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Phytochemistry and pharmacology of *Camilla sinensis*- A Review

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Abstract

Many herbal remedies individually or in combination have been recommended in various medical treatises for the cure of different diseases. The therapeutic value of Camilla sinensis (or Thea sinensis) known as 'Tea' has been recognized in different systems of traditional medication for the treatment of different diseases and ailments of humans. It contains several phytoconstituents belonging to category of polyphenols, flavonoids, alaloids and volatile oils. It has been reported to be stimulant, cure flatulence (gas), regulating body temperature and blood sugar, indigestion, improving urinary problems and improving mental processes. Several studies using modern techniques have authenticated its use as anti diabetic, anti-inflammatory, anti pyretic, anti cancer, antiallergic, hepatoprotective, anti cariogenic, anticataractogenic, anti microbial and hypolipidemic. There are number of reports on clinical uses of Camilla sinensis in various disorders particularly in cancer and diabetes that have shown promising results. This paper explains the evidence-based information regarding the phytochemistry and pharmacological activity of this plant.

Keywords: Green tea, Phytochemistry, Pharmacological activity, Traditional uses.

INTRODUCTION

Traditional or indigenous drugs used by different ethnic groups of the world for treatment of disease have special significance of having been tested on long time scale .They are relatively safe easily available and affordable to masses. Traditional drugs have given important lead in drug research; result in the discovery of novel molecules. Artemisinine for the cure of multi drug

resistant malaria, Theophylline for bronchodialation, caffine for CNS stimulation, Glycyretinic Acid for peptic ulcer treatment, Silymarin for hepatoprotection and Vincristine and Vinblastine for certain cancers have already been isolated from plants and sincere efforts for curing immunity related problems, AIDS, Alzheimers and Diabetes are on the way. For variety of reasons, popularity of complimentary medicines is on increase. Traditional plant therapies coupled with dietary measures as prescribed Ayurvedic and other indigenous systems of medicines. In Australia and U.S., a sizeable population uses at least one form of unconventional therapy including herbal medicines [1, 2].

Camilla sinensis (L.) O. Kuntze or *Thea sinensis* (vern. Tea) belonging to family Theaceae, is an evergreen shrub or tree that can grow to a height of 30 feet, but is usually clipped to a height of 2-5 feet in cultivation. The tree or shrub is heavily branched with dark green, hairy, oblong-ovate leaves cultivated and preferentially picked as young shoots [3].

Traditional uses

Tea has been used throughout India, China, Japan, and Thailand for a long time. In traditional Chinese and Indian medicine systems, tea has been used as a stimulant, diuretic, astringent, and to improve heart health [4]. Other traditional uses of tea include treating flatulence (gas), regulating body temperature and blood sugar, promoting digestion, and improving mental processes [5]. In Japanese folkloric medicine tea is used to prevent tooth decay [6]. Tea has been considered to be anti-inflammatory, antioxidative and anti carcinogenic [7, 8].

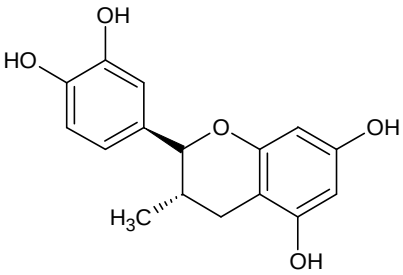
Phytochemistry

Several chemical constituents of tea have been identified. The variation in chemical composition is further complicated with fermentation and other treatments. The most abundant components of tea are polyphenols, like gallic acid and catechin, and their derivatives theogallin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate also called EGCG. Bitter flavour of tea leaves is attributed to the presence of these polyphenols. [9-14]. Upon fermentation, catechins partially change into oligomeric quinones, such as theaflavine, theaflavine acid and thearubigene, or to the non-water-soluble flavonoids such as quercetin, kaempferol and myrecetin [10, 15]. The essential oil contains more than 300 components including aldehydes, phenylethyl alcohols, phenols, hexenal, hexenol, linalool, dihydroactinidiolide and p-vinylphenol along with vitamin B and ascorbic acid [15].

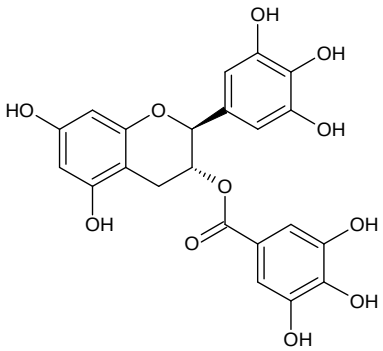
The fresh leaves contain of tea alkaloids like caffeine (3%–4%), theobromine (0.15%–0.2%), theophylline (0.02%–0.04%), and other methylxanthines [10]. These alkaloids provide stimulating effect to the tea. The extract also includes pyrroloquinoline quinone, a newly discovered vitamin [16]. Tea leaves contain many compounds, such as polysaccharides, vitamin-B, ascorbic acid, trigalloylglucose, quinic acid, carotenoids, lignin, proteins, chloroplhyll and purines [3, 15, 17]. Tea also contains minerals like potassium, sodium, calcium, fluoride, aluminium, manganese and iron were 92–151, 35–69, 1.9–3.5, 0.80–2.0, 1.0–2.2, 0.52–1.9, 0.020–0.128 mg/l, respectively [18].

Tea flowers found to contain acylated oleanane-type triterpene olibaoglycosides, floratheasaponins [19].

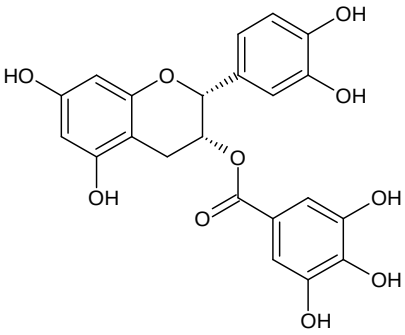
Structures



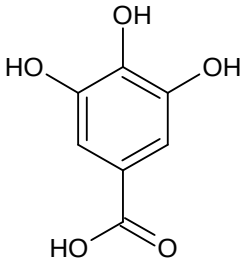
Catechin



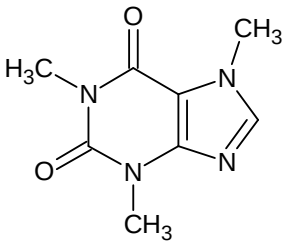
Epigallocatechingallate



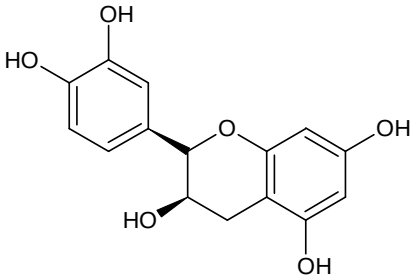
Epicatechin gallate



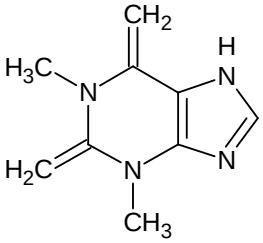
Gallic acid



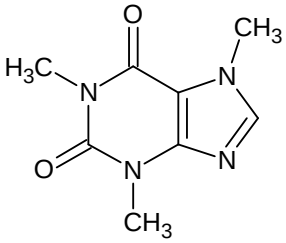
Caffine



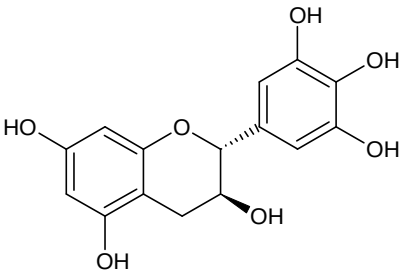
Epicatechin



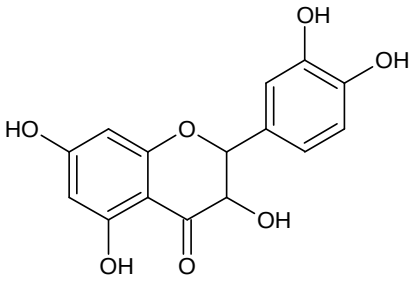
Theophylline



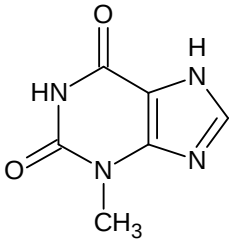
Theobromine



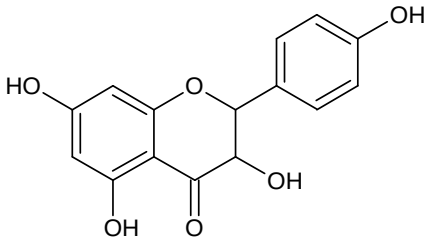
Gallocatechin



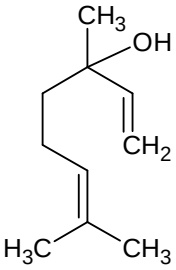
Quercetin



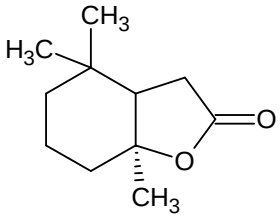
Methylxanthine



Kaempferol



Linalool



Dihydroactinidiolide

Fig.2. Structures of phytoconstituents of *Camilla sinensis*

Pharmacological Activities

Antimutagenic and Anticarcinogenic Effects

Tea has demonstrated activity against various mutagens and its anticarcinogenic activities have been extensively examined. Tea consumption has been shown to protect against chemical-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast and colon carcinogenesis in specific bioassay models [20] reported that EGCG significantly inhibited tumor promotion of teleocidin in a two-stage carcinogenesis experiment on mouse skin. Significant anticarcinogenic effects of EGCG and GTE on various organs, such as skin, stomach, duodenum, colon, liver, pancreas, and lung in rodent models have been confirmed [21]. It has been found that women who drank black tea and powdered green tea were less likely to develop bladder cancer [22-26]. In a study, researchers found that women who consumed the tea experienced the least spread of cancer particularly premenopausal women in the early stages of breast cancer and ovarian cancer. Studies in laboratory animals have found that tea polyphenols inhibit the growth of esophageal cancer cells. It has been found that tea polyphenols inhibit the growth of human lung

cancer cells in test tubes. According to a study, tea inhibits the occurrence of pancreatic and prostate cancer in humans [17]. Scientific studies suggested that EGCG and tea polyphenols have anti-inflammatory and anti-cancer properties that may help prevent the onset and growth of skin tumors [27-29]. It has been found that the risk of stomach cancer decreases with the quantities of tea consumed [30]. The mechanisms may involve the inhibition of the growth of *Helicobacter pylori*, the causative microorganism in gastric carcinogenesis and the development of gastric and duodenal ulcers [31]. It has been reported that (-)-epigallocatechin gallate, inactivate the urease enzyme [32-33] for the conversion of urea into ammonia that buffers the bacteria from digestion by gastric juice, and thereby suppress proliferation of bacteria [34]. Endogenously formed N-nitroso compounds can increase the risk of gastric and esophageal cancers [35]. According to a study, catechins reduced N-nitroso compound formation by reacting with the nitrosating species and self oxidized to quinone reducing the gastric levels of nitrosating substances and inhibiting the nitrosation of susceptible secondary amines and amides to carcinogenic nitrosamines and nitrosamides [36-37]. Studies have been done which support the role of tea in modulating microflora in the intestine by selectively increasing the growth of bifidobacteria and lactobacilli (acidophytes) in the gut wall [38-39]. This reduced the formation of ammonia, skatole, harmful amines procarcinogens in the large intestine and the carcinogenic load on the intestine. The production of acids was also lowered leading to a decrease in the pH value of the feces [39]. Therefore, bacteria profile in the intestine can be modulated by tea drinking and tea may affect the carcinogenic process in the intestine. Tea had been found to inhibit the expression of cyclooxygenases and inducible nitric oxide synthase in colonic tissues, which are constantly found to be elevated in subjects with ulcerative colitis [40] and colorectal cancers [22, 41]. The suppression of cyclooxygenase-2 by non-steroidal anti-inflammatory drugs, e.g., sulindac, had been found to reduce cancer development in patients with large bowel adenoma [42-44]. Tea polyphenols consistently inhibit cyclooxygenase-2 activity in human colon tumour tissues [45] and tea co administration produced an enhancing effect with the cyclooxygenase inhibitors [46-47]. It had been proposed that (-)-epigallocatechin gallate at physiological concentrations arrests cell growth at Go/G1 phase by inhibiting topoisomerase I activity and induces apoptosis in several human colon carcinoma cell lines. These findings suggested that it could be combined with other anticancer drugs in the treatment of colon cancer [48]. The tea polyphenol, (-)-epigallocatechin-3-gallate (EGCG) has been reported to inhibit the development and progression of prostate cancer in TRAMP mice and in humans by suppressing the cell proliferation, prostate specific antigen (PSA) expression, and AR transcriptional activity in the different LNCaP sublines. Intraperitoneal administration of EGCG also suppressed the growth of relapsing R1Ad tumors and decreased tumor-derived serum PSA [49]. Studies revealed that EGCG causes down regulation of matrixmetalloproteinases-2 (MMP-2) in human breast cancer cell line MCF-7 by decreasing the expression of MT1-MMP (membrane type-1-matrix metalloproteinase), NF-κB (nuclear factor-kappa B), VEGF (vascular endothelial growth factor), FAK (focal adhesion kinase), disrupting the functional status of integrin receptors and decreased activation of phosphatidyl-inositol-3-kinase (PI-3K), extracellular regulated kinase (ERK) [50]. The mechanism of antimutagenesis and anticarcinogenesis include the modulation of extracellular and intracellular metabolic and proliferative processes. The oral administration of tea extract enhanced the inhibitory effects of doxorubicin on tumor growth 2.5-folds [14]. It has been demonstrated that tea polyphenols are powerful antioxidants with anticarcinogenic properties. These polyphenolic compounds, especially epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), and epicatechin-3-gallate (ECG), which account for 30-40 percent of the extractable

solids of tea leaves, are believed to mediate many of the cancer chemopreventive effects. Mechanisms of action may include antioxidant and free-radical scavenging activity, and stimulation of detoxification systems through selective induction or modification of phase I and phase II metabolic enzymes. In addition, tea may inhibit biochemical markers of tumor initiation and promotion, including the rate of cell replication and thus inhibition of the growth and development of neoplasms [3].

Antidiabetic and antioxidant activity

The water extract of *Thea sinensis* (green tea cold extract) in dose of 100mg/kg body weight was found to reduce the blood glucose level of KK-Ay mice in 4-8 weeks after repeated administration and tend to decrease the plasma insulin levels under the similar conditions. However, green tea cold extract did not affect the affect the blood glucose levels in normal mice. Green tea cold extract decreased blood glucose levels in insulin tolerance test suggesting its anti diabetic activity [51]. Tea powder suspension in dose of 300mg/kg found to lower the blood glucose levels in diabetic db+/db+ mice and in streptozotocin-diabetic mice after 2-6 h of administration with out affecting the serum insulin levels whereas no affect was seen in control mice. The glucose levels in normal healthy humans were substantially improved after the administration of green tea powder suspension [16]. It has been known that some constituents enhance the basal and insulin-stimulated glucose uptake of rat adipocytes [52], to inhibit intestinal glucose uptake by inhibiting the sodium-dependent glucose transporter of rabbit intestinal epithelial cells [53], and to reduce serum glucose level in alloxan-diabetic rats [54]. Ethyl acetate fraction of ethanol-extract (EEA) and ethanol extract (EE) of tea flower exhibited substantial quenching activity to hydroxyl radicals (SC50 11.6 and 19.7μg/ml, respectively). EEA quenched 80% of hydroxyl radicals generated by Fenton's reaction, and 40% of DPPH radical was scavenged in the Fe (II)-H_2O_2 -luminol system. Flavones, polyphenols and catechins present in EE and EEA fractions were responsible for the stronger scavenging abilities to free radicals [55]. The antioxidant activity of catechins has been studied in various experimental and human conditions. It is now generally accepted that catechins possess antioxidant activity in vitro and in vivo. Iron-induced oxidative stress was investigated in rat brains. Infusion of tea extract prevented oxidative injury induced by iron. Both iron-induced lipid peroxidation products and iron-induced decrease in dopamine were suppressed [56].

Antihyperlipidemic activity and cardiovascular effects

The antihyperlipidemic activity of aqueous extract of leaves of *Camellia sinensis* (CS) was studied against Triton induced hyperlipidemia in rats. CS was administered in a dose of 200 mg/kg (p.o) to Triton induced hyperlipidemic rats. Fenofibrate was used as reference standard. CS showed a significant decrease in the levels of serum cholesterol, phospholipid, triglyceride, LDL, VLDL and significant increase in the level of serum HDL. Aqueous extract decreased serum level of total cholesterol by 69.72%. On the other hand aqueous extract of CS increased the serum HDL cholesterol level by 24.11%. The reduction of LDL cholesterol level by aqueous extract was 30.31%. Presence of flavanoids and tannins were presumed to be responsible for the antihyperlipidemic activity [57]. Studies had revealed that green tea consumption lowers the hepatic cholesterol synthesis in man and animals by directly inhibiting HMG-CoA reductase and by promoting its inactivation by AMP kinase [58]. It has been reported that catechins show anti-thrombogenic, and lipid lowering effects by scavenging free radicals, chelating redox active transition-metal ions, inhibiting redox active transcription factors, inhibiting pro-oxidant

enzymes and inducing antioxidant enzymes. They found to inhibit the key enzymes involved in lipid biosynthesis and reduce intestinal lipid absorption, thereby improving blood lipid profile, regulate vascular tone by activating endothelial nitric oxide, prevent vascular inflammation that plays a critical role in the progression of atherosclerotic lesions [59]. The methanolic extract from the flowers of tea plant (*Camellia sinensis*) was found to suppress serum triglyceride elevation in olive oil-treated mice. Oleanane triterpenoids oligoglycosides, floratheasaponins A-I showed inhibitory effects on serum triglyceride elevation [19]. In a study on humans, it was revealed that moderate tea intake is associated with a lower prevalence of ventricular arrhythmias among patients hospitalized with acute myocardial infarction [60]. Green tea extract (GTE) dissolved in water blunted Ang II-induced blood pressure increase and cardiac hypertrophy in Ang II-treated rats by decreasing the expression of the NAD(P)H oxidase subunit gp91(phox) and the translocation of Rac-1, as well as NAD(P)H oxidase enzymatic activity. Furthermore, it specifically reduced Ang II-induced Src, EGFR, and Akt phosphorylation showing that GTE blunts Ang II-induced cardiac hypertrophy specifically by regulating ROS production and the Src/EGFR/Akt signaling pathway activated by Ang II. [61].

Anti-inflammatory, antinociceptive and antipyretic activity

Pharmacological studies had shown that methanol-water (1:1) extract of dried tea (*Camellia sinensis*) root extract (TRE) possess anti-inflammatory, analgesic and antipyretic activities at in dose of 100 mg/kg i.p. It was found that TRE inhibited the arachidonic acid-induced paw oedema in rats which indicated that TRE produced the anti-inflammatory activity by inhibiting both the cyclooxygenase and lipooxygenase pathways of arachidonic acid metabolism. TRE also enhanced peritoneal cell count and the number of macrophages in normal mice. Saponins present in TRE may be responsible for these activities of TRE [62]. Two saponins (TS-1 and TS-2) isolated from tea root extract (TRE) were tested for anti-inflammatory using carrageenan-induced paw oedema in rats [63]. Studies have been performed in which the anti-inflammatory activity of the hot water extract of black tea (Camellia sinensis, Sikkim variety) was evaluated along with certain standard drugs. The extract showed significant inhibitory activity against carrageenin, histamine, serotonin and prostaglandin-induced pedal inflammation. The extract inhibited exudative inflammation. The tea extract also inhibited cotton pellet-induced granuloma formation and adjuvant-induced polyarthritis. Black tea extract showed significant inhibition against glucose oxidase-mediated inflammation [64].

Antimicrobial activity

Antimicrobial activities of tea have been well demonstrated and tea has been shown to inhibit the growth *of Salmonella typhi, Campylobacter jejuni, Campylobacter coli, H. pylori, Shigella, Salmonella, Clostridium pseudomonas, Staphylococcus aureus, Staphylococcus epidermidis, Vibrio parahaemolyticus a*nd *Vibrio cholerae* O1. The extracts also proved effective against pathogenic methicillin-resistant S. aureus (MRSA) and, to some extent, against penicillin-resistant *S. aureus, Candida, Mycoplasma* and *Cryptococcus*. Epigallocatechin gallate enhances the antifungal effect of amphotericin B or fluconazole against antimycotic-susceptible and -resistant *Candida albicans* [65-66]. It has been demonstrated that ethyl acetate fraction of aqueous extract of *C. sinensis* leaves and pure components like catechin, epicatechin, gallocatechin, epigallocatechin, catechin gallate, epicatechin gallate, gallocatechin gallate, and epigallocatechin gallate lysed more than 50% of the *Trypanosoma cruzi* parasite present in the blood of infected BALB/c mice at concentrations as low as 0.12 to 85 pM. The most active

compounds were gallocatechin gallate and epigallocatechin gallate, with minimal bactericidal concentrations that inhibited 50% of isolates tested of 0.12 and 0.53 pM, respectively. The number of amastigotes in infected Vero cells decreased by 50% in the presence of each of these compounds at 100 nM. The effects of the catechins on the recombinant *T. cruzi* arginine kinase, a key enzyme in the energy metabolism of the parasite, were assayed. The activity of this enzyme was inhibited by about 50% by nanomolar concentrations of catechin gallate or gallocatechin gallate, whereas the other members of the group were less effective [67]. In a randomized, one-blind clinical methanolic extract of *C. sinensis* showed inhibition of *Leishmania major* multiplication when administered at doses of 150, 300, 450, 600 and 750 µg/ml at 72 hours ($P<0.05$) [68].

Anti-cariogenic activity

It has been reported that various components (mainly catechins) present in dried tea leaves has in-vitro anti-cariogenic activity. The possible mechanisms include direct anti bacterial activity against *Streptococcus mutans* and *S. sobrinus*, prevention of adherence of bacteria to teeth, inhibition of glucosyl transferase and inhibition of bacterial and human amylases. It has been also reported that tea drinkers are less prone to the dental caries incidences [69].

Hepatoprotective Activity

Green tea showed hepatoprotective activity against lipopolysaccharide (LPS) + D-galactosamine (GalN)–induced liver injury. Green tea extract significantly suppressed LPS + GalN–induced liver injury when added to the diet (30 or 35 g/kg) and fed to rats for 14 d or when force-fed alone (0.4–1.2 g/kg body) 1.5 h before the injection of drugs. Although all five of the fractions extracted from green tea extract with different organic solvents had significant suppressive effects, the caffeine-containing fraction exhibited the strongest effect, suggesting that the protective effect of green tea against LPS + GalN–induced liver injury is attributable mainly to caffeine. Authentic caffeine also significantly suppressed LPS + GalN–induced liver injury when added to the diet (2 g/kg) and fed to rats for 14 d. Dietary green tea suppressed LPS + GalN–induced apoptosis of liver cells, as assessed by DNA fragmentation. However, dietary green tea did not suppress LPS-induced enhancement of plasma concentration of tumor necrosis factor (TNF)-α, the cytokine that is thought to play a pivotal role in the pathogenesis of LPS-induced liver injury, although it significantly suppressed plasma concentrations of interleukin (IL)-1ß, IL-2, IL-4, IL-6, IL-10 and interferon (IFN)-γ. TNF-α + GalN–induced liver injury and apoptosis were also suppressed by dietary green tea. In contrast, dietary caffeine significantly suppressed LPS-induced enhancement not only of plasma IL-1ß, IL-6, IL-10 and IFN-γ concentrations, but also of TNF-α concentration. The results suggest that green tea might suppress LPS + GalN–induced liver injury mainly through the inhibition of TNF-α–induced apoptosis of hepatocytes, rather than through the suppression of TNF-α production, although the suppressed production of TNF-α may be associated with the hepatoprotective effect of caffeine [70].

Anti-cataractogenic Activity

Polyphenolic compounds present in green tea *(Camellia sinensis)* are reported to possess antioxidant property in various pathological conditions. The study was undertaken to evaluate the anticataract potential of green tea leaf (GTL) extract in the development of lens opacification. Enucleated rat lenses were randomly divided into normal, control and treated groups and incubated for 24 h at 37°C. Oxidative stress was induced by sodium selenite in the culture

medium of the two groups (except the normal group). The medium of the treated group was additionally supplemented with GTL extract. After incubation, lenses were subjected to glutathione and malondialdehyde estimation. Enzyme activity of superoxide dismutase, catalase and glutathione peroxidase was also measured in different sets of the experiment. In vivo cataract was induced in 9-day-old rat pups of both control and treated groups by a single subcutaneous injection of sodium selenite. The treated pups were injected GTL extract intraperitoneally prior to selenite challenge and continued for 2 consecutive days thereafter. Cataract incidence was evaluated on 16th postnatal day by slit lamp examination. There was positive modulation of biochemical parameters in the organ culture study. Green tea was also found to reduce the incidence of selenite cataract in vivo [71].

Antiallergic activity

It has been revealed that *O*-methylated derivative of (−)-epigallocatechin-3-*O*-gallate (EGCg), (−)-epigallocatechin-3-*O*-(3-*O*-methyl)-gallate (EGCG‘ ‘3Me), has potent antiallergic activity. Flow cytometric analysis showed that EGCG‘ ‘3Me was able to decrease the cell surface expression of FcεRI (high-affinity IgE receptor) and immunoblot analysis revealed that total cellular expression of the FcεRI α chain decreased upon treatment with EGCG‘ ‘3Me human basophilic KU812 cells. EGCG‘‘3Me reduced FcεRI α and γ mRNA levels and inhibited the FcεRI cross-linking-induced histamine release [72].

CONCLUSION

From the times immemorial, plants have been used as curative agents for variety of ailments. *Camilla sinensis* preparations are widely available and employed to cure flatulence (gas), regulating body temperature and blood sugar, indigestion, improving urinary problems and improving mental processes. Most of the studies have been conducted on crude preparations of *C. sinensis* without mention of their chemical profile. Although the studies of *C. sinensis* have proved its efficacy in several complications but the detailed research work on isolation of bioactives through clinical trials followed by standardization is seriously required. There have been reports on the clinical uses of *C. sinensis* which have shown promising results.

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