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PHYTOCHEMISTRY PROFILE, EFFICACY, AND SAFETY OF GREEN TEA (*Camellia sinensis* (L.) Kuntze) FOR BREAST CANCER CHEMOPREVENTION: A SYSTEMATIC REVIEW

Review Sistematik: Profil Fitokimia Khasiat dan Keamanan Teh Hijau (Camellia sinensis (L.) Kuntze) *untuk Kemopreventif Kanker Payudara*

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ABSTRACT

The consumption of tea (Camellia sinensis (L.) Kuntze), mainly green tea, is famous for various health benefits. This review summarizes the potential use of green tea and epigallocatechin gallate (EGCG) for breast cancer chemoprevention. The data were retrieved from the online publication on the Pubmed database and covered the phytochemistry, preclinical study, and clinical trial of green tea related to its use as a breast cancer chemopreventive agent. Catechins, particularly EGCG, are the chemopreventive bioactive constituents of green tea. Preclinical studies demonstrated that the anti-proliferative and induction of apoptosis potentials of green tea are mediated through several different mechanisms. However, no association between green tea intake and a lowered breast cancer risk in human studies, but it might be favorable for secondary cancer prevention.

Keywords**:** *green tea, epigallocatechin gallate, chemopreventive, breast cancer.*

ABSTRAK

Konsumsi teh (*Camellia sinensis* (L.) Kuntze), terutama teh hijau, terkenal dengan berbagai manfaat kesehatannya. Ulasan ini merangkum potensi penggunaan teh hijau dan *epigallocatechin gallate* (EGCG) untuk kemoprevensi kanker payudara. Data diambil dari publikasi online di database Pubmed dan mencakup fitokimia, studi praklinis, dan uji klinis teh hijau terkait dengan penggunaannya sebagai agen kemopreventif kanker payudara. Katekin, khususnya EGCG, adalah konstituen bioaktif kemopreventif teh hijau. Studi praklinis menunjukkan bahwa teh hijau memiliki potensi anti-proliferatif dan induksi apoptosis yang dimediasi melalui beberapa mekanisme yang berbeda. Namun, tidak ada hubungan antara asupan teh hijau dan penurunan risiko kanker payudara dalam penelitian pada manusia, tetapi mungkin menguntungkan untuk pencegahan kanker sekunder.

Kata kunci: teh hijau, epigallocatechin gallate, kemopreventif, kanker payudara.

INTRODUCTION

Tea (*Camellia sinensis* (L.) Kuntze) is consumed worldwide, particularly in Asia, for its flavor, functional, and therapeutic benefits. It has been long used, and the health benefits have been recognized since ancient times (Hayat *et al*., 2015). About a fifth of the total tea produced and consumed worldwide is green tea. Compared to other tea types, green tea contains the highest content of catechins, which results from the non-oxidized processing of tea leaves (Singh *et al.*, 2017). In green tea production, tea leaves are subjected to steaming to inactivate polyphenol oxidase and are not undergoing the complete fermentation process. It protects catechins from further oxidative polymerization, and hence their concentrations remained high.

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For example, almost half of the ethyl acetate soluble fraction of decaffeinated infusion of green tea was EGCG, while epicatechin gallate, epigallocatechin, and epicatechin were accounted for 12.90, 9.50, and 6.68%, respectively (Liu, Ou, & Huang, 2017).

The health benefits associated with the traditional green tea intake, i.e., dementia, hypertension, and coronary heart diseases, have been confirmed. A significant association between green tea intake with a lower risk of dementia was reported in Japan (Tomata et al., 2016). It is proven to be associated with lower blood pressure and decreased likelihood of having hypertension in the elderly population in China (Yin *et al.,* 2017). Another Chinese study outlined its association with lower incidence and better biomarker profile of coronary heart disease in middle-aged and older populations *(Tian et al.,* 2016).

This article aims to compile the phytochemistry profile and the efficacy and safety of green tea for breast cancer chemoprevention from both preclinical and clinical studies. The use of EGCG as a bioactive compound is emphasized in this article. The effects of green tea intake to the breast cancer risk as well as prevention and treatment of the disease with green tea have been highlighted in numerous works *(Li et al.,* 2014; Najafi et al., 2018; Rafieian-Kopaei & Movahedi, 2017). This article provides additional information on the detailed phytochemical profile of green tea, which has not been covered in previous reviews.

METHOD

A comprehensive electronic literature search for articles was conducted in the PubMed database. The date filter was applied to cover the last ten years of the literature (2010–2020). Four keywords, green tea, epigallocatechin gallate, chemopreventive, and breast cancer, were combined using the appropriate Boolean operators (AND, OR) to ensure all relevant articles were retrieved. The in-vitro and in-vivo studies, randomized controlled trials, and hospital-controlled case reports were included in this review, while comments, review articles, and case reports were excluded. Out of 56 records identified and screened, 30 articles were eligible and included in this review.

RESULTS AND DISCUSSION

The phytochemical profile of green tea

The known bioactive compounds in tea leaves are presented in Figure 1. They were retrieved from the KNApSAcK family (http://www.knapsackfamily.com/KNApSAcK_Family/) and Dr. Duke's Phytochemical and Ethnobotanical (https://phytochem.nal.usda.gov/phytochem/search) databases. Tea typically contains polyphenols, amino acids, volatile flavor compounds, methylxanthines, and various other constituents. The compounds identified in leaves are including (+)-catechin (**1**), gallocatechin (**2**), (-)- epicatechin (**3**), (-)-epigallocatechin (**4**), epiafzelechin (**5**), naringenin (**6**), kaempferol (**7**), isovitexin (**8**), vitexin (**9**), 6,8-di-C-beta-D-arabinopyranosylapigenin, (**10**), epiafzelechin 3-O-gallate (**11**), (-)-epigallocatechin gallate (**12**), (-)-Epicatechin 3-O-gallate (**13**), epicatechin 3-O-(3-O-methylgallate) (**14**), epicatechin 3-O-(4-O-methylgallate) (**15**), epicatechin 3,5-di-O-gallate (**16**), epigallocatechin 3,5,-di-O-gallate (**17**), epigallocatechin 3-O-cinnamate (**18**), epigallocatechin 3-O-p-coumarate (**19**), epigallocatechin 3-O-caffeate (**20**), epicatechin 3-O-p-hydroxybenzoate (**21**), epigallocatechin 3,3',-di-O-gallate (**22**), epigallocatechin 3,4',-di-O-gallate (**23**), assamicain A (**24**), assamicain C (**25**), theaflavin 3'-O-gallate (**26**), theaflavin 3,3'-di-O-

gallate (**27**), oolongtheanin (**28**), isotheaflavin (**29**), oolonghomobisflavan A (**30**), oolonghomobisflavan B (**31**), epigallocatechin-(4β->8)-epicatechin-3-O-gallate (**32**), catechin-(4alpha->8)-epigallocatechin (**33**), gallocatechin-(4α->8)-epicatechin (**34**), procyanidin B2 (**35**), procyanidin B3 (**36**), procyanidin B4 (**37**), procyanidin C1 (**38**), theasinensin A (**39**), prodelphinidin B4 (**40**), epicatechin(4 β ->8)epigallocatechin 3-O-gallate (**41**), theaflavin (**42**), astragalin (**43**), myricetin3-O-galactoside (**44**), kaempferol3-glucosyl-(1->3)-rhamnosyl-(1->6)-galactoside (**45**), quercetin3-glucosyl-(1->3)-rhamnosyl-(1->6)-galactoside (**46**), camellianin A (**47**), camellianin B (**48**), vicenin 3 (**49**), isoschaftoside (**50**), theasinensin F (**51**), theasinensin B (**52**), theasinensin C (**53**), theaflavonin (**54**), tricetinidin (**55**), (Z)-jasmone (**56**), salicylaldehyde (**57**), 8-C-ascorbyl epigallocatechin 3-O-gallate (**58**), theaflagallin (**59**), epitheaflagallin3-O-gallate (**60**), nicotiflorin (**61**), adenine (**62**), xanthine (**63**), caffeine (**64**), theobromine (**65**), theophylline (**66**), indole (**67**), theasaponin (**68**), barringtogenol C (**69**), and α-terpineol (**70**). Hence, the polyphenols are considered the main bioactive constituents of tea, with prominent sub-groups of simple polyphenols, oxidized polyphenols, flavanols, flavonols, and their glucosides, phenolic acids, theaflavins, and thearubigins.

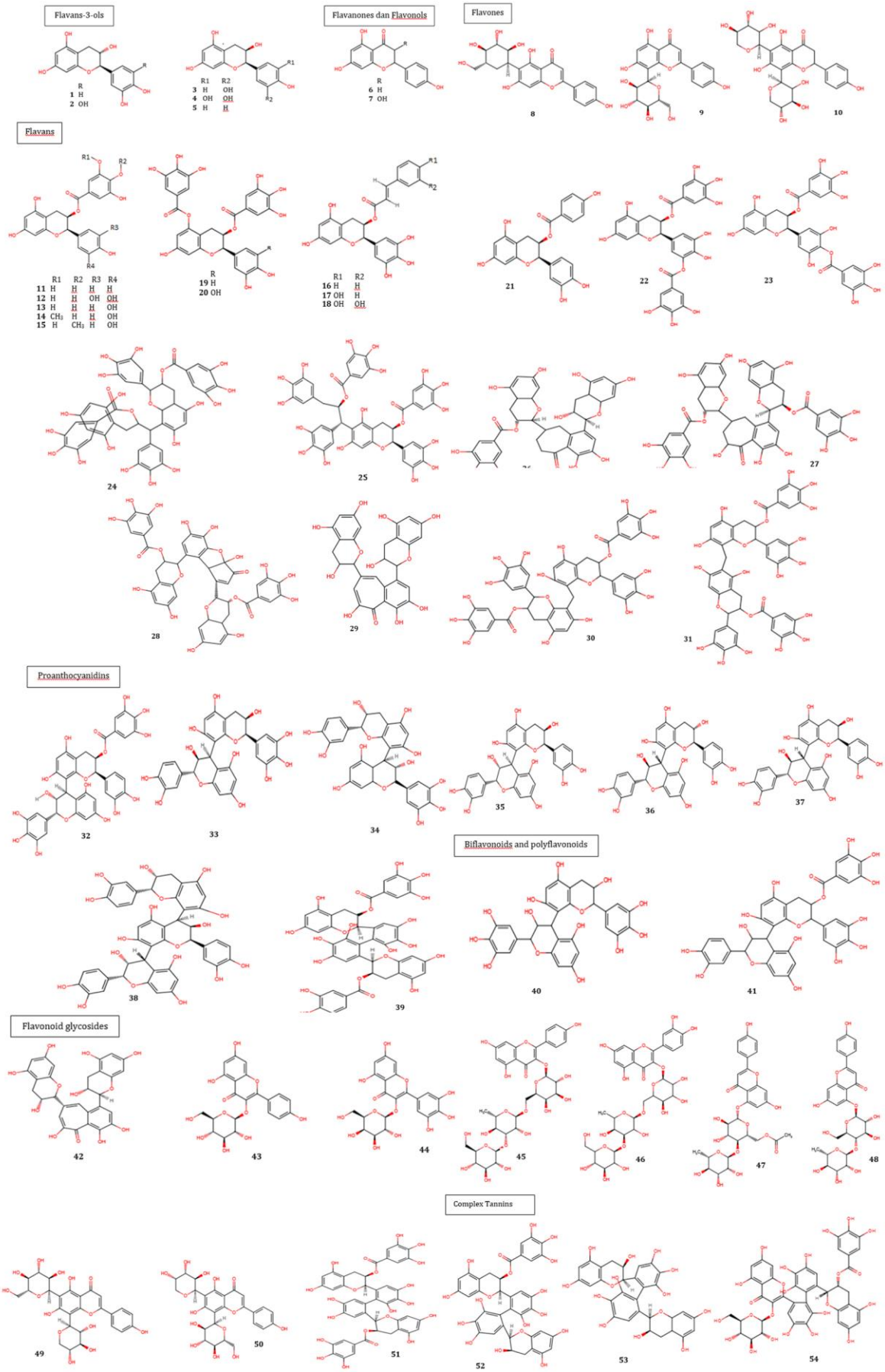
Preclinical studies of chemopreventive-related activities of green tea

The chemopreventive-related activities of green tea have been well-studied. There are reports on the use of infusion and polyphenols fraction of the tea, but most studies evaluate the activity of EGCG. Green tea infusion inhibited 4T1 metastatic breast cells' proliferation and increased up-regulation of caspase-8, caspase-9, caspase-3, caspase-6, caspase-8AP2, *Aifm1*, *Aifm2*, and *Apopt1* genes. Hence, the anti-proliferative mechanisms of green tea infusion on 4T1 were mediated by inducing caspases that were subsequently followed by activating the apoptotic pathway (Mbuthia *et al.,* 2017). The standardized green tea polyphenols fraction showed inhibitory activity on MCF-7 breast cancer cells growth by the mechanisms of cell cycle arrest at both G1/M and G2/M transitions and mitochondrial-mediated apoptosis (Liu *et al*., 2017). The cell proliferation inhibitory and apoptotic induction effects of Ziyang green tea extract with high polyphenol content and selenium on MCF-7 were mediated via similar mechanisms (Wenfeng Li, He, Tian, Shi, & Yang, 2016). Further, green tea catechin extract prevented the carcinogenesis development in MCF10A cells stimulated by long-term exposure to low doses of carcinogens (Rathore & Wang, 2012).

EGCG increased the apoptotic rates of MCF-7 cells while significantly up-regulated mRNA and protein expression of P53 and down-regulated those of Bcl-2. It also induced apoptosis and arrested the progression at the G2/M phase, hindered miR-25 expression, promoted PARP and procaspases expression, and suppressed tumor growth (Huang *et al.,* 2017; Zan *et al.,* 2019). Earlier reports mentioned that the apoptotic in MCF-7 by EGCG was mediated by α9-nAChR signaling pathway, the cell membrane-associated signaling pathways, as well as inhibition of the expression of HSP70 and HSP90 (Hsu & Liou, 2011; Tran *et al.,* 2010; Tu *et al.,* 2011).

EGCG lowered mitochondrial membrane potential, promoted ROS production, changed nuclear morphology, and decreased the viability of A-431 and SK-BR-3 cells in a dose-dependent manner. It partially decreased the phosphorylation of cell proliferation and survival-related proteins (Filippi *et al.,* 2018).

The steroid receptors, mainly estrogen receptor-α (ERα), might mediate the effects of EGCG on breast cancer cells. It dose-dependently down-regulated ERα protein levels in T-47D breast cancer cells. Co-treatment of EGCG and 17β-estradiol (E2) on T-47D also significantly down-regulated ERα protein levels and inverted the E2 proliferative effect. Furthermore, the viability of the cells remained comparable to the control (Hallman *et al.*, 2017).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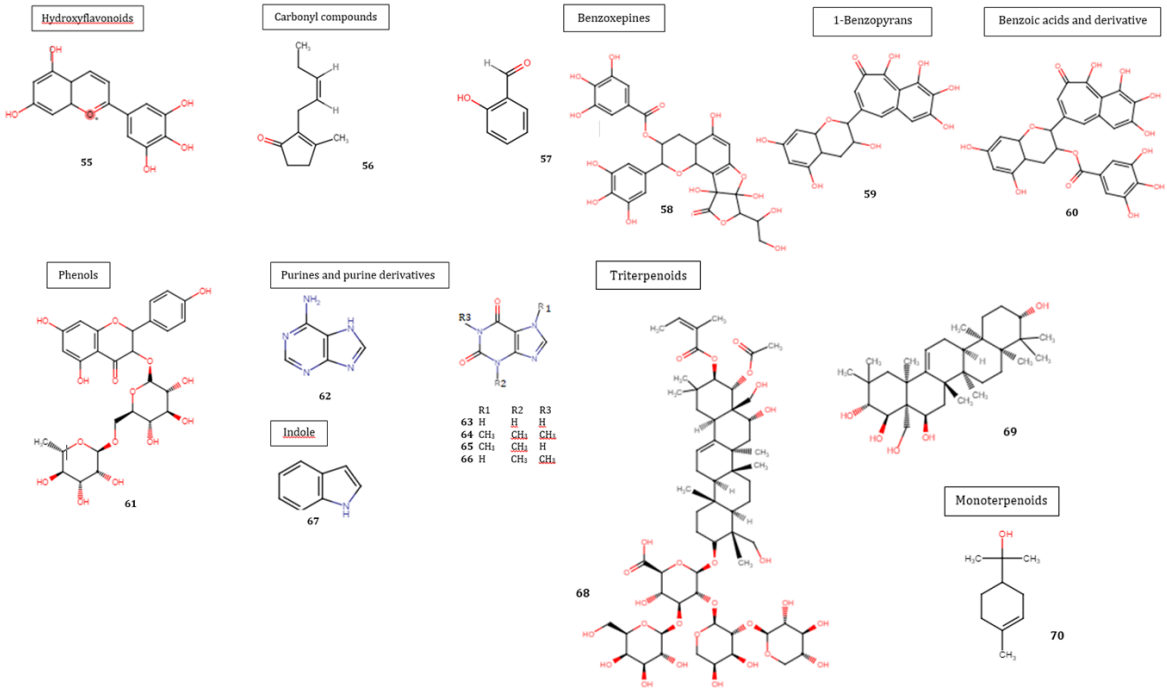

Figure 1. The secondary metabolites of green tea

EGCG inhibited the growth of MDA-MB-231 and MDA-MB-436 progenitors by specifically reduced the expression of ER-α36. However, in ER-α36 knocked-down cells, no significant inhibitory effects were observed. Hence, the down-regulation of ER-α36 expression followed the down-regulation of EGFR (Pan *et al.,* 2016). On the other hand, the proliferation inhibitory activity of EGCG on estrogen-sensitive breast cancer MCF-7/BOS cells was mediated via ER*β* modulation and was blocked by PHTPP (Baker & Bauer, 2015).

The expression of β-catenin significantly increased in patients with ER-negative breast cancer. The inactivation of the related signaling pathway by EGCG resulted in the inhibition of MDA-MB-231 growth. This compound decreased viability and down-regulated β-catenin, phosphorylated Akt, and cyclin D1 expression. Hence, EGCG might be beneficial for treating breast cancer without ER expression, which is clinically more aggressive and has a poorer prognosis (Hong *et al.,* 2017). Also, EGCG induced apoptosis in T-47D cells via inhibition of telomerase and PI3K/AKT pathways, the pro-apoptotic genes up-regulation, and the survival genes down-regulation. The cell death by EGCG is suggested as the result of the mitochondrial function modulation (Moradzadeh *et al.,* 2017).

Aside from directly induced cell death via apoptosis, EGCG also affected the metabolisms of glucose, lactate, and ATP in 4T1 breast cancer cells. EGCG also dose-dependently reduced breast tumor weight and decreased glucose and lactic acid levels in Balb/c mice (Wei *et al.,* 2018). The efficacy of EGCG for the chemoprevention of breast cancer is improved by encapsulating it in a suitable wall material. This strategy enables better stability and bioavailability of EGCG. The positive effects of encapsulations on the cytotoxic effects of EGCG have been demonstrated in MDA-MB 231 and MCF-7 cells (Pace *et al.,* 2013; Radhakrishnan *et al.,* 2016; Zeng *et al.,* 2017).

The combination of green tea with other compounds seems to be an effective strategy to enhance the chemopreventive effects. Such compelling evidence has been demonstrated in the

studies combining EGCG with curcumin, green tea polyphenol with arctigenin and curcumin, and EGCG with quercetin (Chung & Vadgama, 2015; Huang *et al.,* 2013; Wang *et al.,* 2014a; Wang *et al.,* 2014b). Interestingly, the combination of green tea extract and tamoxifen prevented mammary tumorigenesis in C3H/OuJ mice model (Sakata *et al.,* 2011). A recent study reported that administration of green tea polyphenols combined with tamoxifen showed the best breast tumor inhibitory effects in ERα-negative xenografted mice (Li *et al.,* 2017). Hence, the strong evidence for the chemopreventive effects of green tea in the in-vitro studies and animal models is available elsewhere. These support the need for evaluation of the efficacy of the extract in human studies.

Human studies of chemopreventive-related activities of green tea

The clinical studies of green tea are summarized in Table 1. A Japanese study mentioned no association between green tea consumption with a decreased risk of breast cancer. Also, the menopausal status, types of single nucleotide polymorphisms, or dietary intake of folate or isoflavone did not substantially modify the effect of green tea (Iwasaki *et al.,* 2014). A similar result was reported in Hong Kong, where there was no evidence for the association between tea drinking and overall breast cancer risk. However, it reduced among premenopausal women but rose among postmenopausal counterparts were reported. It is postulated that the association might be modified by tumor ER and tea-drinking age starting (Li *et al.,* 2016). Finally, a prospective cohort study concluded that intake of at least five cups of green or black tea per week might be associated with reducing the risk in women with a family history of breast cancer (Zhang *et al.,* 2020). All epidemiological studies are summarized in Table 1.

Minnesota Green Tea Trial (MGTT) evaluated the effectiveness of green tea for the prevention of breast cancer. It used the changes in mammographic density (MD) as the parameters of the chemopreventive potential of green tea. It showed that 12-month supplementation with high doses of green tea extract did not significantly change MD or percent MD (PMD) in all women. However, a statistically significant reduction in PMD was observed in the younger women (50–55 years). The precise mechanisms of this phenomenon are unknown, but the hormonal-mediated pathways might have a role as the younger women showed higher baseline levels of circulating and urinary estrogen levels (Samavat *et al.,* 2017).

Further, green tea might be beneficial for secondary cancer prevention. The use of a high dose of EGCG was generally well tolerated. However, a higher incidence of nausea and dermatologic adverse effects and the elevated alanine aminotransferase (ALT) level was observed in the participant who received green tea extracts (Dostal *et al.,* 2015).

A study showed that the maximum tolerated dose (MTD) of Polyphenon E, an oral green tea extract, was 600 mg twice daily (Crew *et al.,* 2015). The participants who received Polyphenon E showed a significant decrease in the mean serum hepatocyte growth factor (HGF) level compared to the placebo group. However, the decreased HGF level difference was no longer observed after 4 and 6 months of treatment. The decreasing serum cholesterol level in patients treated with Polyphenon E was observed after two months of treatment. Hence, green tea might help secondary cancer prevention among breast cancer survivors with the potential mechanism of action, including modifying growth factor signaling, angiogenesis, and lipid metabolism (Crew *et al.,* 2015).

Interestingly, the ingestion of EGCG-standardized green tea capsules showed a significant reduction in Ki-67 levels in both benign and malignant cell components of patients who underwent surgery. However, caspase-3 and CD34 levels were not affected (Yu *et al.,* 2013).

Hence, the evidence of the efficacy of green tea for the prevention of breast cancer is not as compelling as its preclinical studies. However, it might be beneficial for breast cancer survivors.

Table 1. Summary of epidemiological and clinical studies on the chemopreventive potential of green tea for breast cancer

No	Type of study	Intervention	Number of participants	Key findings	References
1	Placebo-controlled phase II clinical study	Oral decaffeinated green tea extract (standardized to 1,315 mg of total catechins and 843 mg of EGCG), daily for 12 months	1,075 healthy postmenopausal women with MD >50%	A high dose of EGCG did not affect MD in overall participants but decreased PMD in younger ones	(Samavat et al., 2017)
2	Placebo-controlled phase II clinical study	Oral decaffeinated green tea extract (standardized to 1,315 mg of total catechins and 843 mg of EGCG), daily for 12 months	1,075 healthy postmenopausal women with MD >50%	A high dose of EGCG was generally well tolerated	(Dostal et al., 2015)
3	Randomized, double-blinded, placebo-controlled, dose-escalation phase IB study	Oral decaffeinated green tea extract (Polyphenon E) provides a total EGCG intake of 800, 1200, or 1600 mg daily for six months	40 participants with a stage I–III HR-negative breast cancer history	The limit of the safe dose was 1,200 mg daily	(Crew et al., 2012)
4	Randomized, double-blinded, placebo-controlled, dose-escalation phase IB study	Oral decaffeinated green tea extract (Polyphenon E) provides a total EGCG intake of 800, 1,200, or 1,600 mg daily for six months	40 participants with a stage I–III HR-negative breast cancer history	Polyphenon E decreased the serum HGF, VEGF, and cholesterol levels after two months of treatment	(Crew et al., 2015)
5	Pre-surgical trial	Three green tea capsules (standardized to 725 mg EGCG/capsule) daily for 35 day	13 and 15 patients in the treatment and control group, respectively	Green tea significantly declined Ki-67 levels in both benign and malignant cell components but did not affect caspase-3 and CD34	(Yu et al., 2013)
6	Hospital-based case-control study	-	405 pairs of breast cancer patients and healthy control	There were no associations between green tea intake with a reduction in breast cancer risk	(Iwasaki et al., 2014)
7	Hospital-based case-control study	-	756 primary breast cancer patients and 789 hospital control	There were no associations between regular or green tea consumption with	(Li et al., 2016)

No	Type of study	Intervention	Number of participants	Key findings	References
				the overall breast cancer risk	
8	Prospective cohort study	-	50,884 women between the ages of 35 and 74 across with family history of breast cancer	There might be an association between green or black tea uptake at least five cups per week with decreased breast cancer risk.	(Zhang et al., 2020)

CONCLUSION

Available data suggested that polyphenols are the main constituents of green tea. The breast cancer chemopreventive effects of green tea are attributed to catechins, particularly EGCG. The evidence suggested that green tea and the EGCG were effective for breast cancer chemoprevention in various cell lines and animal models. However, the promising anti-proliferative and induction of apoptosis properties of green tea in the in-vivo studies are not demonstrated in clinical studies. There is no association between tea consumption with the decreased risk of breast cancer incidents. The high-dose EGCG supplementation was safe, but it did not change the predictor of breast cancer risk. It might be beneficial for secondary cancer prevention among breast cancer survivors.

REFERENCES

Baker, K. M., & Bauer, A. C. (2015). Green tea catechin, EGCG, suppresses PCB 102-induced proliferation in estrogen-sensitive breast cancer cells. *International Journal of Breast Cancer*, *2015* article ID 163591. https://doi.org/10.1155/2015/163591

Chung, S. S., & Vadgama, J. V. (2015). Curcumin and epigallocatechin gallate inhibit the cancer stem cell phenotype via down-regulation of STAT3–NFκB signaling. *Anticancer Research*, *35*, 39–46.

Crew, K. D., Ho, K. A., Brown, P., Greenlee, H., Bevers, T. B., Arun, B., … Hershman, D. L. (2015). Effects of a green tea extract, Polyphenon E, on systemic biomarkers of growth factor signalling in women with Hormone Receptor-negative breast cancer. *Journal of Human Nutrition and Dietetics*, *28*, 272–282. https://doi.org/10.1111/jhn.12229

Crew, Katherine D., Brown, P., Greenlee, H., Bevers, T. B., Arun, B., Hudis, C., … Hershman, D. L. (2012). Phase IB randomized, double-blinded, placebo-controlled, dose escalation study of Polyphenon E in women with Hormone Receptor-negative breast cancer. *Cancer Prevention Research*, *5*(9), 1144–1154. https://doi.org/10.1158/1940-6207.CAPR-12-0117

Dostal, A. M., Samavat, H., Bedell, S., Torkelson, C., Wang, R., Swenson, K., … Kurzer, M. S. (2015). The safety of green tea extract supplementation in postmenopausal women at risk for breast cancer: Results of the Minnesota Green Tea Trial. *Food and Chemical Toxicology*, *83*, 26–35. https://doi.org/10.1016/j.fct.2015.05.019

Filippi, A., Picot, T., Aanei, C. M., Nagy, P., Szöllősi, J., Campos, L., … Mocanu, M.-M. (2018). Epigallocatechin-3-O-gallate alleviates the malignant phenotype in A-431 epidermoid and SKBR-3 breast cancer cell lines. *International Journal of Food Sciences and Nutrition*, *69*(5), 584–597. https://doi.org/10.1080/09637486.2017.1401980

Hallman, K., Aleck, K., Quigley, M., Dwyer, B., Lloyd, V., Szmyd, M., & Dinda, S. (2017). The regulation of steroid receptors by epigallocatechin-3-gallate in breast cancer cells. *Breast Cancer: Targets and Therapy*, *9*, 365–373. https://doi.org/10.2147/BCTT.S131334

Hayat, K., Iqbal, H., Malik, U., Bilal, U., & Mushtaq, S. (2015). Tea and its consumption: Benefits and risks. *Critical Reviews in Food Science and Nutrition*, *55*(7), 939–954. https://doi.org/10.1080/10408398.2012.678949

Hong, O., Noh, E., Jang, H., Lee, Y., Lee, B. K., Jung, S. H., … Youn, H. J. (2017). Epigallocatechin gallate inhibits

the growth of MDA-MB-231 breast cancer cells via inactivation of the β-catenin signaling pathway. *Oncology Letters*, *14*, 441–446. https://doi.org/10.3892/ol.2017.6108

Hsu, Y.-C., & Liou, Y.-M. (2011). The anti-cancer effects of (-)-epigalocathine-3-gallate on the signaling pathways associated with membrane receptors in MCF-7 cells. *Journal of Cellular Physiology*, *226*, 2721–2730. https://doi.org/10.1002/jcp.22623

Huang, C.-Y., Han, Z., Li, X., Xie, H.-H., & Zhu, S.-S. (2017). Mechanism of EGCG promoting apoptosis of MCF-7 cell line in human breast cancer. *Oncology Letters*, *14*, 3623–3627. https://doi.org/10.3892/ol.2017.6641

Huang, C., Lee, S.-Y., Lin, C.-L., Tu, T.-H., Chen, L. H., Chen, Y. J., & Huang, H.-C. (2013). Co-treatment with quercetin and 1,2,3,4,6-penta-o-galloyl-β-d-glucose causes cell cycle arrest and apoptosis in human breast cancer MDA-MB-231 and AU565 cells. *Journal of Agricultural and Food Chemistry*, *61*, 6430−6445. https://doi.org/10.1021/jf305253m

Iwasaki, M., Mizusawa, J., Kasuga, Y., Yokoyama, S., Onuma, H., Nishimura, H., … Tsugane, S. (2014). Green tea consumption and breast cancer risk in Japanese women: A case-control study. *Nutrition and Cancer*, *66*(1), 57–67. https://doi.org/10.1080/01635581.2014.847963

Li, M.-J., Yin, Y.-C., Wang, J., & Jiang, Y.-F. (2014). Green tea compounds in breast cancer prevention and treatment. *World Journal of Oncology*, *5*(3), 520–528. https://doi.org/10.5306/wjco.v5.i3.520

Li, M., Tse, L. A., Chan, W., Kwok, C., Leung, S., Wu, C., … Yang, X. R. (2016). Evaluation of breast cancer risk associated with tea consumption by menopausal and estrogen receptor status among Chinese women in Hong Kong. *Cancer Epidemiology*, *40*, 73–78. https://doi.org/10.1016/j.canep.2015.11.013

Li, Y., Meeran, S. M., & Tollefsbol, T. O. (2017). Combinatorial bioactive botanicals re-sensitize tamoxifen treatment in ER-negative breast cancer via epigenetic reactivation of ERα expression. *Scientific Reports*, *7*, article ID 9345. https://doi.org/10.1038/s41598-017-09764-3

Liu, S.-M., Ou, S.-Y., & Huang, H.-H. (2017). Green tea polyphenols induce cell death in breast cancer MCF-7 cells through induction of cell cycle arrest and mitochondrial-mediated apoptosis. *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*, *18*(2), 89–98. https://doi.org/10.1631/jzus.B1600022

Mbuthia, K. S., Mireji, P. O., Ngure, R. M., Stomeo, F., Kyallo, M., Muoki, C., & Wachira, F. N. (2017). Tea (Camellia sinensis) infusions ameliorate cancer in 4TI metastatic breast cancer model. *BMC Complementary and Alternative Medicine*, *17*, 202. https://doi.org/10.1186/s12906-017-1683-6

Moradzadeh, M., Hosseini, A., Erfanian, S., & Rezaei, H. (2017). Epigallocatechin-3-gallate promotes apoptosis in human breast cancer T47D cells through down-regulation of PI3K/AKT and Telomerase. *Pharmacological Reports*, *69*, 924–928. https://doi.org/10.1016/j.pharep.2017.04.008

Najafi, M. N., Salehi, M., Ghazanfarpour, M., Hoseini, Z. S., & Khadem-Rezaiyan, M. (2018). The association between green tea consumption and breast cancer risk: A systematic review and meta-analysis. *Phytotheraphy Research*, *32*(10), 1855–1864. https://doi.org/10.1002/ptr.6124

Pace, R. C. C. de, Liu, X., Sun, M., Nie, S., Zhang, J., Cai, Q., … Wang, S. (2013). Anticancer activities of (-)-epigallocatechin-3-gallate encapsulated nanoliposomes in MCF7 breast cancer cells. *Journal of Liposome Research*, *23*(3), 187–196. https://doi.org/10.3109/08982104.2013.788023

Pan, X., Zhao, B., Song, Z., Han, S., & Wang, M. (2016). Estrogen receptor-a36 is involved in epigallocatechin-3-gallate induced growth inhibition of ER-negative breast cancer stem/progenitor cells. *Journal of Pharmacological Sciences*, *120*, 85–93. https://doi.org/10.1016/j.jphs.2015.12.003

Radhakrishnan, R., Kulhari, H., Pooja, D., Gudem, S., Bhargava, S., Shukla, R., & Sistla, R. (2016). Encapsulation of biophenolic phytochemical EGCG within lipid nanoparticles enhances its stability and cytotoxicity against cancer. *Chemistry and Physics of Lipids*, *198*, 51–60. https://doi.org/http://dx.10.1016/j.chemphyslip.2016.05.006

Rafieian-Kopaei, M., & Movahedi, M. (2017). Breast cancer chemopreventive and chemotherapeutic effects of Camellia sinensis (green tea): An updated review. *Electronic Physician*, *9*(2), 3838–3844. https://doi.org/10.19082/3838

Rathore, K., & Wang, H.-C. R. (2012). Green tea catechin extract in intervention of chronic breast cell carcinogenesis induced by environmental carcinogens. *Molecular Carcinogenesis*, *51*(3), 280–289. https://doi.org/10.1002/mc.20844

Sakata, M., Ikeda, T., Imoto, S., Jinno, H., & Kitagawa, Y. (2011). Prevention of mammary carcinogenesis in C3H/OuJ mice by green tea and tamoxifen. *Asian Pacific Journal of Cancer Prevention*, *12*(2), 567–571.

Samavat, H., Ursin, G., Emory, T. H., Lee, E., Wang, R., Torkelson, C. J., … Kurzer, M. S. (2017). A randomized controlled trial of Green tea extract supplementation and mammographic density in

postmenopausal women at increased risk of breast cancer. *Cancer Prevention Research*, *10*(12), 710–718. https://doi.org/10.1158/1940-6207.CAPR-17-0187

Singh, B. N., Prateeksha, Rawat, A. K. S., Bhagat, R. M., & Singh, B. R. (2017). Black tea: Phytochemicals, cancer chemoprevention, and clinical studies. *Critical Reviews in Food Science and Nutrition*, *57*(7), 1394–1410. https://doi.org/10.1080/10408398.2014.994700

Tian, C., Huang, Q., Yang, L., Légaré, S., Angileri, F., Yang, H., … Zhan, X. (2016). Green tea consumption is associated with reduced incident CHD and improved CHD-related biomarkers in the Dongfeng-Tongji cohort. *Scientific Reports*, *6*, 24353. https://doi.org/10.1038/srep24353

Tomata, Y., Sugiyama, K., Kaiho, Y., Honkura, K., Watanabe, T., Zhang, S., … Tsuji, I. (2016). Green tea consumption and the risk of incident dementia in elderly Japanese: The Ohsaki cohort 2006 study. *American Journal of Geriatric Psychiatry*, *24*(10), 881–889. https://doi.org/10.1016/j.jagp.2016.07.009

Tran, P. L. C. H. B., Kim, S.-A., Choi, H. S., Yoon, J.-H., & Ahn, S.-G. (2010). Epigallocatechin-3-gallate suppresses the expression of HSP70 and HSP90 and exhibits anti-tumor activity in vitro and in vivo. *BMC Cancer*, *10*, article ID 276. https://doi.org/10.1186/1471-2407-10-276

Tu, S.-H., Ku, C.-Y., Ho, C.-T., Chen, C.-S., Huang, C.-S., Lee, C.-H., … Ho, Y.-S. (2011). Tea polyphenol (-)-epigallocatechin-3-gallate inhibits nicotine- and estrogen-induced a9-nicotinic acetylcholine receptor up-regulation in human breast cancer cells. *Molecular Nutrition and Food Research*, *55*(3), 455–466. https://doi.org/10.1002/mnfr.201000254

Wang, P., Wang, B., Chung, S., Wu, Y., Henning, S. M., & Vadgama, J. V. (2014a). Increased chemopreventive effect by combining arctigenin,green tea polyphenol and curcumin in prostate and breast cancer cells. *RSC Advances*, *4*(66), 35242–35250. https://doi.org/10.1039/C4RA06616B

Wang, S., Chen, R., Zhong, Z., Shi, Z., Chen, M., & Wang, Y. (2014b). Epigallocatechin-3-gallate potentiates the effect of curcumin in inducing growth inhibition and apoptosis of resistant breast cancer cells. *The American Journal of Chinese Medicine*, *42*(5), 1279–1300. https://doi.org/10.1142/S0192415X14500803

Wei, R., Mao, L., Xu, P., Zheng, X., Hackman, R. M., Mackenzie, G. G., & Wang, Y. (2018). Suppressing glucose metabolism with epigallocatechin-3-gallate (EGCG) reduces breast cancer cell growth in preclinical models. *Food & Function*, *9*, 5682–5696. https://doi.org/10.1039/c8fo01397g

Wenfeng Li, He, N., Tian, L., Shi, X., & Yang, X. (2016). Inhibitory effects of polyphenol-enriched extract from Ziyang tea against human breast cancer MCF-7 cells through reactive oxygen species-dependent mitochondria molecular mechanism. *Journal of Food and Drug Analysis*, *24*(3), 527–538. https://doi.org/10.1016/j.jfda.2016.01.005

Yin, J.-Y., Duan, S.-Y., Liu, F.-C., Yao, Q.-K., Tu, S., Xu, Y., & Pan, C.-W. (2017). Blood pressure is associated with tea consumption: A cross-sectional study in a rural, elderly population of Jiangsu China. *The Journal of Nutrition, Health & Aging*, *21*(10), 1151–1159. https://doi.org/10.1007/s12603-016-0829-4

Yu, S. S., Spicer, D. V., Hawes, D., Tseng, C.-C., Yang, C. S., Pike, M. C., & Wu, A. H. (2013). Biological effects of green tea capsule supplementation in pre-surgery postmenopausal breast cancer patients. *Frontiers in Oncology*, *3*, article ID 298. https://doi.org/10.3389/fonc.2013.00298

Zan, L., Chen, Q., Zhang, L., & Li, X. (2019). Epigallocatechin gallate (EGCG) suppresses growth and tumorigenicity in breast cancer cells by downregulation of miR-25. *Bioenginered*, *10*(1), 374–382. https://doi.org/10.1080/21655979.2019.1657327

Zeng, L., Yan, J., Luo, L., Ma, M., & Zhu, H. (2017). Preparation and characterization of (−)-Epigallocatechin-3-gallate (EGCG)-loaded nanoparticles and their inhibitory effects on Human breast cancer MCF-7 cells. *Scientific Reports*, *7*, 45521. https://doi.org/10.1038/srep45521

Zhang, D., Nichols, H. B., Troester, M., Cai, J., Bensen, J. T., & Sandler, D. P. (2020). Tea consumption and breast cancer risk in a cohort of women with family history of breast cancer. *International Journal of Cancer*, *147*(3), 876–886. https://doi.org/10.1002/ijc.32824