

**Breast cancer chemopreventive and chemotherapeutic effects of *Camellia Sinensis* (green tea): an updated review**Mahmoud Rafieian-Kopaei<sup>1</sup>, Mino Movahedi<sup>2</sup><sup>1</sup> Full Professor, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran<sup>2</sup> Mino Movahedi, MD in Obstetrics and Gynecology, Assistant Professor, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran**Type of article:** Review**Abstract**

**Introduction:** *Camellia sinensis* belongs to the plant family of Theaceae, native to East Asia, the Indian Subcontinent and Southeast Asia, but naturalized in many parts of the world. The aim of this study was to overview its anti-breast cancer chemopreventive and chemotherapeutic effects. This review article is aimed to overview breast cancer chemopreventive and chemotherapeutic effects of *Camellia sinensis* (green tea).

**Methods:** This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases. The initial search strategy identified around 108 references. In this study, 68 studies were accepted for further screening, and met all our inclusion criteria [in English, full text, chemopreventive and chemotherapeutic effects of *Camellia sinensis* and dated mainly from the year 1999 to 2016. The search terms were *Camellia sinensis*, chemopreventive, chemotherapeutic properties, pharmacological effects.

**Result:** The result of this study suggested that the catechin available in *Camellia sinensis* has properties which can prevent and treat breast cancer. It has also been shown to inhibit proliferation of breast cancer cells and to block carcinogenesis. It was found that increased *Camellia sinensis* consumption may lower the risk of breast cancer. *Camellia sinensis* intake was shown to reduce the risk of breast cancer incidence. In addition, potential breast cancer chemopreventive effect of *Camellia sinensis* both in vivo and in vitro was highly confirmed. However, the evidence of low effect and no effect was observed. More clinical trial studies are needed to prove its anti-breast cancer activity decisively.

**Conclusion:** *Camellia sinensis* is broadly utilized as a part of customary medication since antiquated time because of its cost adequacy, and fewer reaction properties. The studies demonstrated anti-breast cancer activity of *Camellia sinensis* and its component by adjusting cell signaling pathways such as angiogenesis, apoptosis, and transcription factor. Furthermore, *Camellia sinensis* and its chemical compound was shown to be extremely useful in the development of novel anticancer medications.

**Keywords:** *Camellia sinensis*, chemopreventive, chemotherapeutic, catechins, Phytochemicals

**1. Introduction****1. Background**

The therapeutic role of herbal medicine in the treatment of various diseases, were investigated and confirmed (1-13). *Camellia sinensis* belongs to family Theaceae, is indigenous to East Asia and cultivated worldwide in tropical and subtropical areas. It is a species of hardy shrub, whose leaves and leaf buds are used to make tea. The seeds of *Camellia sinensis* are used for therapeutic and cosmetic purposes, and emanate from the leaves of another herb. *Camellia sinensis* (green tea) is a Chinese tea, popularly consumed as a healthy beverage, and has been demonstrated to possess various therapeutic activities, including antioxidants (14-17), anti obesity (18) and anticancer (19, 20), wound healing (21), cognitive and memory improvement (22), anti-inflammatory (23), anti arthritic (24), antibacterial (25), antimicrobial (26, 27), antiangiogenic (28), antiviral (29), cholesterol-lowering

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effects (30) and anti-kidney injury (4). The leaves contribute to cure asthma, angina pectoris, vascular disease, and diabetes (3, 31). It has been found to possess neuroprotective effect (32). It can also contribute to the treatment of cardiovascular diseases (33). *Camellia sinensis* possesses healing effects due to its polyphenol content (34, 35), especially flavonols. The main constituent of herb is Catechins, which are a sort of polyphenol, and have a modulatory effect in the various genes in the development and progression of cancer. The major Catechins consist of: epicatechin (EC), -epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG) (36, 37). EGCG is one of the most abundant Catechins containing about 50–80% of the total content of Catechins (38).

### **1.2. Statement of problem**

There are many medicinal herbs containing natural compositions that have properties which can treat and cure many diseases. The diversity of natural compounds in herbs and their various roles in preventing and treating different diseases together with the naturalness and compatibility with the body, and having no adverse effects, motivate people to have more interest in their application, and researchers to have much more inclination towards studies on them and recognize their curative effects. However, there is still elusion regarding their efficacy, pharmacological dosage and toxicity. To achieve this purpose, lots of studies have been carried out to concentrate on the ability of herbs to generate a favorable chemical and pharmacological profile. Breast cancer is a dangerous and fatal disease. To cure such a cancer, the intake of a natural agent with no side effects, is of high importance.

### **1.3. Objective of research**

This review article is aimed to overview breast cancer chemopreventive and chemotherapeutic effects of *Camellia sinensis* (green tea).

## **2. Material and Methods**

This review was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases. The initial search strategy identified around 108 references. In this study, 68 studies were accepted for further screening and met all our inclusion criteria [in English, full text, chemopreventive and chemotherapeutic effects of *Camellia sinensis*]. Inclusion criteria were the following key words used to search for the relevant articles published from 1999 to 2016, their full text should be available in English. Articles included consisted of clinical trials, in vitro, in vivo, review, or meta-analysis studies. Exclusion criteria were when only abstract was available, not in the timeline of study. Those articles not matching our inclusion criteria (in other languages than English, between the timeline of study) were excluded from the study.

## **3. Results**

Increased *Camellia sinensis* consumption may be inversely associated with risk of breast cancer recurrence. Furthermore, it showed that this plant is a promising breast cancer chemopreventive candidate via mechanistic actions of tea polyphenols in growth factor signaling, angiogenesis and lipid metabolism (39). Treatment of 4T1 cells with *Camellia sinensis* aqueous extract, resulted in significant inhibition of 4T1 cell proliferation via 4T1 apoptosis in a dose-dependent manner. This extract was shown to contribute in bone protection against breast cancer-induced bone destruction (40). In another study, it was recommended that further clinical trial study with large sample size on the efficacy of *Camellia sinensis* polyphenols or extracts are required, before a definitive decision can be made for its cancer prevention (41). The individual and combined effects of PCB 102 and EGCG on cell proliferation was evaluated. It was shown that *Camellia sinensis* which possesses potential chemoprevention of breast cancer through the process of EGCG, suppressed the proliferation-stimulating activity of the environmental estrogen PCB 102. Tea or *Camellia sinensis* drinking was not found to be associated with overall breast cancer risk. As the result was drawn on pre- and post-menopausal women, it may be interfered (42). In a clinical trial study, the role of daily *Camellia sinensis* intake was investigated for 12 months on biomarkers of breast cancer risk. The result showed a potential anti-breast cancer for green tea (43). In a clinical trial study, GTE on breast cancer biomarkers was investigated. The result showed that daily intake of GTE is generally well tolerated by a group of mainly postmenopausal women (44). In a human study of the role of coffee and tea consumption, caffeine intake was assessed. Findings suggested that coffee and caffeine intake lower the risk of breast cancer, while tea consumption increased the risk of breast cancer (45). Higher caffeinated coffee intake has lower risk of postmenopausal breast cancer, while decaffeinated coffee intake does not have any effect on breast cancer (46). Estrogen receptor-dependent and independent mechanisms are responsible to the treatment of estrogen receptor-positive and estrogen receptor-negative breast cancer. There was no interaction of herb Catechins with aromatase inhibitors or fulvestrant (47). Combination of Arc and EGCG with Cur in both cell lines, showed the strongest effects on cell cycle arrest

and apoptosis increasing chemoprevention in both prostate and breast cancer (48). *Camellia sinensis* polyphenols and their applications in the prevention and treatment of breast cancer was investigated. The result showed a potential effect of *Camellia sinensis* components on breast cancer (49). Effect of *Camellia sinensis* in women with primary breast cancer was assessed. The result showed a decrease in Ki-67 in both benign and malignant cells in the *Camellia sinensis* group, confirming its anti-breast cancer activity (50). The relationship between *Camellia sinensis* utilization and breast cancer in light of the hormone receptor status of tumors was inspected. No considerable impact adjustment was seen for menopausal status, 4 SNPs, or dietary consumption of folate or isoflavone. This research showed that *Camellia sinensis* intake does not decrease the venture of breast cancer (51). In a Japanese population, it was found that there was no association between *Camellia sinensis* intake and risk of breast cancer (52). The beneficial effect of *Camellia sinensis* in breast cancer therapy is because of the modification of the breast cancer miRNA expression profile, as well as the altered miRNA regulation of potential oncogenes and tumor-suppressor genes (53). In a hormone-resistant breast cancer approach study, the anti-breast cancer effect of *Camellia sinensis* extract was attributed to ER $\alpha$  expression restoring by epigenetic mechanisms regulation and HDAC inhibitor combination (54). The impact of every day utilization of decaffeinated *Camellia sinensis* for 6 months on weight and body arrangement, metabolic parameters and lipid profiles in overweight breast growth survivors, was tried. Consumption of decaffeinated *Camellia sinensis* for 6 months resulted in reduced weight and improvement in HDL and glucose homeostasis (55). Suppression of catechol-O-methyltransferases action in human breast carcinoma cells could expand the proteasome-inhibitory intensity of EGCG and in this way, upgrade its tumor cell development inhibitory action. COMT inhibition probably expands anti-cancer activity of tea polyphenols, and the mix may be utilized as a new method or supplementary therapy for breast carcinoma chemotherapy (56).

The effects of EGCG on the migration and invasion of MCF-7 cells was examined. The result illustrated that the inhibitory effect of EGCG on MCF-7 cell migration and invasion may be caused by a down regulation of VASP expression through the Rac1 pathway in a concentration-dependent manner (57). Among premenopausal women, reduced risk was observed for years of *Camellia sinensis* drinking (P-trend = 0.02), and a dose-response relationship with the amount of tea consumed per month was also observed (P-trend = 0.046). Thus, the result demonstrated that *Camellia sinensis* intake may be loosely associated with a decreased risk of breast cancer (58). In a Chinese population, higher dietary intake of combination of mushrooms and *Camellia sinensis* reduced breast cancer risk in pre- and postmenopausal women (59). There was a protective effect against breast cancer and *Camellia sinensis* intake was investigated. The result showed no relationship between *Camellia* eating and breast cancer venture. Furthermore, results propose that folate pathway restraint might be one mechanism via which *Camellia sinensis* secures against breast cancer (60). The impact of *Camellia sinensis* Catechins on breast cell carcinogenesis has been explored. *Camellia sinensis* Catechins was reported to act in high concentrations or by endocrine treatment (61). Inhibitory impact of EGCG on stifling tumor angiogenesis and breast cancer advancement was explored. The findings support the idea that EGCG specifically targets both tumor cells and tumor vasculature, consequently restraining tumor development, expansion, relocation, and angiogenesis of breast disease (62). The GTC activity at non-cytotoxic levels was investigated. It was identified that GTC was successful in stifling NNK-and B[a] P-instigated cell carcinogenesis. GTC might be utilized as a part of dietary and chemoprevention of breast cell carcinogenesis connected with long haul presentation to low measurements of natural cancer-causing agents (63).

#### 4. Discussion

It is of high importance to identify a healthy lifestyle which will reduce the risk of breast cancer. Although there has been much progress in its treatment, there is still high a rate of mortality from breast cancer. Medical care methodologies are needed for chemoprevention of high risk women and for the treatment of receptor negative breast tumors. In this study, the chemopreventive and chemotherapeutic breast cancer potential of *Camellia sinensis* was reviewed. In addition, the mechanisms of action of *Camellia sinensis* intake against breast cancer was discussed. Furthermore, the phytochemical property of plant against breast carcinogenesis was overviewed. Several studies have demonstrated strong chemopreventive and chemotherapeutic actions of *Camellia sinensis* polyphenols against cancer. This chemopreventive effect was attributed from one side, to its chemical compound (38) and on the other side, to its mechanistic action (39, 54, 60, 64, 65). The plant enjoys an anticancer agent partly by regulating epigenetic processes in ER $\alpha$  silencing in breast cancer lines (54). There are several anti-breast cancer mechanisms of action of *Camellia sinensis*. Inhibiting the Folate pathway is the mechanism of cancer preventive activities of EGCG (60). Another mechanism of action of *Camellia sinensis* is to inhibit the neoplastic process (62). Green tea extraction appeared to be compelling in smothering NNK-and B[a] P-incited cell carcinogenesis. GTC might be utilized as a part of nourishment and chemoprevention of breast cell carcinogenesis (63). All these mechanisms contribute to prevent and inhibit the cancer processes (initiation, promotion and progress) through the herb uptake. However,

clinical studies show contradictory results. Many factors possess a serious effect on the ultimate effect of plant polyphenols on the carcinogenesis process, including the beverage temperature, the period of consumption, and the amount of consumed tea in proportion to diet (66). Polyphenol, epigallocatechin-3-gallate (EGCG) is the main chemical compound and an anticancer agent accessible in *Camellia sinensis* (36). Catechins present in the plant, hold chemoprevention breast cancer activity via inhibitory impacts of epigallocatechin gallate on the development of existing tumors consisting breast disease (67). *Camellia sinensis* polyphenol epigallocatechin gallate (EGCG) and curcumin (Cur) increases the chemopreventive ability of individual compounds.

### 5. Conclusions

*Camellia sinensis* has been widely used in traditional medicine since ancient times due to its cost efficacy, and fewer side effect properties. The studies demonstrated anti-breast cancer activity of *Camellia sinensis* and its constituents, by modulating cell signaling pathways including angiogenesis, apoptosis, and transcription factor. Furthermore, *Camellia sinensis* and its chemical compound were shown to be very helpful in the construction of novel anticancer drugs.

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### Conflict of Interest:

There is no conflict of interest to be declared.

### Authors' contributions:

Both authors contributed to this project and article equally. Both authors read and approved the final manuscript.

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