



## Recent advances in the anticancer molecular mechanisms of bioactive components from tea: a review

Jie Pan<sup>a</sup>, Chuanai Chen<sup>b</sup>, Liang Bai<sup>a\*</sup> and Hui Zhao<sup>a\*</sup>

<sup>a</sup>Tianjin Key Laboratory of Food and Biotechnology, College of Biotechnology and Food Science, Tianjin University of Commerce, Tianjin 300134, China

<sup>b</sup>Tianjin Blood Center, Tianjin 300110, China

\*Corresponding author: Liang Bai and Hui Zhao, Tianjin Key Laboratory of Food and Biotechnology, College of Biotechnology and Food Science, Tianjin University of Commerce, Tianjin 300134, China. E-mail: bailing20101@163.com (LB) and zhaohui@tjcu.edu.cn (HZ)

DOI: 10.31665/JFB.20xx.000xx

Received: August 22, 2024; Revised received & accepted: September 04, 2024

Citation: Pan, J., Chen, C., Bai, L., and Zhao, H. (2024). Recent advances in the anticancer molecular mechanisms of bioactive components from tea: a review. J. Food Bioact. 000: 000–000.

### Abstract

Tea is one of the most popular health drinks around the world, especially in China, Japan, and Southeast Asia. Drinking tea has become a traditional culture and healthy lifestyle for preventing diseases in these countries and regions. Recent scientific researches indicate that tea has good efficacy in anti-cancer. The bioactive components and related anti-cancer mechanisms of tea are constantly being supplemented. Drinking tea can reduce the incidence of cancers. However, there is a lack of a systematic summary of the current tea anticancer research process to date. Here, we conduct an update on the bioactive components and anti-cancer mechanisms of tea.

**Keywords:** Tea; Epidemiological studies; Bioactive components; Anticancer; Molecular mechanisms.

### 1. Introduction

Tea (*Camellia sinensis*), generally contains the leaves and buds of the tea tree and is the most consumed healthy drink in the world. Tea drinking is very popular in Asian countries such as China, Japan, and Indonesia, and has gradually aroused interest in Western countries (Tang et al., 2019). According to the different processing technologies, tea can be divided into six categories, green tea, black tea, white tea, oolong tea, yellow tea, and dark tea (Abudurehman et al., 2022). Research in recent years has shown the beneficial effects of tea, including anti-oxidation, lowering blood sugar, anti-bacteria, and anti-cancer (Ni et al., 2020; Wang et al., 2014). Tea contains many effective functional ingredients and has been widely used in beverages, foods, and medicines (Xu et al., 2023).

In recent years, cancer gradually become a high fatality rate disease worldwide and has become a focus of attention and research in developed and developing countries (Sung et al., 2021). An accumulating body of research shows that tea drinking can decrease the risk of obesity, metabolic syndrome, cancer, and other diseases, and improve the body's immunity (Moreira et al., 2022; Yu et al.,

2023; Zhao et al., 2021). Previous reviews have shown that tea may be a potentially effective substance for reducing the risk of cancer (Yang and Wang, 1993; Yang, 1999). This article reviews the main bioactive components in tea and advances in anticancer molecular mechanisms, emphasizes the importance of bioactive components and related mechanisms in tea to reduce the occurrence of cancer, and provides new ideas for the prevention and treatment of cancer.

### 2. Tea reduces the risk of cancer

Cancer has become a non-hereditary disease with a high fatality rate worldwide and the leading killer of human health, including lung cancer, breast cancer, prostate cancer, and colorectal cancer (Avgerinos et al., 2019; Mizrahi et al., 2020). Tea drinking associated with the risk reduction of cancer has been confirmed by researchers (Liu et al., 2021; Filippini et al., 2020). Especially in Southeast Asia and other areas where drinking tea is popular, people who drink tea regularly have a much lower risk of cancer than normal people (Oh et al., 2019). The last five years of epidemio-

**Table 1. Summary and comparison of recent epidemiological articles of tea and cancer**

Cancer type	Object	Type of tea	Comparison	Metric	Result	P Value
Liver cancer (Li et al., 2023)	Chinese females	Tea	Cumulative consume over 30kg vs none	aHRs (95%CI)	0.56 (95% CI: 0.32–0.97)	0.038
Liver cancer (Li et al., 2023)	Chinese females	Green tea	Cumulative consume over 30kg vs none	aHRs (95%CI)	0.54 (95% CI: 0.30–0.98)	0.051
Bladder cancer (Al-Zalabani et al., 2022)	Overall	Tea	Low vs none	HR (95%CI)	0.87 (95% CI:0.77–0.98)	0.004
Bladder cancer (Al-Zalabani et al., 2022)	Overall	Tea	Middle vs none	HR (95%CI)	0.86 (95% CI:0.77–0.96)	0.004
Bladder cancer (Al-Zalabani et al., 2022)	Overall	Tea	High vs none	HR (95%CI)	0.84 (95% CI:0.75–0.95)	0.004
Ovarian cancer (Zheng et al., 2023)	female	Black tea	Any vs none	RR (95%CI)	0.64 (95% CI:0.51–0.80)	<0.001
Brain cancer (Song et al., 2019)	Asians	Tea	High vs low	RR (95%CI)	0.64 (95% CI:0.21–2.02)	0.026
Brain cancer (Song et al., 2019)	Americans	Tea	High vs low	RR (95%CI)	0.80 (95% CI:0.76–1.50)	0.595
Stomach cancer (Martimianaki et al., 2022)	Europeans	Tea	Regular consumption vs non-regular consumption	OR (95%CI)	1.00 (95% CI:0.90–1.11)	<0.001
Stomach cancer (Martimianaki et al., 2022)	Asians	Tea	Regular consumption vs non-regular consumption	OR (95%CI)	0.62 (95% CI:0.48–0.81)	<0.001
Stomach cancer (Martimianaki et al., 2022)	Chinese and Japanese	Tea	Regular consumption vs non-regular consumption	OR (95%CI)	0.67 (95% CI:0.49–0.91)	<0.001
Stomach cancer (Martimianaki et al., 2022)	Iranians	Tea	Regular consumption vs non-regular consumption	OR (95%CI)	0.50 (95% CI:0.29–0.86)	<0.001
Stomach cancer (Martimianaki et al., 2022)	Americans	Tea	Regular consumption vs non-regular consumption	OR (95%CI)	0.95 (95% CI:0.87–1.05)	<0.001
Kidney cancer (Chen et al., 2022)	Japanese	Tea	5cups/days vs rarely	HR (95%CI)	0.75 (95% CI:0.51–1.12)	0.39
Kidney cancer (Chen et al., 2022)	Japanese males	Tea	5cups/days vs rarely	HR (95%CI)	0.96 (95% CI:0.59–1.56)	0.74
Kidney cancer (Chen et al., 2022)	Japanese females	Tea	5cups/days vs rarely	HR (95%CI)	0.75 (95% CI:0.51–1.12)	0.05
Prostate cancer (Sen et al., 2019)	Europeans	Tea	High vs low	HR (95%CI)	0.98 (95% CI:0.90–1.07)	>0.1
Prostate cancer (Sen et al., 2019)	Europeans	Tea	Moderate vs low	HR (95%CI)	0.98 (95% CI:0.91–1.05)	>0.1
Breast cancer (Zhang et al., 2019)	Chinese females	Green tea	Regular consumption vs none consumption	HR (95%CI)	0.27 (95% CI:0.09–0.86)	<0.05
Breast cancer (Zhang et al., 2019)	Chinese females	Black tea	Regular consumption vs none consumption	HR (95%CI)	0.29 (95% CI:0.04–2.08)	<0.05
Breast cancer (Zhang et al., 2019)	Chinese females	Oolong tea	Regular consumption vs none consumption	HR (95%CI)	1.07 (95% CI:0.49–2.32)	>0.05

Note: aHRs (Multivariable-adjusted hazard ratios), RR (Relative Risk), HR (Hazard ratio), OR (Odds ratio), CI (Confidence interval).

logical studies on tea and cancer showed that regular tea drinking may reduce the risk of a variety of cancers, including liver cancer, breast cancer, brain cancer, bladder cancer, and other cancers (Li et al., 2023; Al-Zalabani et al., 2022; Zheng et al., 2023; Song et al.,

2019; Martimianaki et al., 2022; Chen et al., 2022; Sen et al., 2019; Zhang et al., 2019), Table 1 shows the summary and comparison of recent epidemiological articles of tea and cancer.

Bioactive components in tea have shown good anti-cancer ef-

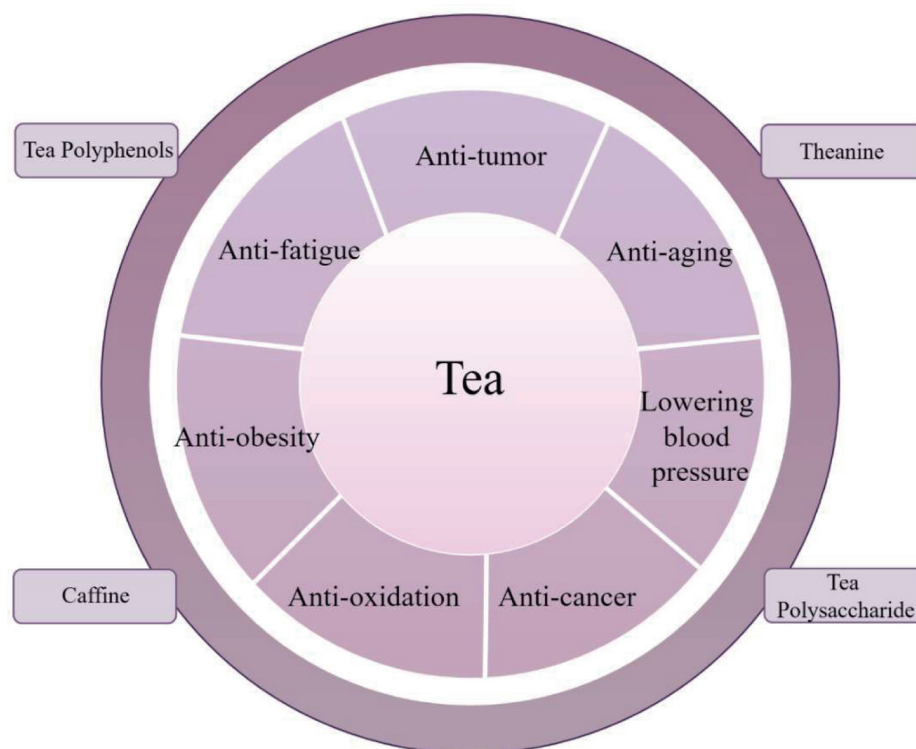


Figure 1. The bioactive components and bioactivities of tea.

fects, such as tea polyphenols, tea pigments, and theanine (Figure 1). At present, there are two main aspects of tea to reduce the occurrence of cancer. One is to kill cancer cells or inhibit their reproduction, and the other is the antioxidant mechanism (Li et al., 2023). Different bioactive components in tea play a preventive role in different mechanisms.

### 3. Bioactive components and their anticancer effects

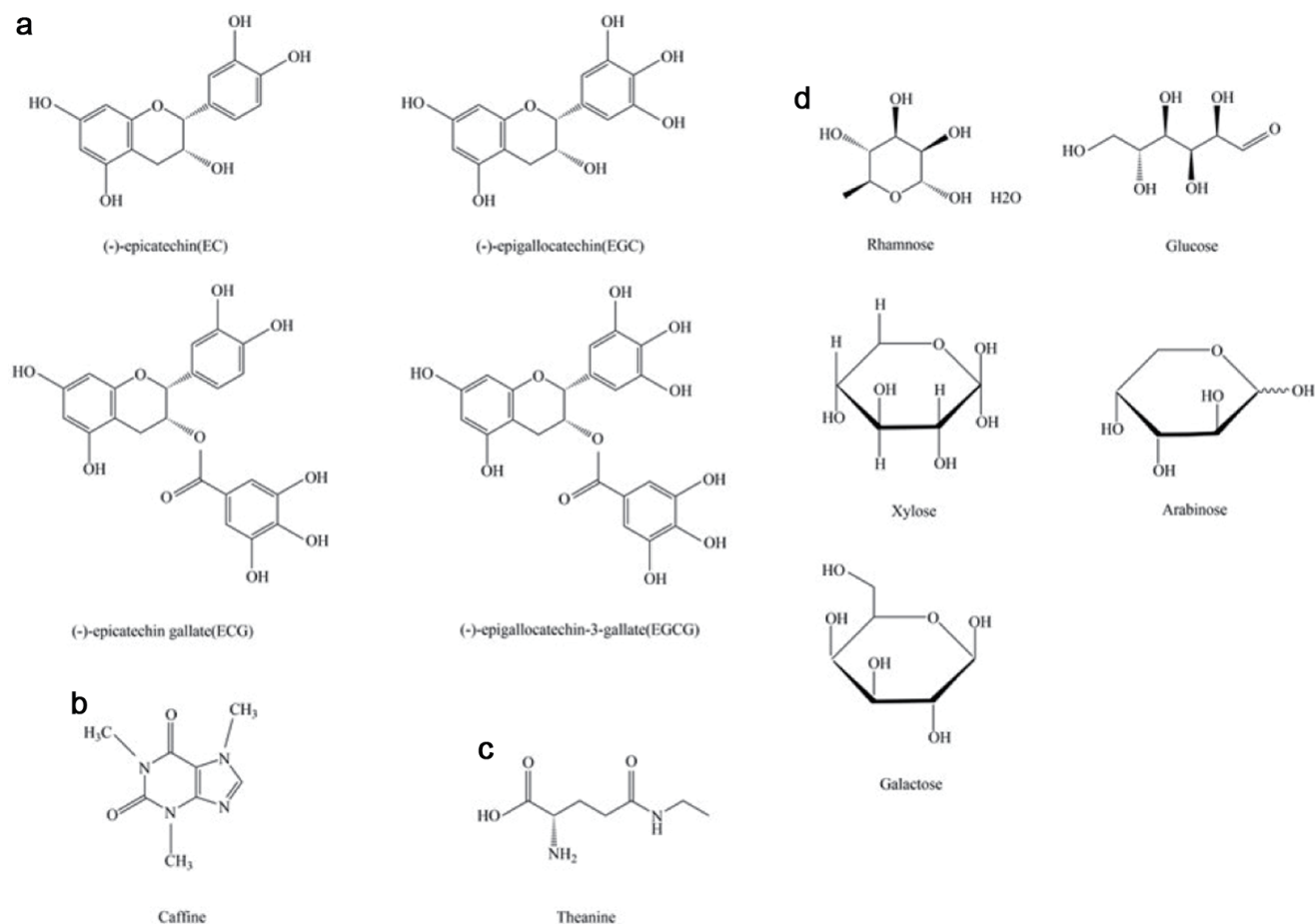
#### 3.1. Tea polyphenols

Tea polyphenols is the general term for polyphenols in tea, and it is one of the main functional substances in the tea industry. Catechins are typical polyphenols, including epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) (Han et al., 2023), their chemical structure is given in Figure 2a. A lot of research shows that tea polyphenols have varying degrees of preventive and alleviative effects on a variety of cancers (Xing et al., 2019). The occurrence and development of cancer are related to the excessive production of oxygen-free radicals in the organism. Tea polyphenols and catechins have strong antioxidant activity and can inhibit reactive oxygen species in oxidative stress animal models. Thereby, playing an important role in inhibiting the occurrence and development of tumors. Studies show that EGCG can reduce lipid peroxidation and protein carbonylation, and lower the risk of the occurrence of reactive oxygen species and toxicity (Zhang et al., 2019; Guo et al., 2019). According to Wu and colleagues' research, green tea polyphenols from (GTPs) suppressed melanoma progression by regulating circ MITF/miR-30e-3p/HDAC2 axis (Wu et al., 2022). Moreover, cel-

lular function assays revealed that GTPs inhibited melanoma cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and promoted apoptosis in vitro.

#### 3.2. Caffeine

Caffeine is one of the most natural components presented in tea (van Dam et al., 2020). Figure 2b shows its chemical structure. Caffeine is an important methylxanthine that has been extensively studied, which has multiple positive biological activities including alleviative effects on nervous diseases, respiratory diseases, diabetes, and cancer (Monteiro et al., 2016). Recent studies have shown that caffeine exhibits synergistic effects in combination with many anticancer drugs. The research from Tran et al demonstrated that the cholesterol-lowering drug simvastatin can inhibit neuroblastoma growth by blocking the mevalonate pathway (Tran et al., 2023). Due to the activity, caffeine is used as an adenosine receptor antagonist. It can synergize with simvastatin to inhibit the growth of neuroblastoma cells and patient-derived xenograft (PDX) tumors and block the feedback activation of the statin-induced mevalonate pathway. Cisplatin is a widely used anticancer agent and has shown efficacy in a variety of cancers, including prostate cancer, lung cancer, ovarian cancer, and esophageal cancer. Caffeine can enhance the anticancer effect of cisplatin by inhibiting FANCD2 monoubiquitination, which demonstrated that caffeine may regulate DNA repair and cell apoptosis by inhibiting the FA pathway in HepG2 human hepatocellular carcinoma cells (Oda et al., 2017). Another research showed all concentrations of caffeine inhibited the activity of the anticancer drug paclitaxel and promoted the growth of paclitaxel-treated cancer cells (Xu et al., 2020). In conclusion, caffeine has a promising combined anti-



**Figure 2.** The structure of the main components in tea. (a) Catechins. (b) Caffeine. (c) Theanine. (d) Tea polysaccharides.

cancer effect, but whether it can be used as a combined anticancer agent needs further study.

### 3.3. Theanine

Theanine is the characteristic amino acid of tea, which is present in green tea and naturally exists as L-Theanine. Theanine has important biological activities, such as lowering blood pressure, anti-fatigue, anti-obesity, and neuroprotective effects (Zhao et al., 2020). Figure 2c shows its chemical structure. Recently, some studies have shown that theanine also has significant anti-cancer activity. L-Theanine could inhibit melanoma cell migration and promote melanoma cell death by enhancing the expression of brain and muscle Arnt-like protein 1 (BMAL1), a clock gene in melanoma cells. Moreover, research further proved that L-Theanine can raise the transcriptional activity of p53 by enhancing the expression of BMAL1 (Zhang et al., 2022). Researchers have discovered that theanine showed a chemoprotective effect against colorectal cancer by inhibiting oxidative stress and inflammatory reactions. Their experiments demonstrated that the theanine significantly reduces the level of prostaglandin (PGE2), cyclooxygenase-2 (COX-2), and myeloperoxidase (MPO) in 1,2-dimethylhydrazine (DMH)-induced colorectal cancer. And it also decreases oxidative stress by inhibiting the level of malonaldehyde (MDA) and enhancing the levels of SOD, GPx, CAT, and GR (Ma et al., 2022).

Prostate cancer (PCa) is an epithelial malignant tumor that occurs in the prostate. The metastasis rate of prostate cancer is high and the metastasis is harmful, even leading to death. L-theanine could suppress invasion, migration and increase cell-cell adhesion of prostate cancer cells in vitro and in vivo. L-theanine also could inhibit the EMT process in PCa, downregulating MMP9, N-cadherin, Vimentin, Snail and upregulating E-cadherin. In addition, L-theanine inhibited transcription of MMP9 and snail by significantly suppressing the ERK/NF- $\kappa$ B signaling pathway and the binding activity of p65 (Fan et al., 2021). Furthermore, oral administration of cystine and theanine exhibits relieved therapy of the side effects of capecitabine-based adjuvant chemotherapy for colorectal cancer patients (Hamaguchi et al., 2020). These results suggest that Theanine may be considered a potential alleviative agent for cancer treatment or chemotherapy side effects mitigation.

### 3.4. Tea polysaccharides

Tea polysaccharides is a complex polysaccharide with various biological activities, like anti-oxidation, anti-aging, anti-bacterial, and anti-tumor. It is composed of rhamnose, xylose, glucose, arabinose, and galactose, and is one of the main bioactive components in tea (Fan et al., 2022). Figure 2d shows their chemical structures. Research showed that miR-93 promoted the progression and metastasis of prostate cancer by inhibiting DAB2 and activating



the Akt/ERK1/2 pathway (Yang et al., 2019). Green tea polysaccharides could promote the expression of DAB2 protein in PC-3 cells by inhibiting the metastasis of PC (Zhou et al., 2021). Tea polysaccharide (TP) could enhance autophagy, lysosome, and cell death signaling pathways in HCCT116 cells through activating EB(TFEB), a key nuclear transcription factor modulating autophagy and lysosome biogenesis, and inhibit mTOR activity and promoted LAMP1 expression. TP significantly promoted lysosomal abundance, lysosomal acidification, and cathepsin activity, and significantly inhibited cell viability to HCCT116 at a concentration of 800 µg/mL. However, there was a slight effect on rat normal intestinal epithelial cell line IEC-6, which indicated that TP might serve as an anticancer agent with minimal side effects. Researchers isolated a water-soluble homogeneous polysaccharide (DTP-1) from black tea bricks and tested its anti-tumor activity in vitro. The results showed that DTP-1 can significantly inhibit the viability of A549 and SMMC7721 at a concentration of 600 µg/mL, but has little effect on normal cells (Liu et al., 2022). In a word, tea polysaccharides may have great potential for cancer treatment.

#### 4. Molecular mechanisms underlying the anticancer effects of tea common cancers

##### 4.1. Lung cancer

Lung cancer is a common primary malignant tumor of the lung. Recently, the incidence and mortality of lung cancer have increased significantly. It is one of the most threatening malignancies to human health and life (Han et al., 2023; Xing et al., 2019; Zhang et al., 2019). Living habits and behaviors are cancer occurrence key factors. The results of a meta-analysis showed that maintaining the habit of drinking tea can effectively reduce the risk of lung cancer among non-smokers, and keeping one or more cups of tea a day can reduce the risk of lung cancer in smokers (Guo et al., 2019).

Researchers found that EGCG could inhibit the expression of lung cancer-related gene STAT1 in A549 cells (Li et al., 2023) (Table 2). Oxidized tea polyphenol (OTP-3), an oxidized derivative of EGCG, could bind to the extracellular domain of EGFR and combine with nimotuzumab to significantly inhibit tumor growth by degrading EGFR in vivo. It can also enhance the effect of nimotuzumab in the treatment of NSCLC, providing evidence for new cancer treatment ideas (Huang et al., 2022). The brown polyphenol oxidized polymer TBS(TBS-C) from tea polyphenols could inhibit the activation of PI3K/AKT/mTOR pathway in A549 and H2030 cells, promote autophagy, and also up-regulate the expression of AKT downstream gene p21, leading to cell cycle arrest in G1 phase. TBS-C significantly inhibited tumor growth by inhibiting the PI3K/AKT/mTOR pathway without toxic damage to other organs in xenograft NSCLC nude mice (Wang et al., 2022). In the experiments of a recent study, EGCG at all concentrations could inhibit the proliferation and migration of A549, HCC827, and H1975 cells. The inhibition of proliferation and migration of A549 and HCC827 cells by EGCG was related to the EGFR signaling pathway. However, the inhibitory effects of EGCG on the proliferation and migration of H1975 cells were not related to the EGFR signaling pathway, suggesting that EGCG can treat NSCLC through multiple mechanisms (Minnelli et al., 2021). The synthesized dimeric(-)-Epigallocatechin-3-Gallate (PBOG) can inhibit EGFR phosphorylation by binding to extracellular domain proteins of epidermal growth factor receptor (EGFR), a marker of NSCLC. Thus, it induces apoptosis, which may be a new idea for

the treatment of lung cancer (Sun et al., 2022). There is a study showed that a high concentration of EGCG could inhibit the proliferation and migration of A549 and H1299 cells and induce apoptosis by inhibiting the NF-κB signaling pathway, which showed significant synergistic effects when EGCG and NF-κB inhibitor BAY11-7082 were used together (Zhang et al., 2019).

Golden-flowered tea can effectively inhibit the growth of non-small cell lung cancer (NSCLC) cells, and the inhibitory effect may be related to cytokine-cytokine receptor interaction, PI3K-Akt signaling pathway, and MAPK signaling pathway (Wang et al., 2022). Furthermore, the brownie inhibited the proliferation of p53-deficient NSCLC(H1299) cells and P53 wild-type NSCLC(A549) cells by phosphorylating the MAPK/JNK pathway, down-regulating epithelial-mesenchymal transition-related genes and anti-apoptotic molecules, and up-regulating metastasis-related genes HSPA6 and pro-apoptotic molecules. This is a p53-independent mechanism, indicating that the foci are a safe and effective agent for the treatment of NSCLC (Xiao et al., 2022). It is suggested that there may be many bioactive components in tea that can be used as natural anticancer agents to enhance the efficacy of anticancer drugs.

##### 4.2. Colorectal cancer

Colorectal cancer is one of the most frequent and lethal malignancies in Europe and the United States. Studies have shown that increasing natural foods such as fruits and vegetables can reduce the incidence of colorectal cancer (Chapelle et al., 2020). In recent years, there have been increasing studies on the effects of tea and its bioactive components on the prevention and treatment of colorectal cancer.

EGCG can inhibit the formation of neutrophil extracellular traps (NETs) and inhibit colon cancer cell migration and invasion by regulating the STAT3/CXCL8 signaling pathway (Zhang et al., 2023) (Table 2). EGCG has anti-proliferation and anti-migration effects on colorectal cancer cells SW480, SW620, and LS411N by inhibiting the expression of STAT3, indicating that EGCG may be a natural substance with bioactivity for anti-colon cancer (Luo et al., 2020). EGCG enhances the sensitivity of colorectal cancer cells to the chemotherapy agent 1-FU by inhibiting the GRP5/NF-κB/miR-78-155p/MDR5 pathway, suggesting that EGCG may be used as a natural chemical sensor for further study (La et al., 2019). Researchers treated colorectal cancer (CRC) model mice with theabrownine (TB) and found that TB significantly reduced phosphatidylinositol 3 kinases (PI3K), protein kinase B (Akt) phosphorylation, as well as downstream mechanism targets of rapamycin (mTOR) and cyclin D1 protein expression. This indicates that TB acquisition can inhibit tumor cell proliferation or promote tumor cell apoptosis. TB also increased the abundance of short-chain fatty acids and short-chain fatty acid-producing related bacteria and decreased the Bacteroides associated with CRC, suggesting that TB can inhibit tumor formation (Leung et al., 2022). In addition, TB may induce the apoptosis of human colon cancer cells HT-29 by inducing intracellular redox imbalance (Yuan et al., 2022). In the study mentioned earlier, tea polysaccharides were also shown to significantly promote the death of colon cancer cell CT26 (Zhou et al., 2021). Theanine alone inhibited tumorigenesis in a rat model of dimethylhydrazine (DMH) induced colon cancer by down-regulating the Akt/mTOR and JAK2/STAT3 pathways and increasing Smad2 tumor suppressor (Shojaei-Zarghani et al., 2021). Several researchers have extracted theaflavins and thearubins from black tea and demonstrated that both induce apoptosis in a dose-dependent manner (Imran et al., 2019).

**Table 2. The bioactive components in tea and related anticancer molecular mechanisms**

Tea type	Composition	Molecular mechanism	Cancer	References
Green tea	GTPs	circ MITF/miR-30e-3p/HDAC2 axis	Melanoma	Wu et al., 2022
Green tea	L-Theanine	BMAL1	Melanoma	Zhang et al., 2022
Green tea	Theanine	PGE2/COX-2/MPO/MDA/SOD/GPx/CAT/GR	Colorectal cancer	Ma et al., 2022
Green tea	L-theanine	ERK/NF-κB/P65	Prostate cancer	Saedmocheshi et al., 2019
Green tea	Tea Polysaccharide	DAB2	Prostate cancer	Yang et al., 2019
Green tea	Tea Polysaccharide	EB/mTOR/LAMP1	Colon cancer	Zhou et al., 2021
Black tea	Homogeneous polysaccharide	A549/SMMC7721	Lung cancer	Liu et al., 2022
Green tea	EGCG	STAT1	Lung cancer	Li et al., 2023
Golden-flowered tea		PI3K-Akt/MAPK	Lung cancer	Wang et al., 2022
Green tea	OTP-3	EGFR	Lung cancer	Huang et al., 2022
Tea	TBs-C	PI3K/AKT/mTOR	Lung cancer	Wang et al., 2022
Green tea	Theabrownin	MAPK/JNK/P53	Lung cancer	Xiao et al., 2022
Green tea	EGCG	EGFR	Lung cancer	Minnelli et al., 2021
Black tea		NRF2	Lung cancer	Datta et al., 2023
Huang qin tea		IL-1β/IL-6/IL-10/TNF-α	Colorectal cancer	Shen et al., 2020
Green tea		PI3K/AKT	Colorectal cancer	Zhang et al., 2020
Green tea	EGCG	STAT3/CXCL8	Colorectal cancer	Zhang et al., 2023; Luo et al., 2020
Green tea	EGCG	GRP5/NF-κB/miR-78 155p/MDR5	Colorectal cancer	La et al., 2019
Pu-erh tea	Theabrownin	PI3K/AKT/Mtor/cyclin D1	Colorectal cancer	Leung et al., 2022
Green tea	Theanine	Akt/mTOR/JAK2/STAT3/Smad2	Colorectal cancer	Shojaei-Zarghani et al., 2021
Cocoa tea		PI3K/Akt	Colorectal cancer	Gao et al., 2020
Green tea		miRNA-181a	Prostate cancer	Safari et al., 2022
Black tea	Theaflavin-3,3'-digallate	67LR/PKCδ/aSMase	Prostate cancer	Sun et al., 2022
Green tea	ECG	acetyl-CoA carboxylase/ATP citrate lyase/fatty acid/PI3K/AKT/mTOR	Prostate cancer	Chen et al., 2021
Green tea	(-)-EC	ZIP9	Prostate cancer	Thomas and , 2021
Green tea	EGCG	Ca <sup>2+</sup>	Prostate cancer	Marchetti et al., 2020
Green tea	EGCG	p53/p21/Bax/Bcl2	Prostate cancer	Chen et al., 2019
Tea	TLNTs	ROS	Breast cancer	Chen et al., 2023
Gylenia pentaphylua tea	Gyp I	AKT/GSK3β/β-catenin	Breast cancer	Tan et al., 2022
Green tea		p53/p21	Breast cancer	Santos et al., 2021
Green tea	EC/EGC/ECG/EGCG	PTP1B	Breast cancer	Kuban-Jankowska et al., 2020
Green tea	EGCG	Arg-1/iNOS/NOX2/NF-κB/STAT3/ECM-receptor interaction/focal adhesion	Breast cancer	Xu et al., 2020

Huang qin tea (HQT) can regulate the expression of inflammatory cytokines, increase the production of IFN-γ, and inhibit inflammation by inhibiting the expression of IL-1β, IL-6, IL-10, and TNF-α. HQT can also regulate intestinal microbial composition

and metabolic pathways, inhibit the formation of aberrant crypt foci (ACF) in precancerous colon ACF rat models, and achieve the effect of inhibiting the formation of colorectal cancer (Shen et al., 2020). Natural nanotherapeutics (NTS) from tea leaves inhibited

inflammation by increasing the secretion of the anti-inflammatory factor IL-10, inhibiting the expression of pro-inflammatory factors, and significantly reducing the incidence and growth of colon tumors by oral administration (Zu et al., 2021). Chinese Hukka stir-fried green tea (HSGT) extracts from five different years showed that all concentrations and years of Chinese HSGT could inhibit the proliferation of HT-15 and enhance the apoptosis of HT-1 cells. They demonstrated that Chinese-aged tea could inhibit the proliferation and cell cycle progression of colon cancer cells and promote the apoptosis of colon cancer cells by blocking the transmission of PI3K/AKT signal (Zhang et al., 2022). Besides, cocoa tea (*Camellia ptilophylla*) can inhibit the phosphatidylinositol-3 kinase (PI3K)/Akt pathway and activate the mitochondrial apoptosis pathway by promoting ROS production in human colon cancer HCT116 cells, and the proliferation of HCT116 cells was inhibited and the apoptosis of HCT116 cells was promoted (Gao et al., 2020).

#### 4.3. Prostate cancer (PCa)

Prostate cancer (PCa) is a disease with extremely complex pathogenesis, including environmental, physiological, and genetic. Relevant data show that PCa is one of the highest prevalences of cancer in the male. Recent studies show bioactive components in tea can prevent or treat prostate cancer (Wasim et al., 2022; Filippini et al., 2020).

Polyphenon E has a dose-dependent inhibitory effect on PC-3 cells (Carastro et al., 2022). Green tea may exert its anti-prostate cancer activity by up-regulating miRNA-181a expression and inducing cell apoptosis (Safari et al., 2022) (Table 2). Epicatechin gallate can down-regulate the expression of acetyl-CoA carboxylase, ATP citrate lyase, and fatty acid synthase in prostate cancer cells and prostate xenograft tissues. Epicatechin gallate could reduce fatty acid synthesis. Further research showed that epicatechin gallate could inhibit the expression of adipogenic genes by inhibiting the PI3K/AKT/mTOR signaling pathway to reduce fatty acid synthesis and attenuate prostate cancer cell metastasis (Chen et al., 2021). (-)-epicatechin can mediate proapoptotic effects on prostate cancer cells PC-3 and MDA-MB-468 breast cancer cells through ZIP9. When the (-)-epicatechin concentration was 100–200 nM, it showed strong agonist activity against cancer cells (Thomas and Dong, 2021). EGCG induced an increase in  $Ca^{2+}$  concentration in PCa cells in a dose-dependent manner, which may be related to sulfhydryl (SH) oxidation. The imbalance of intracellular calcium ion concentration was directly related to the apoptosis of PCa cells, indicating that EGCG could induce the apoptosis of PCa cells (Marchetti et al., 2020). LEGCG, a fat-soluble derivative of EGCG, using the enzymatic esterification reaction of lauric acid and EGCG, could stop the cell cycle in the G0/G1 phase by activating p53/p21. Therefore, the expression of cyclin D1 and CDK4 in DU145 human prostate carcinoma cells is down-regulated, and cell proliferation is inhibited. At the same time, LEGCG also induced apoptosis by increasing the Bax/Bcl2 ratio, cytochrome release, and caspase cleavage in DU145 cells, showing the alleviative effect on PCa from two aspects including inhibiting the proliferation of PCa cells and promoting the apoptosis of PCa cells (Chen et al., 2019).

Theaflavin-3,3'-gallate (TF-3), an important bioactive ingredient in black tea, can reduce the expression of 67 kDa laminin receptor (67LR) in prostate cancer PC-3 cells and prostate cancer mouse models. The receptors have excessive expression in a variety of tumors and play an important role in tumor growth and metastasis. They also found that TF-3 inhibits the proliferation of

prostate cancer cells by regulating the PKC $\delta$ /aSMase signaling pathway. Moreover, the tumor volume significantly reduced after TF-3 treatment in vivo, indicating that TF-3 may have alleviative effects on human prostate cancer (Sun et al., 2022). Metabolic disorders caused by overexpression of lipogenic genes are one of the typical features of prostate cancer. Catechin nanoemulsion from oolong tea waste can increase the activity of Caspase-8, Caspase-9, and Caspase-3 in mouse prostate cancer cells DU-145, and block the cell cycle in the S phase and G2/M phase. Moreover, when the concentration of catechin nanoemulsion was 20  $\mu$ g/mL, the effect on the volume and weight of mouse tumors was the most obvious (Lin et al., 2021). As mentioned earlier, L-theanine can inhibit the invasion, and migration and increase intercellular adhesion of prostate cancer cells both in vivo and in vitro. It indicates that L-theanine has an ideal effect on the treatment of prostate cancer (Ma et al., 2022). Green tea extract to treat N-methyl-N-nitrosourea-induced prostate cancer rats and the results showed that compared with the prostate cancer model group, the prostate weight of rats in the green tea extract group (CEX) was significantly reduced. Moreover, the expressions of NF- $\kappa$ B and p53 in the CEX group were significantly decreased compared with those in the model group, which once again indicated that tea and its bioactive components may have potential preventive and alleviative effects on prostate cancer (Saedmocheshi et al., 2019).

#### 4.4. Breast cancer

Breast cancer is a cancer with high morbidity and mortality in women all over the world. It has been widely discussed by scholars for many years. Studies have shown that the risk of breast cancer is related to lifestyle, including diet and physical exercise. While some natural ingredients in foods may have preventive and alleviative effects on breast cancer (Marin et al., 2023).

EC could reduce tumor volume and improve survival in a triple-negative breast cancer (TNBC) tumor model mouse. In addition, they demonstrated that flavanol EC significantly inhibited the proliferation of 4T1 cells in a dose-dependent manner but had no significant effect on the survival rate of C2C12 cells. The migration of 4T1 cells was also significantly inhibited. The results showed that EC inhibited the proliferation, metastasis, and invasion of mouse breast cancer cells, suggesting that EC may be a new agent for the treatment of breast cancer without side effects (Pérez-Durán et al., 2023) (Table 2). EC31, a derivative of tea polyphenols, could reverse P-gp-mediated taxol resistance in a P-glycoprotein (P-gp) overexpressing LCC6MDR cell line breast cancer xenograft model. It also increased intratumoral paclitaxel levels in LCC6MDR xenografts 6-fold without affecting the pharmacokinetic activity of paclitaxel, suggesting that the tea polyphenol derivative EC31 may be an effective combined anticancer agent (Sun et al., 2023). In the previous study, (-)-epicatechin in green tea could promote apoptosis in MDA-MB-468 breast cancer cells and exhibit receptor agonist activity (Marchetti et al., 2020). Proline dehydrogenase (PRODH) treating TNBC cells found that PRODH could induce cancer cell epithelial-mesenchymal transition and promote cell proliferation. EGCG could significantly inhibit the expression of PRODH and its regulatory proteins in TNBC cells and 50 mg/EGCG could significantly inhibit tumor growth of patient-derived xenograft (PDX) mice. This study again provides evidence for the anti-tumor effect of EGCG, especially in TNBC (Lee et al., 2021). EGCG could significantly reduce the cell survival rate and increase the apoptosis rate of myeloid-derived suppressor cells (MDSCs) through typical signaling pathways such as Arg-1/iNOS/NOX2/NF- $\kappa$ B/STAT3 and atypical signaling pathways such as ECM-receptor interaction

and focal adhesion. EGCG significantly reduced the accumulation of MDSCs and increased the proportion of CD4 and CD8 T cells in the spleen and tumor site of 4T1 breast tumor mice to improve immunosuppression and inhibit the growth of 4T1 breast cancer cells. A concentration of 0.5–5 µg/mL of EGCG was needed to have a significant effect (Xu et al., 2020). EGCG significantly reduced the methylation status of the tumor suppressor gene SCUBE2 by reducing the expression and activity of DNA methyltransferase (DNMT), enhancing its inhibitory effect on breast cancer development, again suggesting the significance of EGCG in the treatment of breast cancer (Sheng et al., 2019).

The extracted and purified exosome-like NTs (TLNTs) from tea leaves, in vitro experiments showed that TLNTs could increase the ROS level in 4T1 cells, which in turn caused mitochondrial damage, cell cycle arrest, and apoptosis (Chen et al., 2023). Both oral and intravenous TLNTs were found to be effective in the treatment of breast cancer via direct pro-apoptosis or microbiota modulation in mice. Oral administration of TLNTs did not cause significant liver and kidney toxicity or immune activation. It is suggested that it may be used as an oral drug for the treatment of breast cancer with fewer side effects. A study on the inhibitory effect of natural nanovehicles from tea flowers (TFEN) on breast tumors showed that TFEN could trigger apoptosis of breast cancer cells and inhibit tumor growth and metastasis in vivo (Chen et al., 2022). The isolated Gypensapogenin I (Gyp I) from *Gypenia pentaphylla* tea showed that Gyp I could inhibit the proliferation of human breast cancer cell line MDA-MB231 through the AKT/GSK3β/β-catenin signaling pathway. Their study showed that Gyp I could regulate the closure of Notch-1 and AKT/GSK3β/β-catenin signaling pathways in TNBC and inhibit the growth of xenograft tumors in nude mice in a dose-dependent manner (Tan et al., 2022). Green tea extract (GTE) was selectively toxic to breast tumor cells MCF-7, but not to non-tumor cells MCF-10A. GTE exerted its detrimental effect on MCF-7 cells by stimulating the expression of p53 and p21 in MCF-7 cells, and also significantly inhibited the cell migration of MCF-7 and MDA-MD-231 cells, suggesting that green tea may have an alleviative effect on breast cancer (Santos et al., 2021). PTP1B, a tyrosine phosphatase regulated by oxidative stress, is involved in the pathogenesis of a.o. Proto-oncogenic pathways for breast cancer formation. Epigallocatechin, epigallocatechin gallate, epicatechin, and epicatechin gallate, derived from green tea, reduced PTP1B phosphatase activity and MCF-7 cell survival, once again proved that tea has a potential antioxidant effect (Kuban-Jankowska et al., 2020).

## 5. Limitations and expectations

Although most studies have shown that tea has preventive and mitigating effects on a variety of cancers at both in vivo and in vitro levels as well as at the cellular level, some epidemiological studies have also shown that there is no significant association between tea consumption and cancer risk. Some studies have even shown that tea consumption can increase the risk of gastric cancer among regular smokers and drinkers (Sen et al., 2019; Li et al., 2019). Therefore, more definitive evidence is still needed to prove the role of tea in the prevention and alleviation of cancer.

In general, the anti-cancer effect of tea is mainly achieved by inhibiting the production of carcinogens, inhibiting tumor cell proliferation and metastasis, tumor growth, and enhancing the body's cellular immunity level.

Studies have shown that certain components of tea can be used as combined anticancer agents. EGCG in combination with cispla-

tin significantly inhibited cell proliferation and increased apoptosis in NSCLC cell lines and xenograft tumors in vivo in a synergistic manner (Wang et al., 2019). Theaflavin-rich black tea (BT) could improve the sensitivity of A549 cells to the anticancer drug cisplatin by regulating the level of nuclear factor erythroid 2-related factor 2 (NRF2) in A549 cells. It also reduced the resistance of A549 cells to anticancer drugs (Datta et al., 2023). In addition, we mentioned above that caffeine has the potential as a combined anticancer agent due to its activity (Tran et al., 2023), and oral administration of cystine and theanine exhibits relieved therapy of the side effects of capecitabine-based adjuvant chemotherapy for colorectal cancer patients (Hamaguchi et al., 2020). All of this evidence suggests that tea may be able to combine with anticancer drugs to enhance their anticancer activity or reduce their side effects, but more evidence is still needed to prove whether this is feasible.

## 6. Conclusions

Current studies have shown that tea, especially green tea has shown some preventive and alleviative effects against common cancers such as breast, endometrial, colon, prostate, and lung cancer. Tea has many other benefits for cancer patients, such as aiding digestion, increasing appetite, and strengthening physique. However, doctors warn that although tea has a certain anti-cancer effect, the effect is limited, and it cannot completely replace surgery and chemotherapy drugs. Therefore, cancer patients should still go to the hospital for routine treatment, supplemented by tea, so that cancer treatments complement each other.

## Acknowledgments

The graphical abstract and Figure 1 were drawn using the Figure-draw platform. We thank Figuredraw for providing a convenient platform for scientific research illustration.

## References

- Abudurehman, B., Yu, X., Fang, D., and Zhang, H. (2022). Enzymatic Oxidation of Tea Catechins and Its Mechanism. *Molecules* 27(3): 942.
- Al-Zalabani, A.H., Wesselius, A., Yi-Wen Yu, E., van den Brandt, P., Grant, E.J., White, E., Skeie, G., Liedberg, F., Weiderpass, E., and Zeegers, M.P. (2022). Tea consumption and risk of bladder cancer in the Bladder Cancer Epidemiology and Nutritional Determinants (BLEND) Study: Pooled analysis of 12 international cohort studies. *Clin. Nutr.* 41(5): 1122–1130.
- Avgerinos, K.I., Spyrou, N., Mantzoros, C.S., and Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism* 92: 121–135.
- Carastro, L.M., Vallebuona, E.J., Cordova, R., Gannon, A.N., Kim, S.J., Costello, C.M., Declet-Bauzo, R.A., Kumar, N., and Park, J.Y. (2022). Polyphenon E Effects on Gene Expression in PC-3 Prostate Cancer Cells. *Int. J. Mol. Sci.* 23(22): 14328.
- Chapelle, N., Martel, M., Toes-Zoutendijk, E., Barkun, A.N., and Bardou, M. (2020). Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population. *Gut* 69(12): 2244–2255.
- Chen, J., Zhang, L., Li, C., Chen, R., Liu, C., and Chen, M. (2019). Lipophilized Epigallocatechin Gallate Derivative Exerts Anti-Proliferation Efficacy through Induction of Cell Cycle Arrest and Apoptosis on DU145 Human Prostate Cancer Cells. *Nutrients* 12(1): 92.
- Chen, L., Guo, Y., Wu, Z., Zhao, S., Zhang, Z., Zheng, F., Sun, L., Hao, Z., Xu, C., Wang, T., and Peng, Y. (2021). Epicatechin gallate prevents the



- de novo synthesis of fatty acid and the migration of prostate cancer cells. *Acta Biochim. Biophys. Sin.* 53(12): 1662–1669.
- Chen, Q., Li, Q., Liang, Y., Zu, M., Chen, N., Canup, B.S.B., Luo, L., Wang, C., Zeng, L., and Xiao, B. (2022). Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer via ROS generation and microbiota modulation. *Acta Pharm. Sin.* B 12(2): 907–923.
- Chen, Q., Zu, M., Gong, H., Ma, Y., Sun, J., Ran, S., Shi, X., Zhang, J., and Xiao, B. (2023). Tea leaf-derived exosome-like nanotherapeutics retard breast tumor growth by pro-apoptosis and microbiota modulation. *J. Nanobiotechnol.* 21(1): 6.
- Chen, Y., Abe, S.K., Inoue, M., Yamaji, T., Iwasaki, M., Nomura, S., Hashizume, M., Tsugane, S., Sawada, N., and JPHC Study Group. (2022). Green tea and coffee consumption and risk of kidney cancer in Japanese adults. *Sci. Rep.* 12(1): 20274.
- Datta, S., Bishayee, A., and Sinha, D. (2023). Black tea bioactive phytoconstituents realign NRF2 for anticancer activity in lung adenocarcinoma. *Front. Pharmacol.* 14: 1176819.
- Fan, M., Zhang, X., Zhao, Y., Zhi, J., Xu, W., Yang, Y., Xu, Y., Luo, K., and Wang, D. (2022). Mn (II)-Mediated Self-Assembly of Tea Polysaccharide Nanoparticles and Their Functional Role in Mice with Type 2 Diabetes. *ACS Appl. Mater. Interfaces* 14(27): 30607–30617.
- Fan, X., Zhou, J., Bi, X., Liang, J., Lu, S., Yan, X., Luo, L., and Yin, Z. (2021). L-theanine suppresses the metastasis of prostate cancer by down-regulating MMP9 and Snail. *J. Nutr. Biochem.* 89: 108556.
- Filippini, T., Malavolti, M., Borrelli, F., Izzo, A.A., Fairweather-Tait, S.J., Horneber, M., and Vinceti, M. (2020). Green tea (*Camellia sinensis*) for the prevention of cancer. *Cochrane Database Syst. Rev.* 3(3): CD005004.
- Gao, X., Li, X., Ho, C.T., Lin, X., Zhang, Y., Li, B., and Chen, Z. (2020). Cocoa tea (*Camellia pitilophylla*) induces mitochondria-dependent apoptosis in HCT116 cells via ROS generation and PI3K/Akt signaling pathway. *Food Res. Int.* 129: 108854.
- Guo, Z., Jiang, M., Luo, W., Zheng, P., Huang, H., and Sun, B. (2019). Association of Lung Cancer and Tea-Drinking Habits of Different Subgroup Populations: Meta-Analysis of Case-Control Studies and Cohort Studies. *Iran. J. Public Health* 48(9): 1566–1576.
- Hamaguchi, R., Tsuchiya, T., Miyata, G., Sato, T., Takahashi, K., Miura, K., Oshio, H., Ohori, H., Ariyoshi, K., Oyamada, S., and Iwase, S. (2020). Efficacy of oral administration of cystine and theanine in colorectal cancer patients undergoing capecitabine-based adjuvant chemotherapy after surgery: a multi-institutional, randomized, double-blinded, placebo-controlled, phase II trial (JORTC-CAM03). *Support. Care Cancer* 28(8): 3649–3657.
- Han, S., Washio, J., Abiko, Y., Zhang, L., and Takahashi, N. (2023). Green Tea-Derived Catechins Suppress the Acid Productions of *Streptococcus mutans* and Enhance the Efficiency of Fluoride. *Caries Res.* 57(3): 255–264.
- Huang, Y., Cuan, X., Yang, X., Zhu, W., Zhao, Y., Jiang, L., Zi, C., Wang, X., and Sheng, J. (2022). Oxidized tea polyphenol (OTP-3) targets EGFR synergistic nimotuzumab at inhibition of non-small cell lung tumor growth. *Bioorg. Chem.* 128: 106084.
- Imran, A., Butt, M.S., Xiao, H., Imran, M., Rauf, A., Mubarak, M.S., and Ramadan, M.F. (2019). Inhibitory effect of black tea (*Camellia sinensis*) theaflavins and thearubigins against HCT 116 colon cancer cells and HT 460 lung cancer cells. *J. Food Biochem.* 43(5): e12822.
- Kuban-Jankowska, A., Kostrzewa, T., Musial, C., Barone, G., Lo Bosco, G., Lo Celso, F., and Gorska-Ponikowska, M. (2020). Green Tea Catechins Induce Inhibition of PTP1B Phosphatase in Breast Cancer Cells with Potent Anti-Cancer Properties: In Vitro Assay, Molecular Docking, and Dynamics Studies. *Antioxidants (Basel)* 9(12): 1208.
- La, X., Zhang, L., Li, Z., Li, H., and Yang, Y. (2019). (-)-Epigallocatechin Gallate (EGCG) Enhances the Sensitivity of Colorectal Cancer Cells to 5-FU by Inhibiting GRP78/NF- $\kappa$ B/miR-155-5p/MDR1 Pathway. *J. Agric. Food Chem.* 67(9): 2510–2518.
- Lee, W.J., Cheng, T.C., Yen, Y., Fang, C.L., Liao, Y.C., Kuo, C.C., Tu, S.H., Lin, L.C., Chang, H.W., Chen, L.C., and Ho, Y.S. (2021). Tea polyphenol epigallocatechin-3-gallate inhibits cell proliferation in a patient-derived triple-negative breast cancer xenograft mouse model via inhibition of proline-dehydrogenase-induced effects. *J. Food Drug Anal.* 29(1): 113–127.
- Leung, H.K.M., Lo, E.K.K., and El-Nezami, H. (2022). Theabrownin Alleviates Colorectal Tumorigenesis in Murine AOM/DSS Model via PI3K/Akt/mTOR Pathway Suppression and Gut Microbiota Modulation. *Antioxidants (Basel)* 11(9): 1716.
- Li, F., Hao, S., Gao, J., and Jiang, P. (2023). EGCG alleviates obesity-exacerbated lung cancer progression by STAT1/SLC7A11 pathway and gut microbiota. *J. Nutr. Biochem.* 120: 109416.
- Li, S., Yin, S., Ding, H., Shao, Y., Zhou, S., Pu, W., Han, L., Wang, T., and Yu, H. (2023). Polyphenols as potential metabolism mechanisms regulators in liver protection and liver cancer prevention. *Cell proliferation* 56(1): e13346.
- Li, X., Yu, C., Guo, Y., Bian, Z., Shen, Z., Yang, L., Chen, Y., Wei, Y., Zhang, H., Qiu, Z., Chen, J., Chen, F., Chen, Z., Lv, J., Li, L., and China Kadoorie Biobank Collaborative Group. (2019). Association between tea consumption and risk of cancer: a prospective cohort study of 0.5 million Chinese adults. *Eur. J. Epidemiol.* 34(8): 753–763.
- Li, Z.Y., Tan, Y.T., Liu, D.K., Gao, L.F., Li, H.L., and Xiang, Y.B. (2023). Cumulative consumption of tea is associated with lower risk of liver cancer: Updated results from the Shanghai Women's Health Study. *Int. J. Cancer* 152(6): 1115–1123.
- Lin, Y.H., Wang, C.C., Lin, Y.H., and Chen, B.H. (2021). Preparation of Catechin Nanoemulsion from Oolong Tea Leaf Waste and Its Inhibition of Prostate Cancer Cells DU-145 and Tumors in Mice. *Molecules* 26(11): 3260.
- Liu, D., Jing, X., Cao, S., Liu, X., Tan, X., Jiang, H., Niu, Z., Su, M., Zhang, J., Zhang, X., Liu, G., and Zhou, Y. (2021). Impact of drinking Chinese green tea on postoperative short outcomes for gastric cancer: a randomized controlled trial. *Eur. J. Clin. Nutr.* 75(11): 1568–1577.
- Liu, M., Gong, Z., Liu, H., Wang, J., Wang, D., Yang, Y., and Zhong, S. (2022). Structural characterization and anti-tumor activity in vitro of a water-soluble polysaccharide from dark brick tea. *Int. J. Biol. Macromol.* 205: 615–625.
- Luo, K.W., Xia, J., Cheng, B.H., Gao, H.C., Fu, L.W., and Luo, X.L. (2020). Tea polyphenol EGCG inhibited colorectal-cancer-cell proliferation and migration via downregulation of STAT3. *Gastroenterol. Rep.* 9(1): 59–70.
- Ma, J., Li, P., An, L., Zhang, T., and Li, G. (2022). Chemoprotective effect of theanine in 1,2-dimethylhydrazine-induced colorectal cancer in rats via suppression of inflammatory parameters. *J. Food Biochem.* 46(2): e14073.
- Marchetti, C., Gavazzo, P., and Burlando, B. (2020). Epigallocatechin-3-gallate mobilizes intracellular Ca<sup>2+</sup> in prostate cancer cells through combined Ca<sup>2+</sup> entry and Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release. *Life Sci.* 258: 118232.
- Marín, V., Burgos, V., Pérez, R., María, D.A., Pardi, P., and Paz, C. (2023). The Potential Role of Epigallocatechin-3-Gallate (EGCG) in Breast Cancer Treatment. *Int. J. Mol. Sci.* 24(13): 10737.
- Martimianaki, G., Alicandro, G., Pelucchi, C., Bonzi, R., Rota, M., Hu, J., Johnson, K.C., Rabkin, C.S., Liao, L.M., Sinha, R., Zhang, Z.F., Dalmarcello, M., Lunet, N., Morais, S., Palli, D., Ferraroni, M., Yu, G.P., Tsugane, S., Hidaka, A., Curado, M.P., Dias-Neto, E., Zaridze, D., Maximovitch, D., Vioque, J., Garcia de la Hera, M., López-Carrillo, L., Hernández-Ramírez, R.U., Hamada, G.S., Ward, M.H., Mu, L., Malekzadeh, R., Pourfarzi, F., Trichopoulos, A., Karakatsani, A., Kurtz, R.C., Lagiou, A., Lagiou, P., Boccia, S., Boffetta, P., Camargo, M.C., Negri, E., and La Vecchia, C. (2022). Tea consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling (StoP) Project consortium. *Br. J. Cancer* 127(4): 726–734.
- Minnelli, C., Cianfruglia, L., Laudadio, E., Mobbili, G., Galeazzi, R., and Armeni, T. (2021). Effect of Epigallocatechin-3-Gallate on EGFR Signaling and Migration in Non-Small Cell Lung Cancer. *Int. J. Mol. Sci.* 22(21): 11833.
- Mizrahi, J.D., Surana, R., Valle, J.W., and Shroff, R.T. (2020). Pancreatic cancer. *Lancet* 395(10242): 2008–2020.
- Monteiro, J.P., Alves, M.G., Oliveira, P.F., and Silva, B.M. (2016). Structure-Bioactivity Relationships of Methylxanthines: Trying to Make Sense of All the Promises and the Drawbacks. *Molecules* 21(8): 974.
- Moreira, G.V., Araujo, L.C.C., Murata, G.M., Matos, S.L., and Carvalho, C.R.O. (2022). Kombucha tea improves glucose tolerance and reduces hepatic steatosis in obese mice. *Biomed. Pharmacother.* 155: 113660.
- Ni, D., Ai, Z., Munoz-Sandoval, D., Suresh, R., Ellis, P.R., Yuqiong, C., Sharp, P.A., Butterworth, P.J., Yu, Z., and Corpe, C.P. (2020). Inhibition of the

- facilitative sugar transporters (GLUTs) by tea extracts and catechins. *FASEB J.* 34(8): 9995–10010.
- Oda, Y., Hidaka, M., and Suzuki, A. (2017). Caffeine Has a Synergistic Anticancer Effect with Cisplatin via Inhibiting Fanconi Anemia Group D2 Protein Monoubiquitination in Hepatocellular Carcinoma Cells. *Biol. Pharm. Bull.* 40(11): 2005–2009.
- Oh, C.C., Jin, A., Yuan, J.M., and Koh, W.P. (2019). Coffee, tea, caffeine, and risk of nonmelanoma skin cancer in a Chinese population: The Singapore Chinese Health Study. *J. Am. Acad. Dermatol.* 81(2): 395–402.
- Pérez-Durán, J., Luna, A., Portilla, A., Martínez, P., Ceballos, G., Ortíz-Flores, M.Á., Solís-Paredes, J.M., and Nájera, N. (2023). (-)-Epicatechin Inhibits Metastatic-Associated Proliferation, Migration, and Invasion of Murine Breast Cancer Cells In Vitro. *Molecules* 28(17): 6229.
- Saedmocheshi, S., Saghebjo, M., Vahabzadeh, Z., and Sheikholeslami-Vatani, D. (2019). Aerobic Training and Green Tea Extract Protect against N-methyl-N-nitrosourea-induced Prostate Cancer. *Med. Sci. Sports Exercise* 51(11): 2210–2216.
- Safari, F., Rayat Azad, N., Alizadeh Ezdiny, A., Pakizehkar, S., Khazaei Koohpar, Z., and Ranji, N. (2022). Antitumor Activities of Green Tea by Up-regulation of miR-181a Expression in LNCaP Cells Using 3D Cell Culture Model. *Avicenna J. Med. Biotechnol.* 14(1): 89–94.
- Santos, R.A., Andrade, E.D.S., Monteiro, M., Fialho, E., Silva, J.L., Daleprane, J.B., and Ferraz da Costa, D.C. (2021). Green Tea (*Camellia sinensis*) Extract Induces p53-Mediated Cytotoxicity and Inhibits Migration of Breast Cancer Cells. *Foods* 10(12): 3154.
- Sen, A., Papadimitriou, N., Lagiou, P., Perez-Cornago, A., Travis, R.C., Key, T.J., Murphy, N., Gunter, M., Freisling, H., Tzoulaki, I., Muller, D.C., Cross, A.J., Lopez, D.S., Bergmann, M., Boeing, H., Bamia, C., Kotanidou, A., Karakatsani, A., Tjønneland, A., Kyrø, C., Outzen, M., Redondo, M.L., Cayssials, V., Chirlaque, M.D., Barricarte, A., Sánchez, M.J., Larrañaga, N., Tumino, R., Grioni, S., Palli, D., Caini, S., Sacerdote, C., Bueno-de-Mesquita, B., Kühn, T., Kaaks, R., Nilsson, L.M., Landberg, R., Wallström, P., Drake, I., Bech, B.H., Overvad, K., Aune, D., Khaw, K.T., Riboli, E., Trichopoulos, D., Trichopoulou, A., and Tsilidis, K.K. (2019). Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Int. J. Cancer* 144(2): 240–250.
- Shen, J., Li, P., Liu, S., Liu, Q., Li, Y., Zhang, Z., Yang, C., Hu, M., Sun, Y., He, C., and Xiao, P. (2020). The chemopreventive effects of Huangqin-tea against AOM-induced preneoplastic colonic aberrant crypt foci in rats and omics analysis. *Food Funct.* 11(11): 9634–9650.
- Sheng, J., Shi, W., Guo, H., Long, W., Wang, Y., Qi, J., Liu, J., and Xu, Y. (2019). The Inhibitory Effect of (-)-Epigallocatechin-3-Gallate on Breast Cancer Progression via Reducing SCUBE2 Methylation and DNMT Activity. *Molecules* 24(16): 2899.
- Shojaei-Zarghani, S., Yari Khosroushahi, A., and Rafrat, M. (2021). Onco-preventive effects of theanine and theobromine on dimethylhydrazine-induced colon cancer model. *Biomed. Pharmacother.* 134: 111140.
- Song, Y., Wang, Z., Jin, Y., and Guo, J. (2019). Association between tea and coffee consumption and brain cancer risk: an updated meta-analysis. *World J. Surg. Oncol.* 17(1): 51.
- Sun, L., Wen, S., Li, Q., Lai, X., Chen, R., Zhang, Z., Cao, J., and Sun, S. (2022). Theaflavin-3,3'-di-gallate represses prostate cancer by activating the PKC $\delta$ /aSMase signaling pathway through a 67 kDa laminin receptor. *Food Funct.* 13(8): 4421–4431.
- Sun, W., Wong, I.L.K., Law, H.K., Su, X., Chan, T.C.F., Sun, G., Yang, X., Wang, X., Chan, T.H., Wan, S., and Chow, L.M.C. (2023). In Vivo Reversal of P-Glycoprotein-Mediated Drug Resistance in a Breast Cancer Xenograft and in Leukemia Models Using a Novel, Potent, and Nontoxic Epicatechin EC31. *Int. J. Mol. Sci.* 24(5): 4377.
- Sun, X.L., Xiang, Z.M., Xie, Y.R., Zhang, N., Wang, L.X., Wu, Y.L., Zhang, D.Y., Wang, X.J., Sheng, J., and Zi, C.T. (2022). Dimeric(-)-epigallocatechin-3-gallate inhibits the proliferation of lung cancer cells by inhibiting the EGFR signaling pathway. *Chem.-Biol. Interact.* 365: 110084.
- Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *Ca-Cancer J. Clin.* 71(3): 209–249.
- Tan, H., Li, M., Han, L., Zhao, Y., and Zhang, X. (2022). Gypensapogenin I Suppresses Cell Proliferation in Triple-Negative Breast Cancer Via Triggering the Closure of AKT/GSK3 $\beta$ /Catenin and Notch-1 Signaling Pathways. *J. Agric. Food Chem.* 70(17): 5438–5449.
- Tang, G.Y., Meng, X., Gan, R.Y., Zhao, C.N., Liu, Q., Feng, Y.B., Li, S., Wei, X.L., Atanasov, A.G., Corke, H., and Li, H.B. (2019). Health Functions and Related Molecular Mechanisms of Tea Components: An Update Review. *Int. J. Mol. Sci.* 20(24): 6196.
- Thomas, P., and Dong, J. (2021). (-)-Epicatechin acts as a potent agonist of the membrane androgen receptor, ZIP9 (SLC39A9), to promote apoptosis of breast and prostate cancer cells. *The Journal of steroid biochemistry and molecular biology* 211: 105906.
- Tran, G.B., Ding, J., Ye, B., Liu, M., Yu, Y., Zha, Y., Dong, Z., Liu, K., Sudarshan, S., and Ding, H.F. (2023). Caffeine Supplementation and FOXM1 Inhibition Enhance the Antitumor Effect of Statins in Neuroblastoma. *Cancer Res.* 83(13): 2248–2261.
- van Dam, R.M., Hu, F.B., and Willett, W.C. (2020). Coffee, Caffeine, and Health. *N. Engl. J. Med.* 383(4): 369–378.
- Wang, J., Sun, P., Wang, Q., Zhang, P., Wang, Y., Zi, C., Wang, X., and Sheng, J. (2019). (-)-Epigallocatechin-3-gallate derivatives combined with cisplatin exhibit synergistic inhibitory effects on non-small-cell lung cancer cells. *Cancer Cell Int.* 19: 266.
- Wang, W., Yang, Y., Zhang, W., and Wu, W. (2014). Association of tea consumption and the risk of oral cancer: a meta-analysis. *Oral Oncol.* 50(4): 276–281.
- Wang, Y., Yuan, Y., Wang, C., Wang, B., Zou, W., Zhang, N., and Chen, X. (2022). Theabrownins Produced via Chemical Oxidation of Tea Polyphenols Inhibit Human Lung Cancer Cells in vivo and in vitro by Suppressing the PI3K/AKT/mTOR Pathway Activation and Promoting Autophagy. *Front. Nutr.* 9: 858261.
- Wang, Z., Hou, X., Li, M., Ji, R., Li, Z., Wang, Y., Guo, Y., Liu, D., Huang, B., and Du, H. (2022). Active fractions of golden-flowered tea (*Camellia nitidissima* Chi) inhibit epidermal growth factor receptor mutated non-small cell lung cancer via multiple pathways and targets in vitro and in vivo. *Front. Nutr.* 9: 1014414.
- Wasim, S., Lee, S.Y., and Kim, J. (2022). Complexities of Prostate Cancer. *Int. J. Mol. Sci.* 23(22): 14257.
- Wu, K., Wei, Y., Yu, Y., Shan, M., Tang, Y., and Sun, Y. (2022). Green tea polyphenols inhibit malignant melanoma progression via regulating circ\_MITF/miR-30e-3p/HDAC2 axis. *Biotechnol. Appl. Biochem.* 69(2): 808–821.
- Xiao, X., Guo, L., Dai, W., Yan, B., Zhang, J., Yuan, Q., Zhou, L., Shan, L., and Efferth, T. (2022). Green tea-derived theabrownin suppresses human non-small cell lung carcinoma in xenograft model through activation of not only p53 signaling but also MAPK/JNK signaling pathway. *J. Ethnopharmacol.* 291: 115167.
- Xing, L., Zhang, H., Qi, R., Tsao, R., and Mine, Y. (2019). Recent Advances in the Understanding of the Health Benefits and Molecular Mechanisms Associated with Green Tea Polyphenols. *J. Agric. Food Chem.* 67(4): 1029–1043.
- Xu, H., Wang, L., Shi, B., Hu, L., Gan, C., Wang, Y., Xiang, Z., Wang, X., and Sheng, J. (2020). Caffeine inhibits the anticancer activity of paclitaxel via down-regulation of  $\alpha$ -tubulin acetylation. *Biomed. Pharmacother.* 129: 110441.
- Xu, P., Yan, F., Zhao, Y., Chen, X., Sun, S., Wang, Y., and Ying, L. (2020). Green Tea Polyphenol EGCG Attenuates MDSCs-mediated Immunosuppression through Canonical and Non-Canonical Pathways in a 4T1 Murine Breast Cancer Model. *Nutrients* 12(4): 1042.
- Xu, X.Y., Zhao, C.N., Li, B.Y., Tang, G.Y., Shang, A., Gan, R.Y., Feng, Y.B., and Li, H.B. (2023). Effects and mechanisms of tea on obesity. *Crit. Rev. Food Sci. Nutr.* 63(19): 3716–3733.
- Yang, C.S. (1999). Tea and health. *Nutrition* 15(11-12): 946–949.
- Yang, C.S., and Wang, Z.Y. (1993). Tea and cancer. *J. Natl. Cancer Inst.* 85(13): 1038–1049.
- Yang, K., Li, Y.W., Gao, Z.Y., Xiao, W., Li, T.Q., Song, W., Zheng, J., Chen, H., Chen, G.H., and Zou, H.Y. (2019). MiR-93 functions as a tumor promoter in prostate cancer by targeting disabled homolog 2 (DAB2) and an antitumor polysaccharide from green tea (*Camellia sinensis*) on their expression. *Int. J. Biol. Macromol.* 125: 557–565.
- Yu, S., Wang, B., Li, G., Guo, X., Yang, H., and Sun, Y. (2023). Habitual Tea Consumption Increases the Incidence of Metabolic Syndrome in Middle-Aged and Older Individuals. *Nutrients* 15(6): 1448.
- Yuan, Y., Bai, Y., Zhang, Y., Wan, H., Hu, Y., Wu, Z., Li, X., Song, W., and Chen,

- X. (2022). Physicochemical and Colon Cancer Cell Inhibitory Properties of Theabrownins Prepared by Weak Alkali Oxidation of Tea Polyphenols. *Plant Foods Hum. Nutr.* 77(3): 405–411.
- Zhang, J.Y., Liao, Y.H., Lin, Y., Liu, Q., Xie, X.M., Tang, L.Y., and Ren, Z.F. (2019). Effects of tea consumption and the interactions with lipids on breast cancer survival. *Breast Cancer Res. Treat.* 176(3): 679–686.
- Zhang, L., Chen, W., Tu, G., Chen, X., Lu, Y., Wu, L., and Zheng, D. (2020). Enhanced Chemotherapeutic Efficacy of PLGA-Encapsulated Epigallocatechin Gallate (EGCG) Against Human Lung Cancer. *Int. J. Nanomed.* 15: 4417–4429.
- Zhang, R., Zheng, S., Guo, Z., Wang, Y., Yang, G., Yin, Z., and Luo, L. (2022). L-Theanine inhibits melanoma cell growth and migration via regulating expression of the clock gene BMAL1. *Eur. J. Nutr.* 61(2): 763–777.
- Zhang, X., Huang, H., Sun, S., Li, D., Sun, L., Li, Q., Chen, R., Lai, X., Zhang, Z., Zheng, X., Wong, W.L., and Wen, S. (2022). Induction of Apoptosis via Inactivating PI3K/AKT Pathway in Colorectal Cancer Cells Using Aged Chinese Hakka Stir-Fried Green Tea Extract. *Molecules* 27(23): 8272.
- Zhang, Z., Zhu, Q., Wang, S., and Shi, C. (2023). Epigallocatechin-3-gallate inhibits the formation of neutrophil extracellular traps and suppresses the migration and invasion of colon cancer cells by regulating STAT3/CXCL8 pathway. *Mol. Cell. Biochem.* 478(4): 887–898.
- Zhao, J., Zhao, X., Tian, J., Xue, R., Luo, B., Lv, J., Gao, J., and Wang, M. (2020). Theanine attenuates hippocampus damage of rat cerebral ischemia-reperfusion injury by inhibiting HO-1 expression and activating ERK1/2 pathway. *Life Sci.* 241: 117160.
- Zhao, L.G., Li, Z.Y., Feng, G.S., Ji, X.W., Tan, Y.T., Li, H.L., Gunter, M.J., and Xiang, Y.B. (2021). Tea Drinking and Risk of Cancer Incidence: A Meta-Analysis of Prospective Cohort Studies and Evidence Evaluation. *Adv. Nutr.* 12(2): 402–412.
- Zheng, F., Chen, K., Zhong, J., Tang, S., Xu, S., Lu, W., Wu, Y., and Xia, D. (2023). Association between Different Types of Tea Consumption and Risk of Gynecologic Cancer: A Meta-Analysis of Cohort Studies. *Nutrients* 15(2): 403.
- Zhou, Y., Zhou, X., Huang, X., Hong, T., Zhang, K., Qi, W., Guo, M., and Nie, S. (2021). Lysosome-Mediated Cytotoxic Autophagy Contributes to Tea Polysaccharide-Induced Colon Cancer Cell Death via mTOR-TFEB Signaling. *J. Agric. Food Chem.* 69(2): 686–697.
- Zu, M., Xie, D., Canup, B.S.B., Chen, N., Wang, Y., Sun, R., Zhang, Z., Fu, Y., Dai, F., and Xiao, B. (2021). ‘Green’ nanotherapeutics from tea leaves for orally targeted prevention and alleviation of colon diseases. *Biomaterials* 279: 121178.