Chapter 17
Tea (Catechins Including (−)-Epigallocatechin-3-gallate) and Cancer

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Abstract Catechins, a group of phenolic compounds (flavan-3-ols), are one of most widely studied plant secondary metabolites regarding their diverse pharmacological actions. Found in many foods and beverages including tea, catechins are reported to be useful for the prevention and treatment of cancer in *in vitro* and *in vivo* studies. Various signalling mechanisms have also been explored for the cancer chemopreventive activities of tea and tea catechins. However, the translational research on these compounds to clinical studies have not been performed in detail as compared to *in vitro* and *in vivo* studies. This chapter critically discusses the role of catechins in cancer prevention and treatment with special focus on their mechanism of action on signaling pathways.

Keywords Tea · Catechins · Cancer · Cancer signalling · Cancer chemoprevention

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1 Introduction

Natural polyphenols present in various fruits, vegetables, tea, coffee, legumes, among others, have played important role in maintaining of human health having nutraceutical, disease preventive and therapeutic effects (Pietta 2000; Petti and Scully 2009; Ganesan and Xu 2017). The young, tender leaves of tea plant (*Camellia sinensis* (L.) Kuntze, Syn.: *Thea sinensis* L., Theaceae) (Fig. 17.1) are used from the ancient time to prepare diverse tea formulations such as green tea, oolong tea, black tea, white tea and matcha powder among others (Kim et al. 2011; Carloni et al. 2013). Tea leaves are also used in traditional medicines in China, Korea and Japan. In Japan, crude drug obtained from tea leaves known as "Chyayou" is used in head and eye disorders such as headache and blindness. It is also included in official Kampo formulations such as "Senkyuchyatyousan" and "Shirenmeimeto". In

Fig. 17.1 Photographs of tea plants and black and green tea; (**a**) tea plantation, (**b**) tea flower, (**c**) young tea leaves, (**d**) green tea and (**e**) black tea

general practice, the tea is used as gargle to prevent from sore throat and cold. Strong tea is recommended in bacterial diarrhea (Watanabe et al. 2018). Tea is believed to be the second most consumed drink worldwide only after water (Kim et al. 2011). The global tea market in 2018 was valued at over 52 billion USD and it is expected to rise to more than 81 billion USD by 2026 (https://www.statista.com/statistics/326384/global-tea-beverage-market-size/). At current times, China is reported to be the leading producer of tea followed by India and Kenya. With the increasing scientific studies on tea and its constituents and their effects in human health, tea is becoming more and more popular as casual drink and also for its functional properties.

Various polyphenolic compounds are present in the tea leaves including flavan-3-ols, commonly known as tea catechins, and phenolic acids such as gallic acid (Carloni et al. 2013). Tea catechins are one of the most widely studied plant natural products for the chemical and pharmacological aspects such as antioxidant, cancer chemopreventive, anti-inflammatory, immunomodulatory activities (Wai et al. 2018; Khan et al. 2019). Among these catechins, (−)-epigallocatechin-3-gallate (EGCG) is the most studied for such activities. The main aim of this chapter is to critically analyse the role of catechins in cancer prevention and treatment with special focus on their mechanism of action on signalling pathways.

2 Chemical Aspects of Tea Catechins

The quantity and composition of catechins and other chemical constituents in tea formulations depend upon various factors related to tea leaves cultivation and collection. This includes variety of tea plant, environmental factors, conditions related to cultivation, collection time, processing of tea leaves after collection and further formulations such as extraction conditions (Zhao et al. 2011; Carloni et al. 2013). Flavan-3-ols, known as catechins (eg. (+)- catechin, (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC) and (−)-epigallocatechin-3-gallate (EGCG)) (Fig. 17.2) are the most widely studied chemical constituents in both tea leaves and tea formulations. However, there are many other biologically important chemicals present such as flavonols (e.g. kaempferol and quercetin derivatives), phenolic acids (gallic acid, caffeic acid, gallic acid glucosides and their derivatives), proanthocyanidins, amino acids (e.g. L-theanine, gamma amino butyric acid (GABA)), methyl xanthines (caffeine, theophylline, theobromine) and volatile compounds (e.g. pentanal, heptanal, 2-butanone) (Kim et al. 2011; Zhao et al. 2011; Ananingsih et al. 2013; Carloni et al. 2013).

After the collection, young tea leaves are further processed and on the basis of processing they are classified into three main categories e.g. non-fermented (white tea, green tea), partially fermented (oolong tea) and fully fermented (black tea) (Zhao et al. 2011). However, there are many other varieties such as matcha tea powder in which tea plants are cultivated under shade (about 90%). Then the leaves are picked, dried then ground to make powder (Kurauchi et al. 2019). During the

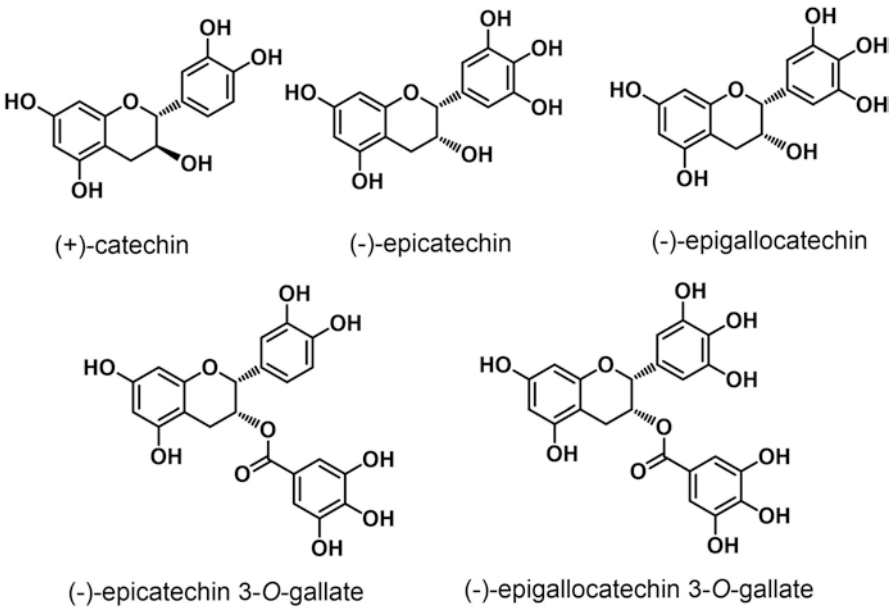

Fig. 17.2 Chemical structures of major tea catechins

fermentation process, the enzymatic oxidation of polyphenols by the enzyme polyphenol oxidase results in the generation of theaflavins and thearubigins, which are responsible for characteristic color and aroma (Zhao et al. 2011). Various research articles have reported the reduced antioxidant activity of the tea infusion/extracts obtained from fermented tea varieties as compared to green tea and its extracts. Studies have reported the anticancer and other health beneficial activities of the extracts obtained from these various varieties and pure isolated compounds such as EGCG (Carloni et al. 2013; Sonoda et al. 2014).

3 Catechins: Bioavailability and Metabolism

Though consumed widely around the globe and the majority of studies have shown the biological activities of tea and catechins in *in vitro* systems, one of the main obstacles in obtaining the similar data in *in vivo* systems is the poor bioavailability of tea catechins (Cai et al. 2018). Lin et al. (2007) investigated the pharmacokinetic profile of EGCG in freely moving rats and reported that the oral bioavailability was only about 5%. The plasma protein binding was about 92%. EGCG crossed blood-brain barrier at lower concentration. Further, the elimination half-life was reported to be 62 ± 11 and 48 ± 13 min for intravenous (10 mg/kg) and oral (100 mg/kg) administrations, respectively. In another study in rats, only about 14% of EGC, 31%

of EC and less than 1% of EGCG was reported to be measured in blood after oral administration (Chen et al. 1997).

Warden et al. (Warden et al. 2001) investigated the absorption of tea catechins in men and women after drinking the black tea containing 15.48, 36.54, 16.74, and 31.14 mg of EGC, EC, EGCG and ECG, respectively, at four time points (0, 2, 4 and 6 h). Only about 1.68% of administered catechins were reported to be present in plasma, urine and faeces after tea ingestion over 6 h and the bioavailability of the gallated forms of catechins was lower than that of the free forms. In another study, Yang et al. (1998) reported that the maximum plasma concentration for EC, EGC, and EGCG, were 0.6, 1.60 and 0.57μM, respectively in humans after administration of 3 g of decaffeinated green tea.

Absorbed catechins undergo phase II metabolism by enzymes such as uridine 5′-diphospho (UDP)-glucuronosyltransferases (UGTs), sulphotransferases (SULTs) and catechol-*O*-methyltransferase (COMT) in liver and are converted to their respective glucoronosyl, sulphate and methylated metabolites (Lambert et al. 2007; Cai et al. 2018). Catechins, their conjugated metabolites and other simple phenolic acid metabolites are then distributed to various organs and tissues.

4 Therapeutic Potential of Catechins

Tea catechins are well studied for their health beneficial activities related to not only cancer but many other pharmacological activities such as antioxidant, anti-obesity, anti-hyperlipidemic, aging, diabetes and many others (Zaveri 2006). A Scopus search (www.scopus.com) with the keyword “tea AND catechins” resulted total 6998 documents and the keyword “tea AND catechin AND activity” resulted total 3798 documents (accessed on May 29, 2020). Cancer chemopreventive activity is one of the widely studied and discussed activity of tea formulations, tea extracts and catechins which are discussed in detail in this chapter. Many review articles are also published in these aspects of tea catechins (Boehm et al. 2009; Khan and Mukhtar 2010; Yang and Wang 2016). Review articles have also extensively covered the other activities such as antioxidant activity (Higdon and Frei 2003; Gramza and Korczak 2005), obesity, diabetes and other metabolic diseases (Higdon and Frei 2003; Gramza and Korczak 2005; Kao et al. 2006; Zaveri 2006; Park et al. 2009; Masterjohn and Bruno 2012; Legeay et al. 2015), cardiovascular diseases (Hodgson and Croft 2010), cognitive functions (Weinreb et al. 2004; Da Silva Pinto 2013; Pervin et al. 2018), antimicrobial activities (Taylor et al. 2005; Reygaert 2014) among others. Not only as a drink or as a potential medicines, tea infusion and catechins are also widely used as food supplements and functional foods (Hara 2011; Namal Senanayake 2013; Sanna et al. 2015; Kurauchi et al. 2019).

5 Catechins and Cancer

Activities of tea extracts and isolated compounds including catechins have been extensively studied for the prevention and treatment of cancer through *in vitro* and *in vivo* systems. A Scopus search results with different key words (e.g. tea AND catechins AND breast cancer, tea AND catechins AND lung cancer) related to cancer is represented in Fig. 17.3. As per the results, activities related to breast cancer, lung cancer, skin cancer and colon cancer are widely reported. Some of the studies are reported below.

5.1 Lung Cancer

Lung cancer is the most common form of cancer worldwide with more than half of the patients in developing countries (Wong et al. 2017). Lung adenocarcinoma, squamous cell carcinoma, small cell carcinoma and and large cell carcinoma are the main types of lung cancers (Wong et al. 2017; Malyla et al. 2020). Various plants based single compounds has been explored for their promising activity against lung cancer. Deng and Lin (2011) reported the potent inhibitory activity of EGCG against matrix metalloproteinase-2 (MMP-2) which in turn inhibited the invasion of highly invasive CL1-5 lung cancer cells. Wnt signalling is an important pathway in non-small cell lung cancer (NSCLC) progression as overexpression of Wnt-1, -2, -3, -5a is common in resected NSCLC and associated with poor survival while inhibition of Wnt reduces NSCLC proliferation. Xie et al. (2017) reported that ECGC

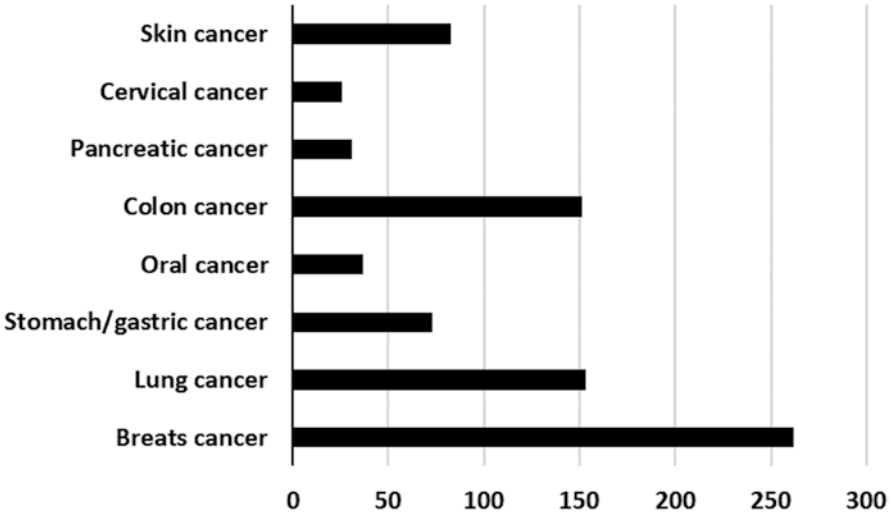

Fig. 17.3 No. of publication related to tea catechins and cancer of different organs

inhibited the lung cancer stem cells through Wnt/b-catenin pathway along with suppression of proliferation and induction of apoptosis. Similarly, Zhong et al. (2012) reported the *in vitro* anti-proliferative activity of green tea catechins against human lung cancer cells (NCI-H446 and MSTO-211H) by upregulation of let-7 (a microRNA function as tumor suppressor). Furthermore, another *in vitro* study on human lung adenocarcinoma cell line (A549) showed that green tea catechin, EGCG possess potent anti-cancer activity by attenuating the cell proliferation *via* Bcl-xL expression (Sonoda et al. 2014) .

5.2 Colorectal Cancer

Colorectal cancer also known as colorectal adenocarcinoma is reported to be the third leading cause of cancer mortality globally (Rawla et al. 2019). The application of EGCG to HT-29 colon cancer cell lines resulted into ER stress by upregulation of immunoglobulin-binding (BiP), PKR-like endoplasmic reticulum kinase (PERK), phosphorylation of eukaryotic initiation factor 2 alpha subunit (eIF2α), and activation of transcription 4 (ATF4), and inositol-requiring kinase 1 alpha (IRE1α) (Md Nesran et al. 2019). Haratifar et al. (2014) studied the effects of casein micelles of EGCG in HT-29 cells and reported that nanoencapsulation did not reduce the antiproliferative activity of EGCG and can be a good drug deliver carrier for EGCG.

5.3 Breast Cancer

Breast cancer is the most common cancer in women (Hu et al. 2019). Various in vitro, in vivo and human studies have been performed to evaluate the effectiveness of tea catechins in breast cancer. For example, Zhang et al. (Zhang et al. 2012) studied the effect of oral administration of 400 mg EGCG (three times/day) in breast cancer patients receiving radiotherapy. Compared to the group receiving only radiotherapy, patients receiving radiotherapy+EGCG expressed lower serum levels of vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and reduced activation of metalloproteinase-9 and metalloproteinase-2 (MMP9/MMP2). Treating cultures of highly-metastatic human MDA-MB-231 breast cancer cells with the serum obtained from radiotherapy + EGCG treated patients resulted into supressed cell proliferation and invasion, arrest of cell cycles at the G0/G1 phase. Treated cells also showed reduced activation of MMP9/MMP2, expressions of Bcl-2/Bax, c-Met receptor, NF-κB, and the phosphorylation of Akt. Based on these data, authors suggested that EGCG may act as an effective adjuvant in radiotherapy for breast cancer patients.

5.4 Prostate Cancer

Prostate cancer, the second most commonly diagnosed cancer in men globally, is the six leading cause of death worldwide (Culp et al. 2020). Among different tea catechins, EGCG is reported as most effective agent in prostate cancer based on *in vitro* and animal studies (Davalli et al. 2012; Du et al. 2012; Miyata et al. 2019). However, the randomized, placebo-controlled clinical trial of polyphenon-E (a standard mixture of tea catechins including EGCG) in 97 men with high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP) showed that the administration of the catechin mixture for 1 year did not reduce the likelihood of prostate cancer with baseline HGPIN or ASAP (Kumar et al. 2015).

5.5 Gastric Cancer

Gastric cancer is one of the most common cancers worldwide as it is reported to be fifth most common cancer with third highest rate of mortality (Rawla and Barsouk 2019). Hibasami et al. (1998) reported that the treatment of human stomach cancer KATO III cells with green tea extract and EGCG resulted into growth inhibition and apoptosis. Similarly, Yang et al. reported that the EGCG inhibited the proliferation and induced apoptosis in SGC-7901 cells in vitro by canonical Wnt/β-catenin signalling pathway. EGCG also inhibited gastric tumour growth by inhibiting Wnt/β--catenin signalling in vivo (Yang et al. 2016).

6 Molecular Mechanisms of Anticancer Activity of Tea Catechins

Various molecular mechanisms have been purposed for the chemopreventive activities of tea catechins. Some of these mechanisms are discussed in brief in sections below. A graphical representation of these mechanisms is presented in Fig. 17.4.

6.1 Induction of Apoptosis

Lim et al. (2006) studied the effects of epicatechin gallate on cell growth and apoptosis in squamous carcinoma cell line, SCC7. Authors reported that epicatechin gallate suppressed the cyclin D1 expression in SCC7 cells by 90% in a dose- and time-dependent manner. It also inhibited the cell growth by 50% *via* G1 cell cycle arrest. Qin et al. (2007) reported that EGCG promotes apoptosis of human bladder cancer cells (T24) *in vitro* by inhibiting PI3K/Akt activation and modulation of

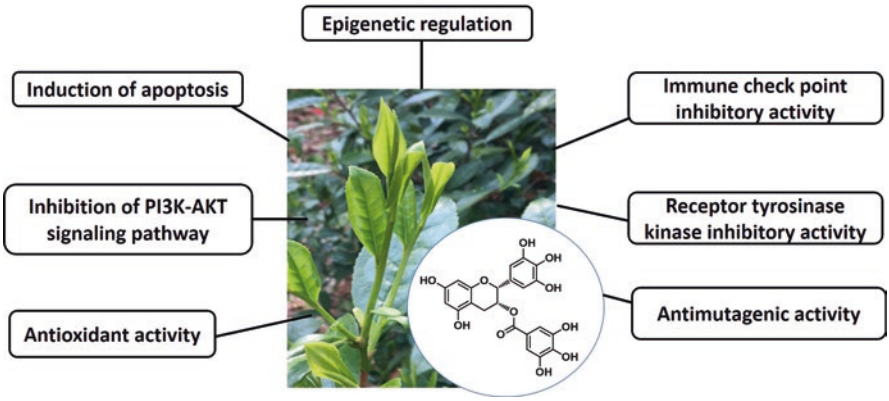

Fig. 17.4 Molecular mechanisms of actions of anticancer activity of tea extracts and catechins

Bcl-2 family proteins. Apoptosis of T24 cells were further supported by activation of caspase-3 and poly (ADP-ribose) polymerase protein expression. Similarly, to identify the molecular pathways involved in EGCG-induced apoptosis of human bladder cancer cells (TCCSUP), Philips et al. (2009) analyzed various gene expression following treatment of 40μg/mL EGCG for 24 h. The results showed down-regulation of key genes involved in cell survival (*Tmepai-* by fourfold, Wnt2 by 3.2-fold) and inflammation (*Ccl20* and *IL-8* by >10-fold).

6.2 Autophagy

Autophagy is an intracellular process that is involved in the degradation of cellular components via lysosomal pathway triggered by several stressful conditions such as organelle damage, the presence of misfolded proteins, and nutrient deprivation (Levy et al. 2017; Yun and Lee 2018). Autophagy is believed to play dual role in cancers through tumor suppression and promotion (Yun and Lee 2018). Effective targeting of autophagy stimulation is being considered as an therapeutic option in various cancers (Levy et al. 2017). Zhao et al. (2017) studied the molecular mechanisms of autophagy regulation by EGCC in human hepatocellular carcinoma HepG2 cells and found that EGCG reduced the α-fetal protein (AFP) secretion, which is involved in malignant differentiation, and induced the AFP aggregation which was further degraded by autophagic process.

6.3 PI3K-AKT Signaling Pathway

The phosphoinositidine-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/m-TOR) signaling pathway is considered the most common pathway in human cancers (Van Aller et al. 2011). Various therapeutic targets are being studied for the treatment of cancer in PI3K-Akt pathway including dual PI3K–mTOR inhibitors, PI3K inhibitors, Akt inhibitors and mTOR complex catalytic site inhibitors (Engelman 2009). Van Aller et al. (2011) studied the inhibitory activity of tea catechins, catechin gallate, epicatechin gallate, gallocatechin gallate and EGCG on the PI3K-Akt pathway and reported that EGCG acted as dual inhibitor of PI3K/mTOR. Gu et al. (2018) investigated if EGCG induce apoptosis of human lung cancer cell (H1299) targeting PI3K/Akt signaling pathway. As compared to control (EGCG untreated), the expression of PI3K and Akt showed no significant differences, while expression levels of their phosphorylated form (p-PI3K and p-Akt) were significantly reduced.

6.4 Receptor Tyrosinase Kinase Inhibitory Activity

Receptor tyrosine kinases (RTKs) exert crucial function to control cellular processes and balance between cell proliferation and death. RKTs are promising therapeutic targets for the management of cancer. The tea catechins, including EGCG have ability to suppress RTK signaling thus exert protective effects against dysregulated RTKs in cancer cells (Larsen et al. 2010). EGCG suppress the activation of epidermal growth factor receptor family (ErbB1), HER2 (neu/erbB2) and HER3 (neu/erbB3) belonging to subclass I of the RTK superfamily, in different human cancer cells. The activation of insulin like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) receptors are also downregulated by EGCG (Shimizu et al. 2008). EGCG also inhibits the tumorigenicity of human lung cancer cell (H1299) stimulated by AXL RTK. In addition, oral administration of EGCG and green tea extract suppressed tumour growth in SCID/Beige mice and reduced p-AXL, ALDH1A1, and SLUG in tumours (Namiki et al. 2020).

6.5 Epigenetic Regulation

EGCG and other catechins are also widely studied for their epigenetic regulatory activity (Khan et al. 2020). EGCG was reported to reduce the cellular proliferation and induce apoptosis in MCF-7 breast cancer cell lines and HL60 promyelocytic leukemia cell lines through downregulation of human telomerase reverse transcriptase (hTERT) gene expression (Berletch et al. 2008). EGCG also reduced the level of B-cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1) and

zeste homolog 2 (Ezh2) in SCC-13 cells, which was associated with the reduction in histone H3 lysine 27 trimethylation, a hallmark of PRC2 complex action (Balasubramanian et al. 2010). Similarly, in human prostate cancer LNCap cells, treatment of green tea polyphenols resulted into the re-expression of glutathione-S-transferase p1 (GSTP1) (Pandey et al. 2010). Similarly, in HCT 116 human colon cancer cells, EGCG treatment reduced the expression of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) (Moseley et al. 2013).

6.6 Immune Check Point Inhibitory Activity

There is a growing interest in the research of immune check point inhibitors as therapeutic targets in cancer specially in immunotherapy. However, there is also growing attention towards the small molecule immune check point inhibitors (Sasikumar and Ramachandra 2018; Smith et al. 2019). Rawangkan et al. (2018) reported the inhibitory activity of EGCG against programmed cell death ligand 1 (PD-L1) expression in non-small-cell lung cancer cells which was initiated by interferon and epidermal growth factor (EGF).

6.7 Anti-mutagenic Activity

Various mutagenic processes are believed to play crucial role in carcinogenesis. Many studies have evaluated the antimutagenic activities of green tea extracts and catechins. Yamada and Tomita (1994) studied the antimutagenic activities of aqueous extracts of green tea, oolong tea and black tea using *Salmonella typhimurium* test strains, TA 98 and TA 100. These extracts reduced the reverse mutation induced by Trp-P-1, Glu-P-1, and B[a]P, and crude dimethyl sulfoxide (DMSO) extracts of grilled beef.

6.8 Antioxidant Activity

Reactive oxygen species and reactive nitrogen species play important role in human body physiology. However, the over production of these agents results in various disease conditions including cancer (Valko et al. 2006; Reuter et al. 2010; Sosa et al. 2013). Tea extracts and catechins are well studied agents for their antioxidant activities *in vitro* and *in vivo* and these activities are often reported to be related with the reduced incidence of cancer (Koo and Noh 2007; Almajano et al. 2008; Lambert and Elias 2010; Kim et al. 2014; Bernatoniene and Kopustinskiene 2018) in individuals taking green tea. However, many detailed clinical trials did not show such effects (Yuan et al. 2011).

7 Combination Therapy with Other Anticancer Drugs

Various studies have also been performed to investigate the combination of cancer chemopreventive drugs/compounds with other anticancer drugs (Suganuma et al. 2011; Fujiki et al. 2015). Przystupski et al. (2019) studied the effect of catechin pretreatment on the cytotoxic effects of cisplatin on human ovarian cancer cells' SKOV-3. Authors reported that the pretreatment of cells with catechin enhanced the cytotoxicity of cisplatin by promoting apoptosis and by changing the activity of membrane proteins involved in cisplatin uptake, metabolism, and efflux. Similarly, La et al. (2019) reported that the EGCG enhanced the colorectal cancer cells' sensitivity to 5-FU through GRP78/NF-κB/miR-155-5p/MDR1 pathway inhibition.

8 Conclusions

Different tea formulations are used worldwide as drink and for potential health beneficial activities. The isolated compounds such as catechins are widely used in food supplements and are also widely studied for their cancer chemopreventive and other pharmacological activities. Various *in vitro* and *in vivo* studies have also revealed the molecular mechanisms of these compounds as anticancer agents, but the clinical and epidemiological studies have provided mixed results (Yuan et al. 2011). The bioavailability and pharmacokinetic properties of these compounds are also of great concern. Future studies should explore more detailed evidence in clinical studies and evaluate the long-term safety and efficacy as therapeutic agents along with clear understanding of their pharmacokinetic properties.

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