






# Investigations on the Anticancer Potential of Green Tea and Formulation Options

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**Abstract:** The tea plant *Camellia sinensis* is widely cultivated in over 30 countries for its leaves. Processing methods determine the three main types of tea: green, black, and oolong. These teas contain various components: EC, EGC, ECG, EGCG, GC, and GCG. Polyphenols in tea can be qualitatively and quantitatively estimated using titration, UV-visible spectroscopy, FTIR, HPTLC, HPLC, HPCE, FTNIR, and 1H-NMR. This study focuses on the potential benefits of green tea in preventing and treating different types of cancer, including oral, lung, colorectal, breast, prostate, skin, liver, stomach, mammary gland, small intestine, esophagus, bladder, pancreas, thyroid, and urinary cancers. Synergistic anticancer effects have been observed for catechins and curcumin, as well as for tea polyphenols and ascorbic acid. Additionally, green tea exhibits antioxidant and anti-hypertensive activity, supports oral and bone health, inhibits solar ultraviolet radiation, and helps prevent obesity and insulin resistance. Various formulations of green tea have been reported, including effervescent green tea, green tea microfine powder, capsules of freeze-dried green tea fresh leaves, and green tea beverages. The collection and estimation of polyphenols in green tea have demonstrated their diverse composition and potential uses. The synergistic action of green tea polyphenols with other herbal drugs has shown promising anticancer effects. Furthermore, the mechanisms underlying the anticancer effects of green tea polyphenols have been elucidated. Recent patented dosage forms of green tea have also been identified, expanding its application options. Green tea, derived from the *Camellia sinensis* plant, contains a variety of polyphenols with potential health benefits. It has shown promise in preventing and treating various types of cancer, providing antioxidant and anti-hypertensive effects, contributing to oral and bone health, inhibiting solar ultraviolet radiation, and preventing obesity and insulin resistance. The collection, estimation, composition, and uses of polyphenols in green tea, along with their synergistic effects with other herbal drugs, have been explored. Understanding the mechanisms of the anticancer effects of green tea polyphenols contributes to their potential therapeutic applications. Recent patented dosage forms offer novel options for utilizing green tea's beneficial properties.

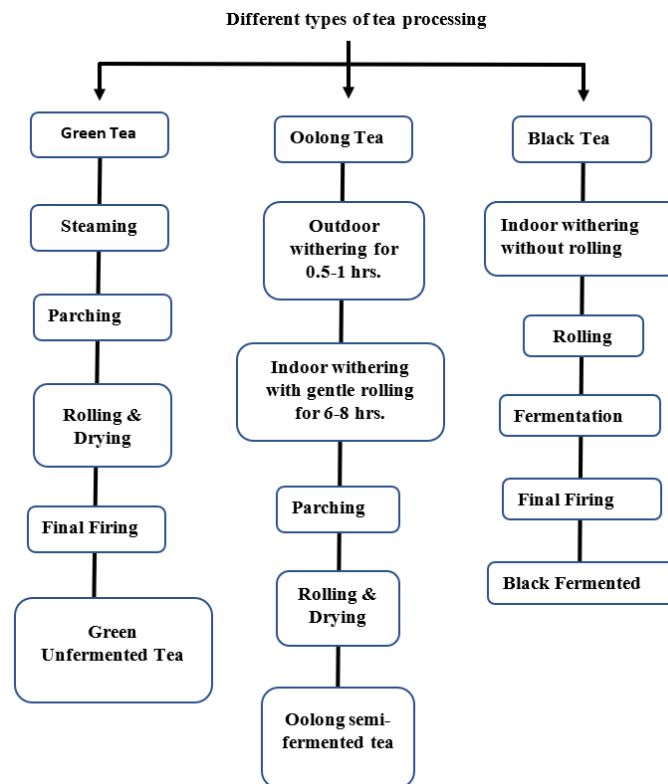
**Keywords:** Cultivation and processing; Green tea extract; tea components; anticancer activity.

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## 1. Introduction

### 1.1. Cultivation and collection of tea.

Increased awareness of the health-promoting properties of the tea beverage has led to an increase in the level of its consumption. Tea, scientifically known as *Camellia sinensis*, is grown in about 30 countries and consumed globally [1]. China is a major producer, followed by India, Kenya, and Sri Lanka [2]. It is an important beverage crop cultivated in the tropics and subtropics under acid soil conditions. Tea shrubs are evergreen, 4-15 cm long and 2-5 cm broad, trimmed below 2 meters for the collection of their leaves [3]. Cultivation and harvesting of tea do not follow any typical cropping pattern. The young, light-green tip (bud) and the first 2-3 leaves with short white hairs on the underside are handpicked every 1-2 weeks for tea production [4].



**Figure 1.** The processing of tea of different varieties.

### 1.2. Types of tea and processing methods.

Tea, the processed leaves and buds of the *Camellia sinensis* herb, is the most widely consumed drink throughout the world [5,6]. A useful consideration of tea's physiological and pharmacological effects includes background knowledge of cultivation, the composition of the leaves, the availability of different varieties of tea, and, most significantly, the chemical modifications that occur during the processing of different commercial products [7]. Tea production is carried out in relatively few countries, and India has the largest production capacity of different world-class varieties. Variations in production methods result in different types of tea with distinct polyphenol profiles [8]. Tea is categorized into three primary varieties based on processing, as described in Figure 1; they are: a. Non-fermented green tea is produced by drying and steaming the fresh leaves to inactivate polyphenol oxidases and, therefore, is non-oxidized; b. Semi-fermented Oolong tea is produced by subjecting the fresh leaves to partial fermentation before drying, c. Fermented tea undergoes post-harvest fermentation

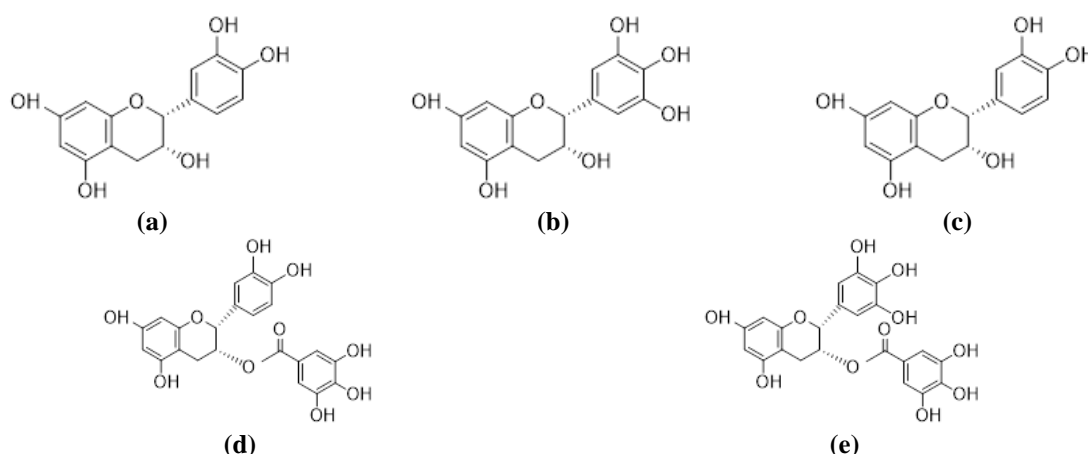
before drying and steaming, while black tea fermentation is due to oxidation catalyzed by polyphenol oxidase, and Pu-Erh (a Variety of fermented tea traditionally produced in Yunnan Province) tea is accomplished by using microorganisms [9].

### 1.3. Composition of green tea polyphenols.

The major chemical constituents present in green and black tea include alkaloids like - theophylline, caffeine, and theobromine; polyphenols like - flavan- 3-ols called catechins that include (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-) epigallocatechin's gallate (EGCG), (-) epicatechin gallate (ECG), Gallo catechins gallate (GCG), Gallo catechins (GC); carbohydrates, amino acids (AA), proteins, chlorophyll, minerals, volatile compounds, trace elements, and some other unidentified compound [10]. Green and black tea differ in their polyphenol and other compound content, as shown in Table 1. The dry green tea leaves possess 6 -16% catechins, of which EGCG constitutes 10- 50% and represents the most potent phenolic due to a high degree of gelation and hydroxylation [11]. Thea-flavins (TFs) and Thearubigins (TRs) are other groups of polyphenolic compounds found in both black and oolong teas [12]. The basic structure of polyphenols is described below in Figure 2.

**Table 1.** Composition of green tea and black tea

S.N.	Components	Green tea	Black tea
1.	Amino acids	4	13-15
2.	Volatiles	<0.1	<0.1
3.	Carbohydrates	25	15
4.	Proteins	15	---
5.	Catechins	30-42	3-10
6.	Flavanols	5-10	6-8
7.	Ascorbic acids	1-2	--
8.	Gallic acids	0.5	--
9.	Minerals	6-8	15
10.	Methylxanthines	7-9	8-11
11.	Theogallin's	2-3	--
12.	Organic acids	1.5	--



**Figure 2.** The basic structure of polyphenols: (a) (-)-epicatechin (EC); (b) (-) epigallocatechin (EGC); (c) (-)-catechin (CT); (d) (-)-epicatechin gallate (EGC); (e) (-)-epigallocatechin gallate (EGCG).

## 2. Estimation of Polyphenols

### 2.1. Titration methods.

Quantitative analysis of tea extract tannins can be performed by redox titration with a standard potassium permanganate solution. In the titration of the extract against  $KMnO_4$  using

indigo carmine, the dye passes through many shades to a final yellow, with a faint pink marking the endpoint [13,14].

### 2.2. UV-visible spectroscopy method.

The FC reagent method involves measuring the absorbance of the color produced by the reaction of FC reagent with polyphenols in the tea extract, in the presence of sodium carbonate (by incubation for 30 minutes in the dark) at 760 nm; standard pyrogallol is used for comparison and calculation [15,16]. Another photometric method to measure total polyphenols using the Folin-Ciocalteu reagent employed a 540 nm wavelength [17]. Still, other similar studies report keeping the mixture in the dark for 60 min at room temperature and measuring absorbance at 747 nm [18].

The chloroform extraction is carried out in a separating funnel by vigorously shaking the tea extract with chloroform, then allowing the mixture to stand, allowing the aqueous and organic layers to separate at room temperature. The lower chloroform layer is collected and diluted with chloroform for further analysis at 277 nm against pure chloroform as a blank using a UV-visible spectrophotometer [19].

### 2.3. Near-IR method.

Sinija *et al.* [20] developed and validated a Fourier transform near-infrared (FT-NIR) spectroscopic technique for measuring caffeine content in instant green tea and granules. FTNIR spectroscopy with chemometrics, using the PLS–first derivative plus straight-line subtraction method, could predict the caffeine content in tea samples within 2-5 min, with an R<sup>2</sup> value of more than 0.98 and an SE of less than 2 using 6 factors [20].

Determination of total polyphenol content in green tea by Near-infrared spectroscopy (NIRS) was attempted with a method of multivariate calibration, and a comparison of various algorithms like interval PLS (iPLS), partial least squares (PLS), and synergy interval partial least squares (siPLS) indicated that the NIR spectroscopy with siPLS algorithm was superior for analysis of polyphenolic content in green tea [21].

Wang *et al.* [22] developed an approach based on near-infrared spectroscopy (NIRS), Ultraviolet-visible spectroscopy (UV-Vis), and chemometric algorithms for discrimination among five varieties of green tea and for the estimation of the total polyphenol content (TPC) in these tea varieties. It was demonstrated that the proposed method can be efficiently utilized for fast, accurate economic analysis of green tea [22].

### 2.4. <sup>1</sup>H-NMR.

Proton NMR spectroscopy has also been used as a reliable method for metabolic characterization and the simultaneous determination of active ingredients of green tea, such as phenolics. Epigallocatechin-3-gallate (EGCG), Epigallocatechin (EGC), Gallic acid (GA), Caffeine (CA), Theanine (TH) [23].

### 2.5. High-performance thin-layer chromatography (HPTLC).

Behera *et al.* [24] reported the HPTLC method to separate and estimate phenolic compounds and flavonoids in *Careya arborea* leaf extract using Butanol: Acetic acid: water as a mobile phase on silica gel 60 F<sub>254</sub> plates. Peaks were detected at 366 nm after developing with a spray of anisaldehyde (9 ml of 98% sulphuric acid + 85 ml methanol + 10 ml acetic acid

+ 0.5 ml anisaldehyde), drying in air, and heating at 120°C for 2 min [24]. Other visualizing agents and mobile phases that have been reported for the quantitation of different components of tea extract are summarized in Table 2. It requires drying in cool air followed by heating at 120°C for 2 min [25].

**Table 2.** Mobile phase and visualizing agent for detecting different components by HPTLC.

Components	Mobile phase	Detecting agent
Flavonoids	Ethyl formate, toluene, formic acid, water	NP reagent at 366 nm
Polyphenols	Toluene, acetone, formic acid	Dipped in Fast Blue Salt B reagent at white light
Alkaloids	Ethyl acetate, methanol, water	No derivatization. Evaluation is done under 254 nm
Amino Acids	1-butanol, acetone, acetic acid, water	Spraying ninhydrin

### 2.6. High-performance liquid chromatography (HPLC).

Bonoli *et al.* reported quantification of the catechins on RP HPLC-DAD (Luna 5 mm C18, 25 cm, 3.0 mm i.d column) using a gradient of double-distilled water/ methanol/ formic acid as mobile phase A, and acetonitrile/ formic acid as mobile phase B for better separation [26]. Another validated HPLC-DAD method has been reported for simultaneously estimating 15 phenolic antioxidants (flavan-3-ols) in various herb extracts, tea, and coffee varieties. The absorbance of analytes and quantitation were monitored at the  $\lambda_{max}$  for each analyte with peak identification. Gallo catechin, catechin, epicatechin, and epigallocatechin gallate, epigallocatechin, were monitored at 240 nm. Gallic acid, theobromine, theophylline, caffeine, and epicatechin gallate at 270 nm, chlorogenic acid hemihydrate at 330 nm, myricetin, and quercetin at 370 nm [27].

### 2.7. High-performance capillary electrophoresis (HPCE).

Bonoli *et al.* reported an analysis of green tea extract for polyphenolic content using high-performance capillary electrophoresis (HPCE) [28]. The capillary cartridge was contained under activated fused silica tubing (50 mm i.d., 375 mm o.d.), supplied from Beckman. The total capillary length was 47 cm, whereas the effective length was 40 cm. UV detection was performed at 200 nm; rise time was set at 0.17 s, and the data rate was 10 Hz. Peak identification was performed by spiking the green tea extract with standard compounds. Another study investigated the compatibility and reliability of HPLC and capillary electrophoresis (CE) for the separation and quantification of tea polyphenols in the presence of other ingredients, including caffeine, adenine, theophylline, quercetin, gallic acid, and caffeic acid. Both were found to be reliable and compatible with CE, which is faster and more precise [28].

## 3. The Activity of Tea Polyphenols

Tea polyphenols benefit oral and bone health; they are antioxidants and anti-hypertensives, showing preventive effects in cancer, coronary heart disease, ultraviolet skin irritation, obesity, and insulin-resistant diabetes I.

### 3.1. Inhibition of tumorigenesis.

Various studies in the past decade have investigated the anticancer activity of tea on different organs, as depicted in Figure 3. Results from many studies in cell culture and tumor

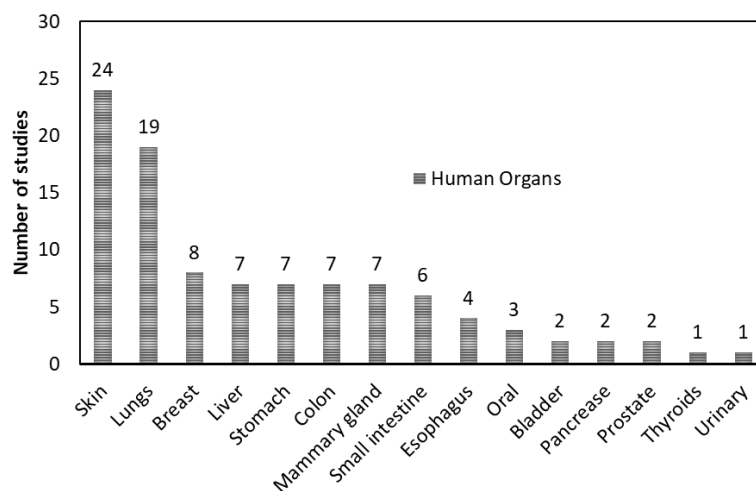
bioassays in animal models support the role of tea in cancer prevention. The effect of tea on skin cancer is the most widely investigated, followed by its effect on lung cancer. The treatment with tea has shown a remarkable reduction in the number and size of tumors in experiments using A/J mouse models of lung carcinogenesis using carcinogens like cisplatin, NNK, N-nitrosomethylurea, and N-nitroso diethylamine benzo (a) pyrene. A decreased tumor incidence is observed with epigallocatechin-3-gallate (EGCG) and theaflavins in mice treated with N-nitroso diethylamine.

However, a study suggested that caffeine is the key effective constituent responsible for black tea's inhibitory activity against lung tumorigenesis in Fisher-344 rats [29]. It may be related to the antiproliferative, proapoptotic, and antiangiogenic potential of tea constituents. Green tea consumption may also reduce body fat and weight, thereby inhibiting tumorigenesis. Table 3 provides details on the inhibition of tumorigenesis by tea across various organs.

However, results of epidemiological studies on tea and cancer have been inconsistent; some show that tea consumption is protective, whereas others show no association or even an increased risk of certain cancers.

**Table 3.** Showing carcinogenic inhibition by tea in rats and mice.

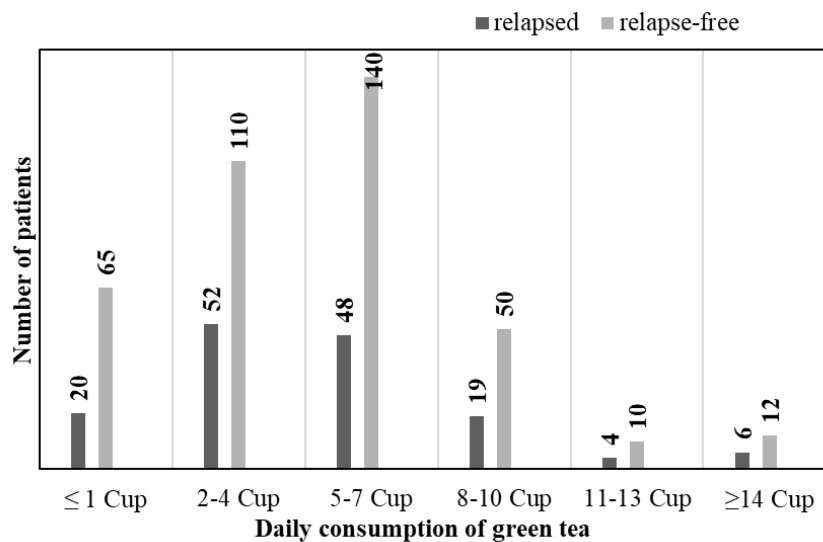
Organs	Carcinogens	Tea preparation	Tumor outcome	Stage of tumorigenesis
Skin (mouse)	BaP/TPA, UVA + UVB, UVB, DMBA/TPA, UVB/TPA	Caffeinated and decaffeinated green tea, Caffeinated and decaffeinated black tea Both polyphenols EGCG and Caffeine	Papillomas and carcinomas Decrease multiplicity Decrease incidence Decrease size	Progression of Initiation promotion
In the lungs of rats and mice	NNK, NDEA	DGT (0.6 %) DC DGT (0.6 %) AC DBT (0.6 %) AC DBT (0.6 %) DC Green tea (1.25 %) DC Green tea (1.25 %) AC Green tea (0.63 %) DC Green tea (1.25 %) AC	↓multiplicity 67% ↓multiplicity 85% ↓multiplicity 64% ↓multiplicity 63% ↓multiplicity 56% ↓multiplicity 44% ↓multiplicity 36% ↓multiplicity 52%	Decreased slightly Decreased by 30 % Decreased slightly Decreased slightly Decreased by 40 % Decreased by 36 % Decreased slightly Decreased by 50 %
Mammary gland (rat, mouse)	DMBA IQ spontaneous	Black tea, green tea polyphenols EGCG, Catechins	Decrease multiplicity Decrease incidence	Post initiation
In the colon of rats and mice	DMH AOM MNU	Tea polyphenols, EGCG Green tea Black tea	Adenomas and carcinomas Decrease multiplicity Decrease incidence	Post initiation



**Figure 3.** Studies show the protective effects of green and/or black tea against tumorigenesis in animal models.

3.1.1. Breast cancer.

In a Japanese study of premenopausal patients with stage I and II breast carcinoma and with an expanded articulation of progesterone receptor (PgR) and estrogen receptor (ER), consumption of green tea was found to be associated with less number of axillary lymph hub metastases, while in postmenopausal more utilization of green tea before the start of clinical symptoms was linked to better prognosis in stage I and II growth of breast carcinoma, as well as reduced chances of reappearance ( $P < 0.05$  for unrefined disease-free endurance); the repeat rate was 16.7 or 24.3% among those consuming  $\geq 5$  cups or  $\geq 4$  cups every day, individually as shown in Figure 4 [30]. In another prospective study on 1160 females with breast cancer, green tea in different amounts showed that intake of more than 3 cups/day reduced the risk of cancer recurrence [31]. Further, across two prospective studies involving 35004 women and a case-control study involving 581 persons, green tea consumption was not associated with breast cancer risk. While the comparison between  $> 5$  cups/day drinkers and  $< 1$  cups/day showed that those consuming  $> 5$  cups/day had a 27% lower risk of breast cancer [32]. A United States study on 501 Asian American patients with breast cancer and 594 control patients who were given green tea in different amounts found a decrease in the incidence of breast cancer along with increased consumption of green tea [33].



**Figure 4.** Daily green tea consumption before the onset of and without recurrence of breast cancer.

3.1.2. Lung cancer.

The inhibition of lung tumorigenesis by tea was demonstrated independently in several laboratories in the early 1990s. Table 4 summarizes the experimental conditions and results of several sets of experiments. In China, a case-control study on women, 649 lung cancer patients, and 675 controls indicated that the risks decreased with increasing consumption among non-smoking women [43].

**Table 4.** Impact of antioxidant capacity by using different tea preparations.

Assay	Tea types	Consumed daily quantity	Time periods	References
FRAP	Green	20 g dry leaves/500 mL (300 mL consumed)	20 min	[34]
FRAP	Green tea solid	2 g/300 mL (equivalent to 3 cups)	30min	[35]
FRAP	Black Tea solid	2 g/300 mL (equivalent to 3 cups)	30 min	[35]
TAS	Green	5 g dry leaves/300 mL	60 min	[36]

Assay	Tea types	Consumed daily quantity	Time periods	References
TRAP	EGCG	400 mg		[37,38]
PCOOH	Green tea Catechin (GTC)	254 mg	60 min	[39]
8-OHdG (urine, WBC)	Green	6 cups	7 days	[40]
Oxidative DNA damage (Lymphocytes)	Not Specified	6 cups	2 weeks	[41]
MDA (Plasma)	Green tea Extract	10 cups (equivalent)	4 weeks	[42]

### 3.1.3. Gastrointestinal cancer.

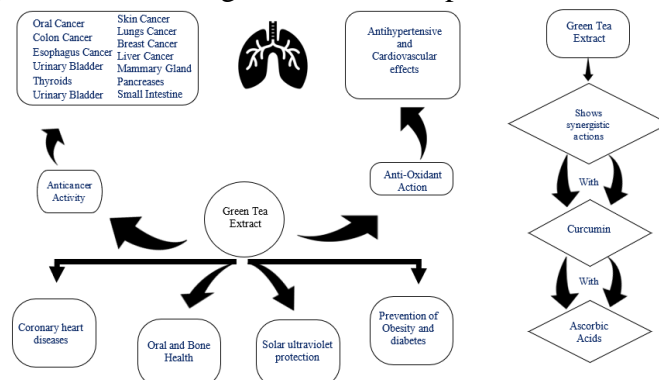
A case-control study in Japan with 887 gastric cancer patients and 28619 controls showed that those who drank 6 or more cups each day were at a decreased risk of gastric cancer [44]. Another cross-sectional study of 636 men who were given green tea (10 or more cups/day vs. 0-9 cups/day) found that the risk of chronic atrophic gastritis was lower among those drinking 10 or more cups/day of green tea [45]. In China, 166 cases of chronic atrophic gastritis, 133 gastric cancers, and 433 controls receiving 1-21 cups/week, it was observed that the incidence of gastric cancer was strongly associated with tea consumption [46]. However, no relationship could be established between green tea consumption and death due to stomach cancer or even the occurrence of chronic atrophic gastritis [47–49]. A prospective interventional study conducted in China on 778 patients compared abnormal cell proliferation and the alleviation of esophageal precancerous lesions between the treatment group (5 mg/day of decaffeinated green tea, DCGT) for 1 year and the placebo group, and did not show any difference [50].

### 3.1.4. Prostate cancer.

A 30% decrease in risk of prostate malignant growth has been reported with tea consumption of more than 500 mL/day in a case-control study on 1,254 Canadians. There was no relationship between coffee intake and cancer occurrence, except for a decrease in cancer occurrence [51]. In China, in a case-control study, 130 prostate adenocarcinoma patients and 274 controls received green tea, reducing prostate cancer by increasing the frequency, duration, and amount of green tea consumption [52,53].

### 3.1.5. Ovarian cancer.

There were control studies in China, in which 254 ovarian cancer patients and 652 controls were given green tea, which resulted in a decreased risk of ovarian cancer with the increase in frequency and duration of green tea consumption.



**Figure 5.** Anticancer activity of green tea.

These are the anticancer mechanisms of green tea [54,55]. Another mechanism of green tea is shown in Figure 5.

### 3.2. Mechanism of tumor inhibition by tea.

Green tea polyphenols (GTP) stimulate the mitogen-activated protein kinase (MAPK) pathway. The protective properties of GTP are derived from its inhibition of cytochromes P450, an enzyme involved in the bioactivation of carcinogens [56]. Other *in vivo* studies have also shown that the biological response to green tea involves Phase II detoxification enzymes [57]. In colorectal cancer, GTP reduced prostaglandin E2 synthesis in rectal mucosa by 50% within 4 hours of consumption [58]. Animal tumor bio-assay by tea, studies in the past two years with a focus on mainly four cancer sites, such as colon, mammary, skin, and lung, and some other sites of cancers [59].

Further, the chemopreventive action of green tea depends on antioxidant activity; detoxification of enzymes; effects on cellular growth via molecular regulatory functions; and apoptosis [60].

### 3.3. Synergistic anticancer activity.

#### 3.3.1. Catechin and curcumin.

A combination of curcumin and catechin shows synergistic anticancer and cancer-protective activity on human colon adenocarcinoma HCT 15, HCT 116, and human larynx carcinoma Hep G-2, and the cancer-protective and anticancer activity was increased in their combination drug compared with curcumin/catechin alone [61,62].

#### 3.3.2. Tea polyphenols and ascorbic acid.

The inhibitory rates on SPC-A-1 cells as determined by the MTT test for a combination of ascorbic acid and EGCG were 45.5%. For TF3 combined with ascorbic acid at a molar proportion of 6:1 was and 54.4% effects of theaflavin monomers, Ascorbic acid, and EGCG on the cell viability and differentiation of SPC-A-1 cells was highest inhibition rate of 40.39% at 100  $\mu\text{mol/L}$  for TF2A [63]. The combinations of ascorbic acid with EGCG and ascorbic acid with TF3 increased their inhibition on SPC-A-1 cells at a higher concentration, as indicated by  $\text{CI} < 1$ . Polyphenols and AA inhibit the growth of SPC-A-1 cells and induce G1-phase arrest, characteristics of anticancer activity. The cell may arrest in the G0/G1 stage and undergo apoptosis, or recover from G0/G1 and enter the S stage.

#### 3.3.3. Antioxidant capacity of tea *in vitro* and *in vivo*.

Tea flavonoids have been found *in vitro* to enhance gap junctional communication, stimulate  $\beta$ -cell proliferation, and inhibit hepatic cytochrome P450-dependent enzymes [64,65]. Improved plasma antioxidant after one dose of tea in healthy volunteers, 30 min to an hour after ingestion, Table 5.

**Table 5.** Impact of green tea extract and catechins on body weight.

Parameter	Bodyweight						
	GTEs [23]	DGT [27]	GTEs [25]	GTEs [24]	GTCs [28]	EGCG [29,30]	EGCG [32]
Therapy	0.13 gm/day	Diet in 2%	In a diet with 1%	Diet with 2%	In diet 0.3 %	0.2-0.5% in fluids	In diet 0.32%

Period	240 hrs.	42 days	42 days	14 days	48 weeks	44 weeks	112 days
Animal model	Male ZR	C57BL/6J	Mice ob/ob	Male SDR	Mice SAMP10	Mice C57BL/6J	Mice C57BL/6J
Effects	Decreases	---	Decreases	Decreases	Decreases	Decreases	Decreases

GTEs=green tea extracts; GTCs=green tea catechins; ZR= Zucker rat; SDR=Sprague-Dawley rat; ob/ob=leptin-deficient.

### 3.3.4. Anti-hypertensive effect and cardiovascular disease risk.

High blood pressure can accelerate atherosclerosis, and studies of green tea polyphenols in hypertensive animals have reported a link between reduced blood pressure and tea consumption [66]. However, more recent studies do not support tea's hypotensive effect. A Japanese study of 3,336 men aged 48 to 56 years found that green tea intake did not correlate with blood pressure. Similar outcomes are reported in a study of 13 normotensive Australian men who consumed 5 cups of green or black tea daily for 1 week, and in the UK, 57 males and females consuming 6 cups daily for 4 weeks showed no significant effects on blood pressure. However, a minor transient change in diastolic (3 – 5 mm Hg) and systolic (6-11 mm Hg) was observed after half an hour of caffeine ingestion in an Australian study that lasted for an hour.

### 3.3.5. Coronary heart disease.

Men and women from the Massachusetts area Health Study who consumed 1 or more cups of tea per day in the last decade had a 44% decrease in myocardial infarction (MI) incidence compared with those who consumed no tea. The results of this case-control study (n = 338/group) were free from other coronary risk factors, and an important linear trend across levels of tea consumption was observed ( $p = 0.012$ ).

### 3.3.6. Oral health.

Drinking tea was associated with lower levels of dental caries in a cross-sectional study of 6,014 secondary school children in England [67]. Tea consumption may have a beneficial effect on caries due to its natural fluoride content. In addition, green tea extracts inhibit oral bacteria such as *Escherichia coli*, *Streptococcus salivarius*, and *Streptococcus mutans* [40]. Oolong tea polyphenols seem to inhibit bacterial adherence to tooth surfaces by reducing the hydrophobicity of streptococci and by obstructing their carcinogenicity by reducing the rate of acid production. Tea decoctions prepared from several black and green teas also inhibit amylase activity in human saliva, reducing maltose release by 70% and effectively lowering the cariogenic potency of starch-containing foods. While not directly correlated with oral health, it is worth noting that impetigo contagiosa, a streptococcal and staphylococcal skin infection, was treated with tea preparations and ointment in 64 patients, with outcomes as effective as those of standard antibiotic therapies [68,69].

### 3.3.7. Bone health.

Tea intake was an independent protective factor against the risk of hip fractures in women and men aged 50 years or older in the Mediterranean Osteoporosis Study. Hegarty *et al.* [70] found, in a study of 1,256 British women aged 65 to 76 years, that tea drinkers had higher bone mineral density than non-tea drinkers. Higher mineral density in the bone of the lumbar spine ( $p = 0.004$ ), greater trochanter ( $p = 0.004$ ), and Ward's triangle ( $p = 0.02$ ) were free

from smoking status, hormone replacement therapy, coffee consumption, and the addition of milk in the tea [70].

### 3.3.8. Protection against solar/UV-induced erythema.

Wavelengths in the UVB range (290-320 nm) are responsible for causing the erythema that accompanies exposure to sunlight. Purified polyphenol ingredients isolated from green tea were confirmed to have chemopreventive activities. Skin sites on the back were treated with equimolar concentrations of EGCG, ECG, EC, EGC, and 5% green tea polyphenol solution. The 5% Green tea polyphenols (GTP) solution was most effective in protecting against erythema, while EGCG and ECG, both of which contain a galloyl group at the 3 positions, were most efficient in inhibiting erythema, whereas EGC and EC had little effect. However, there is increasing UVA (320-400 nm) responsiveness that affects the skin. The green tea polyphenols also prevented UVA-induced erythema when applied to the skin of healthy volunteers after 30 minutes of exposure to solar radiation. Erythema was examined at 24, 48, and 72 hours later [71].

### 3.3.9. Prevention of obesity by green tea polyphenols.

There has been dramatic growth in the rate of obesity, defined as a body mass index (BMI) of 30 or greater, which is associated with increased healthcare costs, decreased quality of life, and increased risk for premature death. Presently, more than 60% of the US population is overweight or obese [72]. The effects of green tea and green tea polyphenols (GTP) have been tested in several animal models of obesity (Table 6). Hasegawa *et al.* [73] reported that a daily oral intake of 130 mg powdered green tea to male Zucker rats fed a 50% sucrose diet with 15% butter resulted in a reduction in body weight within 2 days. Besides, rats treated with powdered green tea had significantly lower adipose tissue levels (5–9% decrease) and liver weight (11% decrease) [73]. Green tea polyphenols treatment (2% in the diet) reduced body fat build-up in Sprague–Dawley rats after 14 days but did not affect body weight gain. Treatment with 1% green tea extract containing 30% (w/w) total catechins for 42 days resulted in decreased body weight compared with control mice. A current study compared the action of supplementation with decaffeinated green tea powder, tea catechins, and other heat-treated tea catechins in Sprague–Dawley rats. Sae-tan *et al.* [74] similarly studied the actions of decaffeinated green tea (DGT) in both diet-induced obesity in C57BL/6J mice and hereditary obesity in the leptin-deficient mouse. All three studies showed a significant decrease in final body weight and epididymal, mesenteric, perirenal, and retroperitoneal adipose tissue. Supplementation of high-fat intake C57BL/6J mice nourished with 0.2 and 0.5% tea catechin resulted in the reduction of body weight gain, visceral adipose tissue weight (44–87% decrease), and liver triglyceride (53–75% decrease). Tea catechin therapy also reduces total plasma cholesterol and glucose levels in non-fasting conditions [74]. Treatment of high-fat intake C57BL/6J mice with 0.32% dietary EGCG for 112 days decreased body weight gain by 33–41% compared to high-fat-intake controls. By contrast, Raederstorff *et al.* [75] reported that supplementation with 0.25%, 0.5%, and 1.0% EGCG produced no significant alteration in body weight and liver weight in Wistar rats fed a high-fat, high-cholesterol diet for 28 days. EGCG (1%) reduced total plasma cholesterol and non-HDL cholesterol and hepatic total cholesterol concentration by 37%, 55%, and 17%, respectively, compared with a control group [75].

### 3.3.10. Prevention of insulin resistance and diabetes.

The development of insulin resistance is an early marker of type 2 diabetes (T2D) and is associated with elevated plasma free fatty acids and obesity [76,77].

## 4. Formulations of Green Tea

Many formulations of green tea are available, such as effervescent green tea, green tea microfine powder, capsules of freeze-dried green tea fresh leaves, green tea beverages, etc, as shown in Table 6.

**Table 6.** Patented products of green tea.

S.N.	Title	Inventor	Patent No.	Date of Patents
1.	Effervescent green tea extract formulation	Weihong Xiong; Danyi Quan; Dinesh C Pate] an of Salt Lake City UT (Us)	US 6,299,925 B1	Oct. 9, 2001
2.	Method for producing green tea microfine powder	Toshio Shibata, Shizuoka-ken (JP)	US 6,416,803 B1	Jul. 9, 2002
3.	Green tea extract for treating obesity	Max Rombi, Bordighera (IT)	US 6,830,765 B2	Dec. 14, 2004
4.	Green tea formulations	Danyi Quan, 4156 S. Megan Cir., Salt Lake City, UT (US) 84107; Wade W. Xiong, 4156 S. Megan Cir., Salt Lake City, UT (US) 84107	US 7,815,960 B2	Oct. 19, 2010
6.	Catechins and green tea extract for the treatment of amyloidosis in Alzheimer's disease and other amyloidoses	Paula Y. Choi, Bothell, WA (US); Gerardo Castillo, Seattle, WA (US); Alan D. Snow, Lynnwood, WA (US)	US 2002/0086067 A1	Jul. 4, 2002
7.	Extracts and methods comprising green tea species	Randall S. Alberte. Estero, FL (US): (76) Inventors S.t T. Gt". e RS); So, SEN's FS)	US 2008/0113044 A1	May 15, 2008
8.	The production process of purified green tea extract	Yukiteru Sugiyama, Kamisu (JP): Hideaki Ueoka, Kamisu (JP)	US 7,981,449 B2	Jul. 19, 2011
9.	Capsules containing freeze-dried, powdered green tea leaves	Peter Rohdewald, Altenberge, Germany	5,993,867	Nov.30, 1999
10.	The production process of packaged green tea beverages	Kazuhiro Otsuka, Tokyo (JP); Wataru Mizuno, Tokyo (JP); Koji Hanaoka, Tokyo (JP); Yuji Matsui, Tokyo (JP); Hideyuki Takatsu, Tokyo (JP)	US 7,323,205 B2	Jan. 29, 2008

#### 4.1. Effervescent formulation.

Xiong *et al.* [78] formulated a natural effervescent formulation containing a green tea extract, along with other ingredients, such as plant extracts, ionic materials, and vitamins. The liquid form of administration and the effervescent properties increase the bioavailability of green tea components, such as polyphenols, thereby enhancing absorption in the human body [78,79].

#### 4.2. Microfine powder.

Toshio Shibata *et al.* described the preparation of micro-fine powder of crude green tea. The screened green tea is spread in a flat box, and distilled water is sprayed, followed by agitation in an infrared irradiation chamber, where the green tea microfine powder is heated with infrared radiation at 40°C to 60°C for 130 - 180 min [80].

#### 4.3. Freeze-dried powder in capsules.

Green tea preparation contains polyphenols by cooling green tea leaves until the activity of the oxidized phenols drops to 1% of the value at normal temperature. This process packs products in capsules that are soluble in hot water [80].

#### 4.4. Packaged beverages.

Nagao *et al.* [81] described a process to produce packaged green tea beverages containing non-polymer catechins. In this process, an aluminosilicate with an iron release rate not greater than 0.8 mg/kg in a catechin-containing solution is brought into contact with a green tea mixture, extract, or concentrate. The present invention can provide beverages containing high concentrations of catechins [81].

### 5. Conclusion

The tea plant *Camellia sinensis* contains several components, such as EC, EGC, ECG, EGCG, GC, and GCG, in varying amounts. Green tea and black tea are found to be beneficial in the prevention and treatment of different types of cancer, *viz.*, oral, lung, colorectal, breast, prostate, skin, liver, stomach, mammary gland, small intestine, esophagus, bladder, pancreas, prostate, and urinary cancer based on different types of population studies. The cancer-preventive and anticancer activities of tea are potentiated when combined with other drugs. The synergistic anticancer activity of catechin, curcumin, tea polyphenols, and ascorbic acid has been demonstrated by several researchers. Green tea also produces antioxidants and has anti-hypertensive activity, supporting oral and bone health, inhibiting solar ultraviolet radiation, preventing obesity, and reducing insulin resistance. This article discussed various formulations of green tea, including effervescent green tea, green tea microfine powder, capsules of freeze-dried green tea fresh leaves, and patented green tea beverages.

### Author Contributions

Conceptualization, A.C. and S.M.; investigation, S.Sa. and S.Sm.; formal analysis, S.Sa. and S.Sm.; writing—original draft preparation, A.C.; writing—review and editing, S.M.T. and S.M.; supervision, S.M.T. and S.M. All authors have read and agreed to the published version of the manuscript.

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## Conflicts of Interest

The authors declare no conflict of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
EC	Epicatechin
EGC	Epigallocatechin
ECG	Epicatechin Gallate
EGCG	Epigallocatechin Gallate
GC	Gallo Catechins
GCG	Gallo Catechin Gallate
AA	Amino Acid
TFS	Thea-Flavins
TRS	Thearubigins
KMNO <sub>4</sub>	Potassium Permanganate
FTIR	Fourier Transform Infrared Spectroscopy
HPTLC	High-Performance Thin-Layer Chromatography
HPLC	High-Performance Liquid Chromatography
HPCE	High-Performance Capillary Electrophoresis
FTNIR	Fourier Transform Near-Infrared Spectroscopy
<sup>1</sup> H-NMR	Nuclear Magnetic Resonance
NIRS	Near-Infrared Spectroscopy
PLS	Partial Least Squares
IPLS	Interval Partial Least Squares
SIPLS	Synergy Interval Partial Least Squares
UVVS	Ultraviolet-Visible Spectroscopy
TPC	Total Polyphenol Content
PGR	Progesterone Receptor
ER	Oestrogen Receptor
US	United States
GTP	Green Tea Polyphenols
UK	United Kingdom
BMI	Body Mass Index

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