et al.* (2006)
30	Potent inhibitor of influenza virus replication and also suppressed viral RNA synthesis	Influenza virus subtypes A/H1N1, A/H3N2 And B virus	Song *et al.* (2005)
31	Protect erythrocytes against ter-butyl hypreoxide induced oxidative stress., thus protect against development of long-term complications of diabetes	Erythrocytes from type 2 Diabetics mammal.	Rizvi *et al.* (2005)
32	Suppress postprandial hypertriacylglycerolemia by slowing down triglycerol absorption through the inhibition of pancreatic lipase.	Murine model	Ikeda *et al.* (2005)
33	Possess biologic activity in antioxidant, antiangiogenesis and antiproliferative assays.	*In vitro* and *in vivo* animal studies.	Cooper *et al.* (2005)
34	There is inhibitory effect of theaflavins and EGCG on UVB-induced STAT1 (Ser727), ERKs, JNKs, PDK1 and p90RSK2 phosphorylation.	UVB induced phosphorylation of STAT1 (Ser727) in mouse epidermal JB6 Cl41 cells was observed.	Zykova *et al.* (2005)
35	Act as chemopreventive, natural healing and anti-aging agents for human skin.	Epidemiological studies on human.	Hsu *et al.* (2005)
36	Tea represents an important source of dietary antioxidants.	Healthy and obese people tested for reactive oxygen species (ROS) production. Inflammatory marker: CRP, estimated. *in vitro* studies of human neutrophils also made.	Zieliñska-Przyjemska and Dobrowolska -Zachwieja (2005)
37	Heteroactivation of cytochrome P450 1A1 occurs by teas and tea polyphenols. A crude extract of black tea polyphenols inhibited 7-ethoxyresorufin deethylase.	7-ethoxyresorufin deethylase as an index of cytochrome P4501A1 (CYP1A1) activity in liver microsomes from rats pretreated with 3-methylcholanthrene.	Anger *et al.* (2005)
38	Tea extracts, particularly Darjeeling tea extract, are effective in counteracting the clastogenicity (chromatid breaks, in particular) of the most potent form of As, sodium arsenite.	Chinese hamster v79 cells	Sinha *et al.* (2005)
39	Inhibit multidrug resistance(MDR) in *Staphylococcus aureus.*	*Staphylococcus aureus*	Gibbons *et al.* (2004)
40	Inhibit of P-glycoprotein (P-gp) in multidrug-resistant P-gp overexpressing cells.	KB-C2 cells	Kitagawa *et al.* (2004)
41	Have trypanocidal action against trypomastigote and amastigote forms and inhibit arginine kinase enzyme activity.	Blood of infected BALB/c mice [parasite is *Trypanosoma cruzi.*]	Paveto *et al.* (2004)
42	Have antiproliferative activity and prevents hepatotoxicity. Long-term intake of Catechins is beneficial against lipid and glucose metabolism disorders	Hepatoma cells and hepatoma-treated rats.	Crespy and Williamson (2004)
43	Green tea has protective effect on adenomatous polyps and chronic atrophic gastritis formations.	Epidemiological studies of green tea consumption in relation to gastrointestinal cancer.	Borrelli *et al.* (2004)
44	Lower risk of simple infections, like bacterial and viral, to chronic debilitating diseases, including cancer, coronary heart disease, stroke and osteoporosis.	Epidemiological studies, *in vitro* as well as *in vivo*, on human.	Siddiqui *et al.* (2004)
45	Has inhibitory effects on the production of a virulence factor of the periodontal-disease-causing anaerobic bacterium *Porphyromonas gingivalis*	*Porphyromonas gingival*	Sakanaka and Okada (2004)
46	Act as reactive oxygen species scavengers (antioxidant activity) and act as protective agent against oxidative DNA damage in animal models	Human and animal models	Higdon and Feri (2003)
47	Act as inhibitor of BACE1 activity in non-competitive manner with a substrate in Dixon plots.	BACE1{ beta-secretase} activity assay	Jeon *et al.* (2003)
48	Cytotoxic to breast cancer cells, thus have potential in the treatment of breast cancer.	Human and rodents breast cancer cells *in vitro*	Rosengren (2003)
49	Help in inhibition of cancer cell proliferation and of a cancer specific oxidase(ECTO-NOX).	Cultured HeLa cells (NADH oxidase {ECTO-NOX} activity assay)	Morré *et al.* (2003)
50	Inhibit carcinogen-induced increases in the oxidized DNA base, 8-hydroxy-2'-deoxyguanosine *in vivo*.	Animal models of skin, lung, colon, liver, pancreatic cancer and atherosclerosis	Frei and Higdon (2003)

Table 1: Continued

S. No.	Properties	Model used	References
51	Promotes health and reduce disease occurrence and possibly protect against Parkinson's disease and other neurodegenerative diseases.	Cell cultures and animal models	Pan *et al.* (2003)
52	Demonstrate cancer preventive activity.	Cell cultures and animal models	Lambert and Yang (2003)
53	Inhibit the development of prostate and breast cancer, exhibiting antioxidant and anticarcinogenic activities.	Epidemiological studies on human and animal studies.	González de Mejía. (2003)
54	Protect the cells from arsenic induced cytotoxicity.	Chinese hamster V-79 cells in culture.	Sinha *et al.* (2003)
55	Act as a biological antioxidant in a cell culture experimental model and protect cells from oxidative stress-induced toxicity.	Cultured rat calvarial osteoblasts. Oxidative stress was induced in cultured osteoblasts, either by adding H_2O_2 or by the action xanthine oxidase (XO) in the presence of xanthine.	Park *et al.* (2003)
56	Act as a biological antioxidant and protect veins from oxidative stress-induced toxicity.	Human saphenous veins. Oxidative stress was induced exogenously in the vein segments, either by adding H_2O_2, or by using of xanthine oxidase in the presence of xanthine.	Han *et al.* (2003)
57	Have anti-diabetic activity and have role in reducing oxidative stress in experimental diabetes.	Murine model	Sabu *et al.* (2002)
58	Have antioxidant activity.	Murine model	Ioannides and Yoxall (2003)
59	Tea polyphenols could play a role in the pathogenesis of cancer and heart disease.	Epidemiological and clinical studies of human.	McKay and Blumberg (2002)
60.	The polyphenols of green tea cause the strong inhibition of some gelatinase activities	Rainbow trout gelatinase activities	Saito *et al.* (2002v)
61	Green tea extract show direct scavenging activity against NO and O(2)(-) and green tea tannin mixture, at the same concentration, showed high scavenging activity.	A nitric oxide (NO) and superoxide (O_2^-)) generating system *in vitro*	Nakagawa and Yokozawa (2002)
62	Black, green and oolong teas were all shown to increase insulin activity. Thus, tea contains *in vitro* insulin-enhancing activity and the predominant active ingredient is epigallocatechin gallate.	Mammalian epididymal fat cell assay *in vitro.*	Anderson and Pallansky (2002)
63	The greater inhibitory potency of tea in the *Salmonella* assay might be related to the relative levels of the nine major constituents, perhaps acting synergistically with other (minor) constituents, to inhibit mutagen activation as well as scavenging the reactive intermediate(s).	*Salmonella* assay, using rat liver in the presence of S9.	Santana-Rios *et al.* (2001)
64	Green tea has preventive effects on both chronic inflammatory diseases and lifestyle-related diseases (including cardiovascular disease and cancer), resulting in prolongation of life span.	TNF-alpha-deficient mice and TNF-alpha transgenic mice, which overexpress TNF-alpha only in the lungs.	Sueoka *et al.* (2001)
65	Inhibits breast cancer and endothelial cell proliferation.	Breast cancer growth and endothelial cells in *in vitro* assays and in animal models.	Sartippour *et al.* (2001)
66	Inhibit cell proliferation and induce apoptosis.	NNK-induced lung tumorigenesis mice model.	Yang *et al.* (2000)
67	Treatment of human skin with varying doses of GTP (1-4 mg/2.5 cm^2 of skin area) before a single dose of UVB exposure decreased dose dependently the formation of UVB-induced CPDs in both epidermis and dermis.	Mouse models of photocarcinogenesis	Katiyar *et al.* (2000a)
68	Posses anti-inflammatory and anticarcinogenic potential, which can be exploited against a variety of skin disorders.	Chemical carcinogenesis and photocarcinogenesis in murine skin.	Katiyar *et al.* (2000b)
69	Possess antimutagenic/antioxidant activity	Modified Ames tests, superoxide scavenging assays and assays for protection against DNA scission used.	Pillai *et al.* (1999)

Table 2: Studies carried out on Epigallocatechin-3-gallate (-)-EGCG

S. No.	Properties	Model used	References
1	Act as an anti-oxidant and anti-inflammatory agent for cardiovascular protection.	Animal and human epidemiological studies	Tipoe *et al.* (2007)
2	Inhibits cell cycle and induces apoptosis in pancreatic cancer.	Human pancreatic cancer cells.	Shankar *et al.* (2007b)
3	Reduces autoimmune symptoms in a murine model for human Sjogren's syndrome, through activation of MAPK elements and protect human salivary acinar cells from TNF-alpha-induced cytotoxicity.	The NOD mouse, a model for human Sjogren's syndrome (SS).	Hsu *et al.* (2007a)
4	Inhibits SMC-ECM interaction and the action mechanisms are through interference with SMC's integrin beta1 receptor and binding to extracellular matrix (ECM) proteins.	Rat vascular smooth muscle cell (SMCs) adhesion and migration experiment on collagen and laminin.	Lo *et al.* (2007)
5	Combined inhibitory effects of (-)-EGCG and NS-398, a selective cyclooxygenase-2 inhibitors, occurs on the growth of human prostate cancer cells both *in vitro* and *in vivo*.	Human prostate cancer cells LNCaP, PC-3 and CWR22Rnu1 and *in vivo*, athymic nude mice implanted with androgen-sensitive CWR22Rnu1 cells.	Adhami *et al.* (2007)
6	Protective effect when applied topically before UVA exposure. No benefit was detected when EGCG was applied after UV exposure.	12-week-old Wistar albino rats.	Sevin *et al.* (2007)
7	Catechin and (-)-EGCG treated collagen exhibited 56 and 95% resistance, respectively, against collagenolytic hydrolysis by collagenase..	Assay of collagenolytic activity by collagenase.	Madhan *et al.* (2007)
8	(-)-EGCG in green tea polyphenols (GTP) is the most potent chemopreventive agent that can induce apoptosis, suppress the formation and growth of human cancers including colorectal cancers (CRC).	Epidemiological and laboratory studies.	Kumar *et al.* (2007)
9	Functions as prooxidants to activate oxidative-stress-responsive transcription factors in yeasts.	*Saccharomyces cerevisiae* *Schizosaccharomyces pombe* under weak alkaline conditions.	Maeta *et al.* (2007)
10	Prevents UVB-induced skin tumor development in mice.	UVB-induced skin tumor in mice.	Katiyar *et al.* (2007)
11	Induces caspase 14 in epidermal keratinocytes via MAPK pathways and reduces psoriasiform lesions in the flaky skin mouse model.	Normal human epidermal keratinocytes (NHEK) and flaky skin mouse model.	Hsu *et al.* (2007b)
12	(-)-EGCG, when was included in the incubation with vitamin E or C, more antioxidant activities were consistently observed than when vitamins were added alone.	Human intestinal $CaCO_2$ cells	Intra and Kuo (2007)
13	Improves endothelial function and insulin sensitivity, reduces blood pressure and protects against myocardial I/R injury in SHR.	Spontaneously hypertensive rats (SHR; model of metabolic syndrome with hypertension, insulin resistance and overweight).	Potenza *et al.* (2007)
14	Inhibits proliferation of human breast cancer cells *in vitro* and *in vivo* and also found to induce apoptosis and inhibit the proliferation when the tumor tissue sections were examined by immunohistochemistry.	*In vitro* cell culture models and *in vivo* athymic nude mice models of breast cancer.	Thangapazham *et al.* (2007)
15	The antibacterial activity of (-)-EGCG was enhanced in the presence of ascorbic acid and ascorbic acid was the most effective for retaining the concentration of stable EGCG.	Methicillin-resistant Staphylococcus aureus (MRSA).	Hatano *et al.* (2007)
16	(-)-EGCG treatment reduces expression of two integrins (alpha5 and beta3) and a chemokine (MCP1), resulting in a lower adhesion of mast cells associated with a decreased potential to produce signals eliciting monocyte recruitment.	Human mast cell line HMC-1.	Melgarejo *et al.* (2007)
17	(-)-EGCG treatment inhibited the hyphal formation from the yeast form of C. albicans, causing growth-inhibition of the candidal cells and there occurs synergic anticandidal effect of EGCG combined with amphotericin B.	Murine model of disseminated candidiasis caused by *Candida albicans*.	Han (2007)
18	(-)-EGCG inhibited early but not late stage PCa.	Male TRAMP (Transgenic Adenocarcinoma Mouse Prostate)	Harper *et al.* (2007)
19	(-)-EGCG can induce apoptosis of MKN45 cells in time- and dose-dependent manner. The apoptotic pathway triggered by EGCG in MKN45 is mitochondrial-dependent.	Human gastric cancer cell line MKN45.	Ran *et al.* (2007)

Table 2: Continued

S. No.	Properties	Model used	References
20	(-)-EGCG treatment causes mice survival rates increased from 11% to 60%, while parasitemia diminished to 50%. The treatment also produced oligosomal fragmentation of epimastigotes DNA, suggesting a programmed cell death (PCD)-like process.	*Trypanosoma cruzi* epimastigote form and murine model of acute Chagas' disease.	Güida *et al.* (2007)
21	Inhibition of tumorigenesis in ApcMin/+ mice occurs by a combination of (-)-EGCG and fish oil.	Apc (Min/+) mice	Bose *et al.* (2007)
22	(-)-EGCG treatment protects against glyceraldehyde-derived advanced glycation endproducts (AGE)-induced neurotoxicity.	Neuron cells	Lee and Lee (2007)
23	(-)-EGCG presynaptically facilitates Ca2+-dependent glutamate release via activation of protein kinase C in rat cerebral cortex	Nerve terminals purified from rat cerebral cortex.	Chou *et al.* (2007)
24	(-)-EGCG has a preventive effect on the growth and liver and pulmonary metastases of orthotopic colon cancer in nude mice and this anticancer effect could be partly caused by activating the	Colon tumor implanted orthotopically in the cecum of nude mice.	Yuan *et al.* (2007)
25	Nrf2-UGT1A signal pathway. Exhibition of antioxidative-iron chelating activities of (-)-EGCG underlying its neuroprotective/ neurorescue mechanism of action, further suggesting a potential neurodegenerative-modifying effect for EGCG.	Human SH-SY5Y neuroblastoma cells.	Weiureb *et al.* (2007)
26	(-)-EGCG inhibits the binding of epidermal growth factor EGF to the EGFR and the subsequent dimerization and activation of the EGFR by altering membrane organization.	HT29 colon cancer cells.	Adachi *et al.* (2007)
27	(-)- EGCG suppresses expression of receptor activator of NF-kappaB ligand (RANKL), which indicated an inflammation suppression effect of EGCG in osteomyelitis treatment.	Osteoblast-like NRG cells infected with *Staphylococcus aureus.*	Ishida *et al.* (2007)
28	The O-acyl derivatives of (-)-EGCG have the potential to be developed as cancer chemopreventive agents.	7,12-dimethylbenz[a]anthracene (DMBA)/12-O-tetradecanoylphorbol 13-acetate (TPA)--induced cancer in Swiss albino mice.	Vyas *et al.* (2007)
29	Cells treated with a combination of bicalutamide and (-)- EGCG also demonstrate a dose-dependent decrease in cell number, growth arrest and apoptosis in prostate epithelial cells, that was significantly greater than bicalutamide alone.	NRP-152 and NRP-154 prostate epithelial cells.	Morrissey *et al.* (2007)
30	(-)- EGCG inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells. Activation of FOXO3a by	Human Small-cell lung carcinoma (SCLC) cells.	Sadava *et al.* (2007)
31	(-)- epigallocatechin-3-gallate induces estrogen receptor alpha expression reversing invasive phenotype of breast cancer cells.	Her-2/neu-driven mammary tumor cells.	Belguise *et al.* (2007)
32	(-)-EGCG functions as an antioxidant, preventing oxidative damage in healthy cells, but also as an antiangiogenic agent, preventing tumors from developing a blood supply needed to grow larger.	A comprehensive search of the PubMed database and other secondary data sources, regarding the chemopreventive potential of EGCG	Carlson *et al.* (2007)
33	(-)-EGCG improves systemic hemodynamics and survival in rodent models of polymicrobial sepsis.	Rodent model of polymicrobial sepsis.	Wheeler *et al.* (2007)
34	(-)-EGCG ameliorated histological changes and significantly suppressed collagen deposition in a dose-dependent manner. It also inhibits overexpression of TGF-beta1 and alpha-smooth muscle actin (a symbol of activation of pancreatic stellate cells).	Rat pancreatic fibrosis induced by diethyldithiocarbamate (DDC).	Meng *et al.* (2007)
35	(-)-EGCG suppresses heregulin-beta1-induced fatty acid synthase expression in human breast cancer cells by inhibiting phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase cascade signaling.	MCF-7 breast cancer cell line.	Pan *et al.* (2007)

Table 2: Continued

S. No.	Properties	Model used	References
36	(-)-EGCG acutely improves endothelial function in humans with coronary artery disease.	Patients with coronary artery disease examined for endothelial function and brachial artery flow-mediated dilation.	Widlansky *et al.* (2007)
37	(-)-EGCG caused a Ca(2+) influx into smooth muscle cells via VOCC (probably L-type) and other SKF-96365- and Cd(2+)-sensitive Ca(2+)-permeable channels.	Cultured rat aortic smooth muscle cells.	Campos-Toimil and Orallo (2007)
38	Administration of (-)-EGCG, selenium and thymoquinone, selenium suppress metabolic activity, alter behavioral responses and cause molecular damage in aggressive behavioral activity of ovarian carcinogenesis.	ES-2 ovarian cell line.	Wilson-Simpson *et al.* (2007)
39	O-acetylated (-)-EGCG analogs possessing a p-NH(2) or p-NHBoc (Boc; tert-butoxycarbonyl) D-ring (5 and 7) act as novel tumor cellular proteasome inhibitors and apoptosis inducers with potency similar to natural (-)-EGCG and similar to (-)-EGCG peracetate.	Molecule designed.	Osanai *et al.* (2007)
40	Peracetate-protected (-)-EGCG [Pro-EGCG] enhances levels of proteasome inhibition, growth suppression and apoptosis induction, compared with cells treated with natural (-)-EGCG.	Cultured human breast cancer MDA-MB-231 cells and MDA-MB-231 tumors induced in nude mice.	Landis-Piwowar *et al.* (2007)
41	(-)- EGCG significantly arrests progression of hepatic fibrosis and caused significant amelioration of liver injury (reduced activities of serum alanine aminotransferase and aspartate aminotransferase).	Rat model of hepatic fibrogenesis and cultured hepatic stellate cells (HSCs).	Zhen *et al.* (2007)
42	(-)-EGCG significantly inhibits, in a dose-dependent manner, the survival of osteoclasts differentiated from RAW 264.7 cells and induced the apoptosis, via caspase activation of osteoclasts.	Osteoclasts differentiated from RAW 264.7 cells.	Yun *et al.* (2007)
43	Intraperitoneal injection of EGCG inhibits the growth of gastric cancer by 60.4% by reducing VEGF production and angiogenesis.	Heterotopic tumors were induced in nude mice. by subcutaneously injection of SGC-7901 cells.	Zhu *et al.* (20007)
44	(-)-EGCG inhibits TPA-induced DNA binding of NF-kappaB and CREB by blocking activation of p38 MAPK, which may provide a molecular basis of COX-2 inhibition by EGCG in mouse skin *in vivo*.	Mouse skin *in vivo*.	Kundu and Surh (2007)
45	(-)- EGCG can induce apoptotic changes, including mitochondrial membrane potential changes and activation of c-Jun N-terminal kinase (JNK), caspase-9 and caspase-3.	Human MCF-7 cells.	Hsuuw and Chan (2007)
46	(-)- EGCG inhibits monocyte chemotactic protein-1 expression in endothelial cells via blocking NF-kappaB signaling.	MCP-1 in human endothelial ECV304 cells.	Hong *et al.* (2007)
47	(-)-EGCG has a stronger reactive oxygen species (ROS) scavenging activity than ascorbic acid.	Chemiluminescence analysis.	Tian *et al.* (2007)
48	(-)-EGCG inhibits extracellular signal-related kinases (ERK), activates AMP-activated protein kinase (AMPK), modulates adipocyte marker proteins and down-regulates lipogenic enzymes as well as other potential targets.	Epidemiological, adipocyte cell lines culture, animal and clinical studies.	Moon *et al.* (2007)
49	(-)-EGCG inhibited bladder carcinoma cell growth and suppressed the in vitro migration capacity of cells via downregulation of N-cadherin and inactivation of Akt signaling.	Human bladder carcinoma cells and mice bladder carcinoma xenografts *in vivo*.	Rieger-Christ *et al.* (2007)
50	(-)-EGCG inhibits prostaglandin D(2)-stimulated HSP27 induction via suppression of the p44/p42 MAP kinase pathway in osteoblasts.	Osteoblast-like MC3T3-E1 cells.	Yamauchi *et al.* (2007)
51	Single GUV method reveals interaction of tea catechin (-)-EGCG with lipid membranes.	Single giant unilamellar vesicles (GUVs) of lipid membranes of egg Phosphatidylcholine.	Tamba *et al.* (2007)
52	(-)-EGCG along with ethanol (EtOH) significantly prevents EtOH-dependent cell loss and lactate dehydrogenase leakage.	Human Chang liver cells.	Kaviarasan *et al.* (2007)

Table 2: Continued

S. No.	Properties	Model used	References
53	(-)-EGCG inhibits cardiac myocyte apoptosis and oxidative stress in pressure overload induced cardiac hypertrophy. Also, EGCG prevented cardiomyocyte apoptosis from oxidative stress *in vitro*.	Cardiac hypertrophy was established in rats.	Sheng *et al.* (2007)
54	(-)-EGCG enhances CD8+ T cell-mediated antitumor immunity induced by DNA vaccination.	Murine model.	Kang *et al.* (2007)
55	(-)-EGCG promotes the rapid protein kinase C- and proteasome-mediated degradation of Bad revealing a novel pathway in the neuroprotective mechanism of the action of EGCG.	Human neuroblastoma cell line SH-SY5Y.	Kalfon *et al.* (2007)
56	(-)-EGCG promoted hair growth in hair follicles *ex vivo* culture and the proliferation of cultured DPCs.	Human dermal papilla cells (DPCs) in vivo and *in vitro* and hair growth *in vitro*.	Kwon *et al.* (2007)
57	EGCG and epicatechin gallate inhibited lactate dehydrogenase suggesting that EGCG is effective in reducing acid production in dental plaque and mutans streptococci.	*Mutans streptococci*	Hirasawa *et al.* (2006)
58	(-)-EGCG has cancer chemoprevention, hypercholesterolemia, artherosclerosis, Parkinson's disease, Alzheimer's disease and other aging-related disorders.	Epidemiological, cell culture, animal and clinical studies.	Zaveri (2006)
59	Patients met criteria for partial response (PR) by standard response criteria. after self-initiating oral ingestion of (-)-EGCG containing products.	Four patients with low grade B-cell malignancies	Shanafelt *et al.* (2005)
60	Inhibition of catechol-O-methyltransferase (the enzyme that degrades norepinephrine) is a possible explanation for why the green tea extract is effective in stimulating thermogenesis by (-)-epigallocatechin gallate.	Epidemiological, cell culture, animal and clinical studies.	Shixian *et al.* (2006)
61	(-)-EGCG, the main polyphenol in green tea, binds to the T-cell receptor, CD4. Suggesting potential use of EGCG as adjunctive therapy in HIV-1 infection.	Human CD4+ T cells.	Williamson *et al.* (2006)
62	(-)-EGCG is a powerful antioxidant and when injected into the eye with SNP (sodium nitroprnsside) attenuates the detrimental influence of SNP to retinal photoreceptors.	*In vitro* studies on brain membranes (retina) and Electroretinogram (ERG).	Zhang and Osborne (2006)
63	(-)-EGCG mitigates neurotoxicity mediated by HIV-1 proteins gp120 and Tat in the presence of IFN-gamma, thus EGCG may represent a novel natural compound for the prevention and treatment of HIV-associated dementia (HAD).	Primary neurons in mice.	Giunta *et al.* (2006)
64	(-)-EGCG induced apoptosis in Sarcoma180 cells *in vivo*: mediated by p53 pathway and inhibition in U1B, U4-U6 UsnRNAs expression.	Swiss albino mice having inoculation of Sarcoma180 (S180) cells	Mauna *et al.* (2006)
65	The mechanisms of (-)- EGCG action, particularly the reduction of TNF-alpha are discussed and it is shown that the use of 3H-EGCG reveals a wide range of target organs for cancer prevention.	Epidemiological studies of human.	Fujiki (2005)
66	Mechanisms of cancer prevention by (-)-EGCG are not related to their redox properties, but are due to the direct binding of the polyphenol to target molecules, including the inhibition of selected protein kinases, matrix metalloproteinases and DNA methyltransferases.	Epidemiological, cell culture and animal studies.	Sang *et al.* (2005)
67	(-)-EGCG causes significant induction of cell cycle arrest and apoptosis of melanoma cells that is mediated via modulations in the cki-cyclin-cdk network and Bcl2 family proteins.	Human melanoma cell lines (A-375 amelanotic malignant melanoma and Hs-294T metastatic melanoma) and normal human epidermal melanocytes (NHEM).	Nihal *et al.* (2005)
68	(-)-EGCG selectively inhibits COX-2 without affecting COX-1 expression in human prostate carcinoma cells.	Androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells.	Hussain *et al.* (2005)
69	The inhibition of S. maltophilia dihydrofolate reductase by (-)-EGCG is related to its antifolate activity.	18 isolates of *Stenotrophomonas maltophilia*.	Navarro-Martínez *et al.* (2005)

Table 2: Continued

S. No.	Properties	Model used	References
70	Inhibition of dihydrofolate reductase (DHFR) occurs by EGCG and this explains why tea extracts have been traditionally used in alternative medicine as anticarcinogenic/antibiotic agents or in the treatment of conditions such as psoriasis.	Chicken, bovine liver dihydrofolate reductase (DHFR).	Navarro-Perán *et al.* (2005)
71	(-)-Epigallocatechin gallate attenuates the neuronal NADPH-d/nNOS expression in the nodose ganglion of acute hypoxic rats suggesting that it may attenuate the oxidative stress following acute hypoxia.	Ganglionic neurons of the nodose ganglion (NG) in acute hypoxic rats.	Wei *et al.* (2004)
72	(-)-EGCG suppressed neutrophil infiltration by a direct action on neutrophils	Rat neutrophils *in vitro* and *in vivo*.	Takano *et al.* (2004)
73	Generation of hydrogen peroxide primarily contributes to the induction of Fe(II)-dependent apoptosis in Jurkat cells by (-)-EGCG.	Human T-cell acute lymphoblastic leukemia Jurkat cells.	Nakagawa *et al.* (2004)
74	Epigallocatechin-3 gallate inhibits Her-2/neu signaling, proliferation and transforms phenotype of breast cancer cells.	Her-2/neu-overexpressing breast cancer cells	Pianetti *et al.* (2002)

Table 3: Studies carried out on Epicatechin or Epicatechin gallate (ECG)

S. No.	Properties	Model used	References
1	ECG attenuates UVB-induced keratinocyte death dose-dependently. ECG markedly inhibits UVB-induced cell membrane lipid peroxidation and H_2O_2 generation in keratinocytes, suggesting that ECG can act as a free radical scavenger when keratinocytes are photodamaged.	HaCaT keratinocytes.	Huang *et al.* (2007)
2	Sensitizes meticillin-resistant Staphylococcus aureus (MRSA) to beta-lactam antibiotics, promotes staphylococcal. Thus, Epicatechin gallate -mediated alterations to the physical nature of the bilayer will elicit structural changes to wall teichoic acid that result in modulation of the cell-surface properties necessary to maintain the beta-lactam-resistant phenotype.	Methicillin-resistant *Staphylococcus aureus* (MRSA).	Stapleton *et al.* (2007)
3	Green tea catechin (-)-epicatechin gallate induces tumour suppressor protein ATF3 via EGR-1 activation. Thus, EGR-1, a tumour suppressor protein, could substantiate ECG's role of ATF3 expression in human colorectal cancer cells.	HCT-116 cells.	Cho *et al.* (2007)
4	*In vitro* cytotoxicity exhibited by (-)-catechin gallate, similar to its epimer, Epicatechin gallate and both exhibited antiproliferative effects. CG-induced apoptosis was detected.	Cells derived from tissues of the human oral cavity.	Babich *et al.* (2007)
5	Epicatechin gallate reduces halotolerance in *Staphylococcus aureus*. Thus, this molecule can be used to aid the preservation of salt-containing foods.	*Staphylococcus aureus* grown in the presence of high-salt concentrations.	Stapleton *et al.* (2006)
6	Tea flavan-3-ol gallate esters (i.e. ECG, EGCG) and gallic acid inhibits apoptotic events induced by Abeta-derived peptides, exhibiting neuroprotective effects of catechin gallate esters against beta-amyloid-induced toxicity.	Primary cultures of rat hippocampal cells.	Bastianetto *et al.* (2006)
7	Epicatechin gallate and catechin gallate have capacity to reverse oxacillin resistance in the homogeneous PBP2a producer BB568 and in EMRSA-16.	Methicillin-resistant *Staphylococcus aureus* (MRSA).	Stapleton *et al.* (2004)
8.	Catechin gallates inhibit multidrug resistance (MDR) in *Staphylococcus aureus*.	A wild-type and three multidrug-resistant (MDR) strains of *Staphylococcus aureus*.	Gibbons *et al.* (2004)

Table 4: Studies carried out on Theaflavins and thaernbigins (black tea polyphenols)

S. No.	Properties	Model used	References
1	Theaflavins attenuate hepatic lipid accumulation through activating AMPK in human HepG2 cells, suggesting that theaflavins may be active in the prevention of fatty liver and obesity.	Human HepG2 cells culture and animal experimental model	Lin *et al.* (2007)
2	Black tea polyphenols mimic insulin/insulin-like growth factor-1 signalling to the longevity factor FOXO1a.	Mammalian cell culture.	Cameron *et al.* (2007)

Table 4: Continued

S. No.	Properties	Model used	References
3	A significant decrease in both chromosomal aberrations (CA) and micronuclei formation (MN) were observed in the human lymphocyte cultures treated with either theaflavins and thearubigins.	Human lymphocytes *in vitro*. Mutagens/carcinogens used are benzo[a]pyeme (B[a]P) and aflatoxin B1(AFB1) with S9 activation.	Halder *et al.* (2006)
4	The theaflavin fraction (Tfs) produced a concentration- dependent effect on the contractile mechanism of skeletal muscle and that calcium and nitric oxide may modulate this action of Tfs.	Murine skeletomotor apparatus.	Basu *et al.* (2005)
5	Antioxidative properties of black tea are manifested by its ability to inhibit free radical generation, scavenge free radicals and chelate transition metal ions. Black tea, as well as individual theaflavins, can influence activation of transcription factors such as NFkappaB or AP-1. Theaflavins have also been proved to inhibit the activity of prooxidative enzymes such as xanthine oxidase or nitric oxide synthase.	Epidemiological studies, *in vitro* as well as *in vivo*.	Łuczaj and Skrzydlewska (2005)
6	Both the active polyphenols theaflavins and thearubigins extracted from the black tea (World blend) also showed significant antimutagenic effects against known positive compounds in these strains.	*Salmonella* strains TA97a, TA98, TA100 and TA102 in preincubation tests, both with and without S9 activation.	Gupta *et al.* (2002a)
7	Black tea active polyphenols theaflavins (TF) and thearubigins (TR) have significant anticlastogenic effects in bone marrow cells of mice.	Swiss albino mice measuring chromosome aberrations (CA) and sister chromatid exchanges (SCE).	Gupta *et al.* (2002b)
8	Theaflavin-3,3'-digallate from black tea blocks the nitric oxide synthase by down-regulating the activation of NF-kappaB in macrophages. Gallic acid moiety of theaflavin-3,3'-digallate is essential for their potent anti-inflammation activity.	Lipopolysaccharide-activated murine macrophages, RAW 264.7 cells	Lin *et al.* (1999)

uPA, IGF-1, EGFR, cell cycle regulatory proteins and inhibits NFk B, PI3-K/Akt, Ras/Raf/MAPK and AP-1 signaling pathways, thereby causing strong cancer chemopreventive effects (Shankar *et al*., 2007a). (-) -EGCG revealed a wide range of target organs for cancer prevention (Fujiki, 2005). Both (-)-epigallocatechin-3-gallate and theaflavin-3,3'-digallate (major green and black tea polyphenols, respectively) inhibit the phosphorylation of c-jun and p44/42 (ERK 1/2). The galloyl structure on the B ring and the gallate moiety are important for the inhibition (Yang *et al*., 2000). Most of the relevant mechanisms of cancer prevention by tea polyphenols are not related to their redox properties, but are due to the direct binding of the polyphenol to target molecules, including the inhibition of selected protein kinases, matrix metalloproteinases and DNA methyltransferases. It has been shown that, through several mechanisms, tea polyphenols present antioxidant and anticarcinogenic activities, thus affording several health benefits (González de Mejia, 2003). Animal studies offer a unique opportunity to assess the contribution of the antioxidant properties of tea and tea polyphenols to the physiological effects of tea administration in different models of oxidative stress. Most promising are the consistent findings in animal models of skin, lung, colon, liver and pancreatic cancer that tea and tea polyphenol administration inhibit carcinogen-induced increases in the oxidized DNA base (Frei and Higdon, 2003). Green tea polyphenols and EGCG treatment were also found to induce apoptosis and inhibit the proliferation when the tumor tissue sections were examined by immunohistochemistry (Thangapazham *et al*., 2007). It has been confirmed by various techniques that EGCG inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells (Sadava *et al*., 2007). EGCG may be useful in the chemoprevention of breast carcinoma in which fatty acid synthase (FAS) overexpression results from human epidermal growth factor receptor (HER2 or/and HER3 signaling) (Pan *et al*., 2007). EGCG inhibits the growth of gastric cancer by reducing VEGF production and angiogenesis and is a promising candidate for anti-angiogenic treatment of gastric cancer (Zhu *et al*., 2007). EGCG inhibited the *in vitro* growth of invasive bladder carcinoma cells and decreases the migratory potential of bladder carcinoma cells (Rieger-Christ *et al*., 2007). Black tea polyphenols, theaflavins may have a major impact on the chemoprevention of oral cancer, than the green tea polyphenols (Chandra and Mohan, 2006). EGCG has a preventive effect on the growth of liver and pulmonary metastases of orthotopic colon cancer in nude mice and this anticancer effect could be partly caused by activating the Nrf2-UGT1A signal pathway (Yuan *et al*., 2007). The inhibitory effect of (-)-EGCG on activation of the epidermal growth factor receptor is associated with altered lipid

order in HT29 colon cancer cells (Adachi *et al*., 2007). Activation of Forkhead box O transcription factor (FOXO3a) by the green tea polyphenol epigallocatechin-3-gallate induces estrogen receptor alpha expression reversing invasive phenotype of breast cancer cells (Belguise *et al*., 2007). (-)-EGCG inhibits Her-2/neu signaling, proliferation and transformed phenotype of breast cancer cells (Pianetti *et al*., 2002).

Skin and tea polyphenols: The outcome of the several experimental studies suggests that green tea possess anti-inflammatory and anticarcinogenic potential, which can very well be exploited against a variety of skin disorders (Katiyar *et al*., 2000b, 2001). Green tea polyphenols act as chemopreventive, naturally healing and anti-aging agents for human skin (Hsu, 2005). (-)- EGCG is the major and most photoprotective polyphenolic component of green tea (Katiyar *et al*., 2007). The inhibition of UV light-induced DNA damage in the form of cyclobutane pyrimidine dimers (CPDs) in the skin by green tea polyphenols treatment may, at least in part, be responsible for the inhibition of photocarcinogenesis (Katiyar *et al*., 2000a) (Table 1). Green tea polyphenol induces caspase 14 in epidermal keratinocytes via MAPK pathways and reduces psoriasiform lesions in the flaky skin mouse model (Hsu *et al*., 2007b). Signal transducers and activators of transcription (STATs) play a critical role in signal transduction pathways. Phosphorylation of STAT1 (Ser727) occurs through PI-3K, ERKs, p38 kinase, JNKs, PDK1 and p90RSK2 in the cellular response to UVB. The aflavins and EGCG show an inhibitory effect on UVB-induced STAT1 (Ser727), ERKs, JNKs, PDK1 and p90RSK2 phosphorylation (Zykova *et al*., 2005). EGCG inhibits 12-O-tetradecanoylphorbol-13-acetate (TPA) induced DNA binding of NF-kappaB and CREB by blocking activation of p38 MAPK, which may provide a molecular basis of COX-2 inhibition by EGCG in mouse skin *in vivo* (Kundu and Surh, 2007). ECG dose-dependently attenuates UVB-induced keratinocyte death. Moreover, ECG markedly inhibited UVB-induced cell membrane lipid peroxidation and H2O2 generation in keratinocytes, suggesting that ECG can act as a free radical scavenger when keratinocytes were photodamaged (Huang *et al*., 2007). EGCG prevents UVB-induced skin tumor development in mice and this prevention is mediated through: (a) the induction of immunoregulatory cytokine interleukin (IL) 12; (b) IL-12-dependent DNA repair following nucleotide excision repair mechanism; (c) the inhibition of UV-induced immunosuppression through IL-12-dependent DNA repair; (d) the inhibition of angiogenic factors and (e) the stimulation of cytotoxic T cells in a tumor microenvironment (Katiyar *et al*., 2007).

Antioxidant effects of tea: (-)-Epigallocatechin-gallate ((-)-EGCG) and (-)-epicatechin-gallate ((-)-ECG) exhibit antioxidant behaviour (Ryan and Hynes, 2007). Epicatechins in green tea and theaflavins in black tea were found to be able to reduce the concentration of Reactive alpha-dicarbonyl compounds in physiological phosphate buffer conditions (Lo *et al*., 2006). Tea polyphenols act as antioxidants in vitro by scavenging reactive oxygen and nitrogen species and chelating redox-active transition metal ions (Lo *et al*., 2006). They may also function indirectly as antioxidants through 1) inhibition of the redox-sensitive transcription factors, nuclear factor-kappaB and activator protein-1; 2) inhibition of pro-oxidant enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases and xanthine oxidase and 3) induction of phase II and antioxidant enzymes, such as glutathione S-transferases and superoxide dismutases (Frei and Higdon, 2003). White tea, having high levels of epigallocatechin-3-gallate (EGCG) and several other polyphenols than green tea has greater antimutagenic activity in comparison with green tea, perhaps due to synergistic action of major constituents or polyphenols with other (minor) constituents, to inhibit mutagen activation as well as scavenging the reactive intermediate(s) (Santana-Rios *et al*., 2001) (Table 1). Antioxidative properties of black tea are manifested by its ability to inhibit free radical generation, scavenge free radicals and chelate transition metal ions. Black tea, as well as individual theaflavins, can influence activation of transcription factors such as NFkappaB or AP-1. Theaflavins have been also proved to inhibit the activity of prooxidative enzymes such as xanthine oxidase or nitric oxide synthase (Luczaj and Skrzydlewska, 2005)(Table 4). Green tea polyphenols can act as a biological antioxidant in a cell culture experimental model and protect cells in culture (Park *et al*., 2003) and mammalian veins (Han *et al*., 2003) from oxidative stress-induced toxicity. Tea polyphenols also possess antimutagenic activity (Ioannides and Yoxall, 2003). This protective effect of black tea infusions may be due to the outcome of antioxidative influence of tea components (Sengupta *et al*., 2003). Measurement of protection against DNA scissions produce results that again show that EGCG produces the strongest protective effects. In scavenging assays using a xanthine-xanthine oxidase (enzymatic system), epicatechin gallate (ECG) shows the highest scavenging potential (Pillai *et al*., 1999). Compounds isolated from green tea tannin mixture show that (-)-epigallocatechin 3-O-gallate (EGCg), (-)-gallocatechin 3-O-gallate (GCg) and (-)-epicatechin 3-O-gallate (ECg) had higher scavenging activities than (-)-epigallocatechin (EGC), (+)-gallocatechin (GC), (-)-epicatechin (EC) and (+)-catechin (C), thus showing the

importance of the structure of flavan-3-ol linked to gallic acid for this activity (Nakagawa and Yokozawa, 2002). Tea catechins prevent the molecular degradation in oxidative stress conditions by directly altering the subcellular ROS production, glutathione metabolism and cytochrome P450 2E1 activity (Raza and John, 2007). Tea catechins and polyphenols are effective scavengers of reactive oxygen species *in vitro* and may also function indirectly as antioxidants through their effects on transcription factors and enzyme activities (Higdon, 2003). EGCG scavenged superoxide radical and H_2O_2 in a dose dependent manner. EGCG had protective effect on DNA at low concentrations (2-30 mM), but it enhanced the DNA oxidative damage at higher concentrations (>60 mM), exhibiting a prooxidant effect on DNA (Tian *et al*., 2007). EGCG may attenuate the oxidative stress following acute hypoxia (Wei *et al*., 2004). Various age related diseases owing to free radical injury in the human body like arthritis etc. have been shown to be prevented by tea polyphenols *in vivo* (Haqqi *et al*., 1999).

Tea and cardiovascular health: Green tea is proposed to be a dietary supplement in the prevention of cardiovascular diseases in which oxidative stress and proinflanımation are the principal causes (Tipoe *et al*., 2007). Clinical trials employing putative intermediary indicators of the disease, particularly biomarkers of oxidative stress status, suggest tea polyphenols could play a very important role in the pathogenesis of cancer and heart disease (McKay and Blumberg, 2002). Green tea and its catechins may reduce the risk of Coronary Heart Disease (CHD) by lowering the plasma levels of cholesterol and triglyceride. Studies indicate that green tea catechins, particularly (-)-epigallocatechin gallate, interfere with the emulsification, digestion and micellar solubilization of lipids, the critical steps involved in the intestinal absorption of dietary fat, cholesterol and other lipids (Koo and Noh, 2007) (Table 2). Continuous ingestion of green tea catechins from an early age prevents the development of spontaneous stroke in malignant stroke-prone spontaneously hypertensive rats (M-SHRSP), probably by inhibiting the further development of high blood pressure at later ages (Ikeda *et al*., 2007). EGCG, improves endothelial function and insulin sensitivity, reduces blood pressure and protects against myocardial ischemia-reperfusion (I/R) injury in spontaneously hypertensive rats (Potenza *et al*., 2007). Catechin (GCg or EGCg), like the nitric oxide (NO) donor, may have a therapeutic use as an NO-mediated vasorelaxant and may have an additional protective action in myocardial ischemia-reperfusion induced injury (Hotta *et al*., 2006) (Table 3). Tea catechins with a galloyl moiety suppress postprandial hypertriacylglycerolemia by delaying lymphatic transport of dietary fat in rats and also because postprandial hypertriacylglycerolemia is a risk factor for coronary heart disease, it is suggested suggest that catechins with a galloyl moiety may prevent this disease (Ikeda *et al*., 2005). Acute EGCG supplementation reverses endothelial dysfunction in patients with the coronary artery disease (Widlansky *et al*., 2007).

Tea and apoptosis: (-)-EGCG induces growth arrest and apoptosis through multiple mechanisms and can be used for cancer prevention, mainly pancreatic (Shankar *et al*., 2007b). EGCG could induce apoptosis *in vivo* in Sarcoma 180 cells through alteration in G2/M phase of the cell cycle by up-regulation of p53, bax and down-regulation of c-myc, bcl-2 and U1B, U4-U6 UsnRNAs (Manna *et al*., 2006) (Table 2). EGC inhibits DNA replication and consequently induces leukemia cell apoptosis (Smith and Dou, 2001). EGCG can induce apoptosis of the human gastric cancer cell line MKN45 and the effect is in a time- and dose-dependent manner. The apoptotic pathway triggered by EGCG in MKN45 is mitochondrial-dependent (Ran *et al*., 2007). The O-acetylated (-)-EGCG analogs possessing a p-NH(2) or p-NHBoc (Boc; tert-butoxycarbonyl) D-ring (5 and 7) act as novel tumor cellular proteasome inhibitors and apoptosis inducers with potency similar to natural (-)-EGCG and similar to (-)-EGCG peracetate (Osanai *et al*., 2007). (-)-EGCG might prevent alveolar bone resorption by inhibiting osteoclast survival through the caspase-mediated apoptosis (Yun *et al*., 2007). EGCG treatment has a dose-dependent effect on ROS generation and intracellular ATP levels in MCF-7 cells, leading to either apoptosis or necrosis and that the apoptotic cascade involves JNK activation, Bax expression, mitochondrial membrane potential changes and activation of caspase-9 and caspase-3 (Hsuuw and Chan, 2007). Interesting results has been obtained in a study that EGCG inhibits cardiac myocyte apoptosis and oxidative stress in the pressure overload induced cardiac hypertrophy. Also, EGCG prevents cardiomyocyte apoptosis from oxidative stress *in vitro*. The mechanism may be related to the inhibitory effects of EGCG on p53 induction and bcl-2 decrease (Sheng *et al*., 2007). EGCG induces apoptosis in human prostate carcinoma cells by shifting the balance between pro- and antiapoptotic proteins in favor of apoptosis (Hastak *et al*., 2003). Tea catechins have ability to produce H_2O_2 and that the resulting increase in H_2O_2 levels triggers Fe(II)-dependent formation of highly toxic hydroxyl radical, which in turn induces apoptotic cell death (Nakagawa *et al*., 2000).

Anti-microbial effects of tea: Green tea catechins ECG, CG and EGCG increase the sensitivity of methicillin-resistant *Staphylococcus aureus* (EMRSA-15) to oxacillin (Table 1-3). The gallate moiety was essential for the oxacillin-modulating activity of (-)- ECG (Stapleton *et al*., 2004). (-)-ECG alters the architecture of the cell wall of *Staphylococcus aureus* causing beta-lactam-resistance modification (Stapleton *et al*., 2007). Catechin gallates inhibit multidrug resistance (MDR) in *Staphylococcus aureus* (Gibbons *et al*., 2004) (-)-ECG also reduces halotolerance in *Staphylococcus aureus* suggesting that this molecule can be used to aid the preservation of salt-containing foods (Stapleton *et al*., 2006) (Table 3). Crude extract of green tea as well as two of its main constituents, EGCG and ECG, strongly inhibit *Plasmodium falciparum* growth in vitro (Sannella *et al*., 2007). Green tea catechins inhibit bacterial DNA gyrase by interaction with its ATP binding site (Gradisar *et al*., 2007). EGCG is effective in reducing acid production in dental plaque and mutans *Streptococci*. EGCG and epicatechin gallate inhibits lactate dehydrogenase activity much more efficiently than epigallocatechin, epicatechin, catechin or gallocatechin. (Hirasawa *et al*., 2006). The 3-galloyl group of catechin skeleton plays an important role on the observed antiviral activity against influenza virus (Song *et al*., 2005). Green tea catechins have been found to exhibit anti-*Trypanosoma cruzi* activity, suggesting that these compounds could be used to sterilize blood and, eventually, as therapeutic agents for Chagas disease (Paveto *et al*., 2004). EGCG has anticandidal activity causing blockage of the hyphal formation and has the synergism combined with Amp B against disseminated candidiasis (Han, 2007). EGCG has potential use as adjunctive therapy in HIV-1 infection owing to its binding to the T-cell receptor, CD4 (Williamson *et al*., 2006).Tea catechins possess antifolate activity also (Navarro-Perán *et al*., 2005). EGCG exhibit antifolate activity against *Stenotrophomonas maltophilia* (Navarro-Martínez *et al*., 2005).

Tea consumption and weight loss: Molecular mechanisms of fatty acid synthase gene suppression by tea polyphenols (EGCG, theaflavins) may bring down-regulation of EGFR/PI3K/Akt/Sp-1 signal transduction pathways, suggesting hypolipidemic and anti-obesity effects of tea and tea polyphenols (Lin and Lin-Shiau, 2006) (Table 1). Green tea extract intake is associated with increased weight loss due to diet-induced thermogenesis, which is generally attributed to the catechin epigallocatechin gallate (Shixian *et al*., 2006).

Neuroprotective effect of tea: Green tea polyphenols have demonstrated neuroprotectant activity in cell cultures and animal models, such as the prevention of neurotoxin-induced cell injury (Pan *et al*., 2003). Recent findings from *in vivo* and *in vitro* studies concerning the transitional metal (iron and copper) chelating property of green tea and its major polyphenol, (-)-epigallocatechin-3-gallate, suggests its potential role in the treatment of neurodegenerative diseases (Mandel *et al*., 2006) (Table 2). EGCG may exhibit protective effects against advanced glycation endproducts (AGEs) induced injury in neuronal cells, through its antioxidative properties, as well as by interfering with AGEs-AGE receptor (RAGE) interaction mediated pathways, suggesting a beneficial role for this tea catechin against neurodegenerative diseases (Lee and Lee, 2007). Catechin gallates (through the galloyl moiety) contribute to the neuroprotective effects of both green and black teas.Not only green but also black teas may reduce age-related neurodegenerative diseases, such as Alzheimer's disease (Bastianetto *et al*., 2006).

CONCLUSION

Animal and *in vitro* studies have provided evidence that the polyphenols found in tea may inhibit tumorigenesis in many animal models, including those for cancer of the skin, lung, oral cavity, oesophagus, stomach, small intestine, colon, liver, pancreas, bladder and prostate. The suggested mechanism of action includes the following:

- Antioxidant activity and scavenging free radicals
- Modulating enzymes implicated in the carcinogenic process
- Modifying the pathways of signal transduction, thereby positively altering the expression of genes involved in cell proliferation, angiogenesis and apoptosis, all important stages of cancer progression.
- Antimicrobial actions (association between *Helicobacter pylori* and gastric cancer)

Many studies on health benefits of tea have been linked to the catechin content. Epicatechin can reduce the risk of four of the major health problems: stroke, heart failure, cancer and diabetes. For cancer prevention, evidence is so overwhelming that the Chemoprevention Branch of the National Cancer Institute has initiated a plan for developing tea compounds as cancer-chemopreventive agents in human trials (Siddiqui *et al*., 2004). Thus, epicatechin should be considered essential to the diet. While the exact mechanisms of action are still

unknown, these studies provide possible explanations. The possible beneficial health effects of tea consumption have been suggested and supported by some studies, but others have found no beneficial effects. The studies show contrast with other claims, including antinutritional effects such as preventing absorption of iron and protein, usually attributed to tannin. It is reasonable to conclude that drinking both the green and black tea is compatible with healthy dietary advice in helping to reduce the risk of cancer development, helping to maintain overall health and well-being.

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