Tea Resists Carcinogenesis

Subjects: Pharmacology & Pharmacy
Contributor: Xiangbing Mao

Tea remains one of the most prevalent beverages consumed due in part to its physiological properties. The active compounds in tea, including tea polyphenols, tea polysaccharides, *L*-theanine, tea pigments, caffeine and other minor composition, can directly or indirectly reduce oncogenesis and cancerometastasis. Interestingly, the different types of tea (such as unfermented green tea, partially fermented oolong tea, and fully fermented black tea or pu-erh tea) have the different anti-cancer property.

Keywords: Tea and its components ; Carcinogenesis ; Tea types ; Anti-cancer

1. Introduction

The major tea-producing countries are China, India, Japan, Sri Lanka, Indonesia, and Central African countries [1]. The argument that tea is a cancer preventive agent is no longer new. A pioneering study in the mid-1990s summarized the available epidemiologic information and found that tea consumption is likely to have beneficial effects on reducing the cancer risk in some people [2]. Recently, a meta-analysis found an inverse association between tea consumption and cancer risk [3]. And, some evidence does not support the hypothesis that tea can reduce the risk of cancer [4]. The above conflicting results could be due to variations in the types, dosage, and drinking manner of tea. In fact, the components and quality of tea are variable by the category, growth environment, storage time, and method of production, which will affect the original beneficial effects of tea[5].

2. The Resisting Carcinogenesis of Tea Components

2.1. Tea Polyphenols

Tea polyphenols are one of the most important ingredients in regulating the redox balance of tea. Tea polyphenols can reduce the incidence and development of tumors in the stomach, intestines, liver, lungs, skin and other parts of the whole body [6][7][8][9][10]. Catechins are the most abundant polyphenols in tea, mainly including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) [11]. Among them, EGCG is the major catechin in tea, and may account for 50–80% of the total catechins [12].

Tea polyphenols could decrease the risk of skin cancer through inhibiting ultraviolet light B (UVB)-induced oxidative stress, such as the depletion of antioxidant enzymes, lipid oxidation, and the infiltration of inflammatory cells [7]. In a two-stage model of diethylnitrosamine (DEN)/phenobarbital (PB)-induced hepatocarcinogenesis of Sprague-Dawley rats, oral gavage of tea polyphenols five times weekly could significantly increase the total antioxidant capacity (T-AOC) and glutathione peroxidase (GPX) activity in livers [6]. In the multistage mouse skin carcinogenesis model, peracetylated EGCG treatment could decrease the expression of oxidative enzymes, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 [13]. In addition, tea polyphenols show a pro-oxidative activity. EGCG induced oxidative stress and mitochondrial dysfunction, and played an anti-cancer role in oral cancer [14].

In addition to acting as preventive agents, tea polyphenols can also be used as adjuvant therapies for various cancers. When EGCG is combined with a conventional cancer therapy additive, synergistic effects have been proposed, which are mainly due to its anti-inflammatory and anti-oxidative activities that improve the side effects during cancer treatment [15]. Zhang et al. found that the administration of 400 mg EGCC three times daily potentiated the efficacy of radiotherapy in patients [16]. However, EGCG also has antagonistic interactions with PS-341, which will limit its clinical use. PS-341 is an anti-myeloma drug which activity would be blocked by EGCG through vicinal diols on polyphenols interacting with the boronic acid of PS-341 [17]. As a consequence, pre-clinical studies on tea polyphenols (particularly on the bioactive utilization, mechanism of action, and safety of EGCG) need to be carried out.

2.2. Tea polysaccharides

Tea polysaccharides (TPS) are a group of hetero-polysaccharides bonded with proteins [18]. Yang et al. reported that TPS (400–800 μg/mL) significantly improved the anti-oxidative capacity in a dose-dependent manner, and inhibited the cancerometastasis of gastric cancer in mice [19]. Selenium (Se)-containing TPS (IC50 of 140.1 μg/mL) induced ROS generation, which made cells undergo G2/M phase arrest and apoptosis and exhibited effective inhibition of human breast cancer MCF-7 cell growth [20]. Moreover, compared with the utilization of doxorubicin (DOX) alone, a combination of TPS and DOX has a better suppression efficiency in lung cancer A549 cells [5].

2.3. L-theanine

L-theanine is a natural amino acid, which is found specifically in tea plants and makes up 1–2% of the dry weight of tea leaves [5]. Liu et al. found that theanine and its derivates had no toxicity in mice [21]. Recent studies have shown that, in addition to relieving depression, memory improvement, and neuroprotection [22][23][24], L-theanine may also have anti-tumor activities. Adriamycin (ADR) was used to efficiently treat Ehrlich ascites carcinoma cells and its side effects, such as reducing antioxidant enzyme activity and increasing the level of lipid peroxidation, can be alleviated by the combined utilization of L-theanine [25].

2.4. Tea pigments

Tea pigments are the oxidized products of polyphenols and their derivatives in tea leaves, and mainly consist of theaflavins (TFs), thearubigins (TRs), and theabrownin [26]. The composition of tea pigments in black tea are similar to that of the tea polyphenols in green tea, but the former is chemically stable and may be an ideal chemopreventive agent [27]. In a rat liver precancerous lesion model, the treatment with tea pigments suppressed cancer biomarkers, such as glutathione S-transferase Pi (GST-Pi) mRNA and protein [28]. Furthermore, in an *in vivo* trial on 1,2-dimethylhydrazine (DMH)-induced rat colorectal carcinogenesis, treatment with 0.1% tea pigments reduced aberrant cryptic foci (ACF) and colonic tumor formation [29].

2.5. Caffeine

Caffeine, the most abundant alkaloid in tea, makes up 2–4% of the dry weight, and its structure is identified as 1,3,7-trimethylxanthine [30]. Caffeine has been shown to have both positive and negative health effects. The cancer preventative effects of caffeine in rodent hepatocellular carcinoma (HCC) models have also been demonstrated [31]. Chronic caffeine ingestion inhibited rat breast cancer, neither by interfering with the high prolactin levels that is a necessary step in murine tumor development, nor by causing hypocaloric intake [32]. However, an *in vivo* trial showed that the rats consuming caffeine and unsaturated fat had the earliest tumor development and the most multiple tumor occurrence [33].

3. Tea types and anti-cancer

Along with studying the different components of tea, studies should also be undertaken to analyze their anti-cancer properties. Generally, tea is divided into three main types based on production, namely unfermented green tea, partially fermented oolong tea, and fully fermented black tea or pu-erh tea [34]. There are not a consistent conclusion on the anti-oxidant capacity of tea polyphenols derived from the differently produced teas. The individual effects of green tea, black tea, and oolong tea on cancer are difficult to confirm using epidemiological research, mainly due to many consuming several tea types [35]. However, it appears that when comparing the anti-cancer effects between green tea and black tea, the former is more efficient [36][37]. This can be associated with the stronger antioxidant capacity and protective effects of green tea [35]. Record and Dreosti reported that treatment with black tea provided more protection than green tea in solar irradiation-induced skin cancer in hairless mice [38]. Until now, there has been no direct evidence that oolong tea, a semi-fermented tea, has the ability to fight cancer. Only one *in vitro* experiment showed that oolong tea has the worst inhibiting effect on the invasion and proliferation of AH109A compared with green and black teas [39].

References

1. S. Sang; Tea: Chemistry and Processing. *Encyclopedia of Food and Health* **2016**, *1*, 268-272, 10.1016/b978-0-12-384947-2.00685-1.
2. Chung S. Yang; Zhi-Yuan Wang; Tea and Cancer. *JNCI: Journal of the National Cancer Institute* **1993**, *85*, 1038-1049, 10.1093/jnci/85.13.1038.

3. Xin Zhan; Jie Wang; Shufen Pan; Caijuan Lu; Tea consumption and the risk of ovarian cancer: A meta-analysis of epidemiological studies. *Oncotarget* **2017**, *8*, 37796-37806, 10.18632/oncotarget.16890.

4. Marieke G M Braem; N Charlotte Onland-Moret; Leo J Schouten; Anne Tjønneland; Louise Hansen; Christina C Dahm; Kim Overvad; Annekatrin Lukanova; Laure Dossus; Anna Floegel; et al. Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. *The American Journal of Clinical Nutrition* **2012**, *95*, 1172-1181, 10.3945/ajcn.111.026393.

5. Xiangbing Mao; Xiangjun Xiao; Daiwen Chen; Bing Yu; Jun He; Tea and Its Components Prevent Cancer: A Review of the Redox-Related Mechanism. *International Journal of Molecular Sciences* **2019**, *20*, 5249, 10.3390/ijms20215249.

6. Fan Zhou; Ting Shen; Ting Duan; Yu-Ying Xu; Soo Chin Khor; Jin Li; Juan Ge; Yi-Fan Zheng; Stephen Hsu; Jamie De Stefano; et al. Antioxidant effects of lipophilic tea polyphenols on diethylnitrosamine/phenobarbital-induced hepatocarcinogenesis in rats.. *In Vivo* **2014**, *28*, 495-503, 0.

7. Aili Gao; Huaping Li; Na Jiang; Qing Liu; Xin Zhou; Bihua Liang; Huilan Zhu; Topical treatment of green tea polyphenols emulsified in carboxymethyl cellulose protects against acute ultraviolet light B-induced photodamage in hairless mice. *Photochemical & Photobiological Sciences* **2016**, *15*, 1264-1271, 10.1039/C6PP00073H.

8. Jung Sun Park; Pham Ngoc Khoi; Young Eun Joo; Young Han Lee; Sven A. Lang; Oliver Stoeltzing; Young Do Jung; EGCG inhibits recepteur d'origine nantais expression by suppressing Egr-1 in gastric cancer cells. *International Journal of Oncology* **2013**, *42*, 1120-1126, 10.3892/ijo.2013.1775.

9. Jay Morris; Vondina R. Moseley; April B. Cabang; Katie Coleman; Wei Wei; Elizabeth Garrett-Mayer; Michael J. Wargovich; Reduction in promotor methylation utilizing EGCG (epigallocatechin-3-gallate) restores RXRα expression in human colon cancer cells. *Oncotarget* **2016**, *7*, 35313-35326, 10.18632/oncotarget.9204.

10. Pan Jiang; Xiaoyue Wu; Xuemin Wang; Wenbin Huang; Qing Feng; NEAT1 upregulates EGCG-induced CTR1 to enhance cisplatin sensitivity in lung cancer cells. *Oncotarget* **2016**, *7*, 43337-43351, 10.18632/oncotarget.9712.

11. Xiangbing Mao; Changsong Gu; Daiwen Chen; Bing Yu; Jun He; Oxidative stress-induced diseases and tea polyphenols. *Oncotarget* **2017**, *8*, 81649-81661, 10.18632/oncotarget.20887.

12. Shengmin Sang; Joshua D. Lambert; Chi-Tang Ho; Chung S. Yang; The chemistry and biotransformation of tea constituents. *Pharmacological Research* **2011**, *64*, 87-99, 10.1016/j.phrs.2011.02.007.

13. Yi-Shiou Chiou; Shengmin Sang; Kuang-Hung Cheng; Chi-Tang Ho; Ying-Jan Wang; Min-Hsiung Pan; Cheng-Wei Yang; Yue-Zhi Lee; Hsing-Yu Hsu; Hwan-You Chang; et al. Peracetylated (−)-epigallocatechin-3-gallate (AcEGCG) potently prevents skin carcinogenesis by suppressing the PKD1-dependent signaling pathway in CD34 + skin stem cells and skin tumors. *Carcinogenesis* **2013**, *34*, 1315-1322, 10.1093/carcin/bgt042.

14. Ling Tao; Sarah C. Forester; Joshua D. Lambert; Abstract 5436: The role of reactive oxygen species in (-)-epigallocatechin-3-gallate (EGCG)-induced cell growth inhibition and apoptosis in oral cancer cells. *Prevention Research* **2012**, *72*, 5436-5436, 10.1158/1538-7445.am2012-5436.

15. Elena Lecumberri; Yves Marc Dupertuis; Raymond Miralbell; Claude Pichard; Green tea polyphenol epigallocatechin-3-gallate (EGCG) as adjuvant in cancer therapy. *Clinical Nutrition* **2013**, *32*, 894-903, 10.1016/j.clnu.2013.03.008.

16. G. Zhang; Y. Wang; Y. Zhang; X. Wan; J. Li; K. Liu; F. Wang; K Liu; Q. Liu; C. Yang; et al. Anti-cancer activities of tea epigallocatechin-3-gallate in breast cancer patients under radiotherapy.. *Current Molecular Medicine* **2012**, *12*, 163-76, 10.2174/156652412798889063.

17. Tae Young Kim; Jongmin Park; Bora Oh; Hyun Jung Min; Tae-Sook Jeong; Jae Hoon Lee; Seung Bum Park; Dong Soon Lee; The Korean Multiple Myeloma Working Party (Kmmwp); (−)-Epigallocatechin-3-Gallate (EGCG), Green Tea Component, Antagonize the Anti-Myeloma Activity of Proteasome Inhibitor PS-341 by Direct Chemical Interaction.. *Blood* **2007**, *110*, 4850-4850, 10.1182/blood.v110.11.4850.4850.

18. Ling-Ling Du; Qiu-Yue Fu; Li-Ping Xiang; Xin-Qiang Zheng; Jian-Liang Lu; Jian-Hui Ye; Qing-Sheng Li; Curt Anthony Polito; Yue-Rong Liang; Tea Polysaccharides and Their Bioactivities. *Molecules* **2016**, *21*, 1449, 10.3390/molecules21111449.

19. Jianjun Yang; Bin Chen; Yan Gu; Pharmacological evaluation of tea polysaccharides with antioxidant activity in gastric cancer mice. *Carbohydrate Polymers* **2012**, *90*, 943-947, 10.1016/j.carbpol.2012.06.024.

20. Nianwu He; Xiaolong Shi; Yan Zhao; Lingmin Tian; Dongying Wang; Xingbin Yang; Inhibitory Effects and Molecular Mechanisms of Selenium-Containing Tea Polysaccharides on Human Breast Cancer MCF-7 Cells. *Journal of Agricultural and Food Chemistry* **2013**, *61*, 579-588, 10.1021/jf3036929.

21. Jiannan Liu; Yuping Sun; Huarong Zhang; Dexin Ji; Fei Wu; Huihui Tian; Kun Liu; Ying Zhang; Benhao Wu; Guoying Zhang; et al. Theanine from tea and its semi-synthetic derivative TBrC suppress human cervical cancer growth and

migration by inhibiting EGFR/Met-Akt/NF-κB signaling. *European Journal of Pharmacology* **2016**, *791*, 297-307, 10.1016/j.ejphar.2016.09.007.

22. Takami Kakuda; Neuroprotective effects of the green tea components theanine and catechins.. *Biological and Pharmaceutical Bulletin* **2002**, *25*, 1513-1518, 10.1248/bpb.25.1513.
23. Pradeep J. Nathan; Kristy Lu; M. Gray; C. Oliver; The Neuropharmacology of L-Theanine(N -Ethyl-L-Glutamine). *Journal of Herbal Pharmacotherapy* **2006**, *6*, 21-30, 10.1080/j157v06n02_02.
24. Guilan Li; Jingjing Kang; Xiangyang Yao; Yinqiang Xin; Qi Wang; Yin Ye; Lan Luo; Zhimin Yin; The component of green tea, L-theanine protects human hepatic L02 cells from hydrogen peroxide-induced apoptosis. *European Food Research and Technology* **2011**, *233*, 427-435, 10.1007/s00217-011-1534-5.
25. Yasuyuki Sadzuka; Tomomi Sugiyama; Atsuo Miyagishima; Yasuo Nozawa; Sadao Hirota; The effects of theanine, as a novel biochemical modulator, on the antitumor activity of adriamycin. *Cancer Letters* **1996**, *105*, 203-209, 10.1016/0304-3835(96)04282-6.
26. Michiyo Tomita; Kara I. Irwin; Zi-Jian Xie; Thomas J. Santoro; Tea pigments inhibit the production of type 1 (TH1) and type 2 (TH2) helper T cell cytokines in CD4+ T cells. *Phytotherapy Research* **2002**, *16*, 36-42, 10.1002/ptr.834.
27. C Han; Y Gong; [Experimental studies on the cancer chemoprevention of tea pigments].. *Wei sheng yan jiu = Journal of hygiene research* **1999**, *28*, 343, 0.
28. Yunyun Gong; Chi Han; Junshi Chen; Effect of Tea Polyphenols and Tea Pigments on the Inhibition of Precancerous Liver Lesions in Rats. *Nutrition and Cancer* **2000**, *38*, 81-86, 10.1207/s15327914nc381_12.
29. Xu Dong Jia; Chi Han; Chemoprevention of tea on colorectal cancer induced by dimethylhydrazine in Wistar rats. *World Journal of Gastroenterology* **2000**, *6*, 699-703, 10.3748/wjg.v6.i5.699.
30. D. M. Graham; Caffeine - Its Identity, Dietary Sources, Intake and Biological Effects. *Nutrition Reviews* **2009**, *36*, 97-102, 10.1111/j.1753-4887.1978.tb03717.x.
31. Jun-Ichi Okano; Takakazu Nagahara; Kazuya Matsumoto; Yoshikazu Murawaki; Caffeine Inhibits the Proliferation of Liver Cancer Cells and Activates the MEK/ERK/EGFR Signalling Pathway. *Basic & Clinical Pharmacology & Toxicology* **2008**, *102*, 543-551, 10.1111/j.1742-7843.2008.00231.x.
32. Jeanne A. Petrek; Wendy A. Sandberg; Marlene N. Cole; Morton S. Silberman; Delwood C. Collins; The inhibitory effect of caffeine on hormone-induced rat breast cancer. *Cancer* **1985**, *56*, 1977-1981, 10.1002/1097-0142(19851015)56:8<1977::aid-cncr2820560815>3.0.co;2-7.
33. J. P. Minton; M. K. Foecking; M. G. Sriram; H. Abou-Issa; H. Abou-Issa; Caffeine and unsaturated fat diet significantly promotes DMBA-induced breast cancer in rats. *Cancer* **1983**, *51*, 1249-1253, 10.1002/1097-0142(19830401)51:7<1249::aid-cncr2820510713>3.0.co;2-q.
34. Kuan-Li Kuo; Meng-Shih Weng; Chun-Te Chiang; Yao-Jen Tsai; Shoei-Yn Lin-Shiau; Jen-Kun Lin; Comparative Studies on the Hypolipidemic and Growth Suppressive Effects of Oolong, Black, Pu-erh, and Green Tea Leaves in Rats. *Journal of Agricultural and Food Chemistry* **2005**, *53*, 480-489, 10.1021/jf049375k.
35. Andy H. Lee; Dada Su; Maria Pasalich; Colin W. Binns; Tea consumption reduces ovarian cancer risk. *Cancer Epidemiology* **2013**, *37*, 54-59, 10.1016/j.canep.2012.10.003.
36. Naping Tang; Yuemin Wu; Bo Zhou; Bin Wang; Rongbin Yu; Green tea, black tea consumption and risk of lung cancer: A meta-analysis. *Lung Cancer* **2009**, *65*, 274-283, 10.1016/j.lungcan.2008.12.002.
37. Jusheng Zheng; Bin Yang; Tao Huang; Yinghua Yu; Jing Yang; Duo Li; Green Tea and Black Tea Consumption and Prostate Cancer Risk: An Exploratory Meta-Analysis of Observational Studies. *Nutrition and Cancer* **2011**, *63*, 663-672, 10.1080/01635581.2011.570895.
38. Ian R Record; Ivor E Dreosti; Protection by black tea and green tea against UVB and UVA + B induced skin cancer in hairless mice.. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* **1998**, *422*, 191-199, 10.1016/s0027-5107(98)00192-4.
39. Guoying Zhang; Yutaka Miura; Kazumi Yagasaki; Effects of green, oolong and black teas and related components on the proliferation and invasion of hepatoma cells in culture. *Cytotechnology* **1999**, *31*, 37-44, 10.1023/A:1008076306672.