From tea to treatment; epigallocatechin gallate and its potential involvement in minimizing the metabolic changes in cancer

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Highlights

- Catechins in green tea are associated with slowing the proliferation of prostate cancer cells
- Epigallocatechin gallate, is the most bioactive catechin in green tea
- Epigallocatechin gallate's activity may result from influence over the PI3K/Akt/mTOR pathway
- Many prostate cancer tumours show a dysregulation of the PI3K/Akt/mTOR pathway
- Combating PI3K/Akt/mTOR hyperactivation may be a strategy to reduce prostate cancer aggression

From Tea to Treatment; Epigallocatechin Gallate and its Potential Involvement in Minimizing the Metabolic Changes in Cancer.

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List of Abbreviations

ADT; androgen deprivation therapy

Akt; protein kinase B

ATP; adenosine triphosphate

C; (+)-catechin

CDK; cyclin-dependent kinase

CG; (-)-catechin gallate

CLL; chronic lymphatic leukemia

CRPCa; castration-resistant prostate cancer

CRTC2; CREB regulated transcription coactivator 2

EC; (-)-epicatechin

ECG; (-)-epicatechin gallate

EGC; (-)-epigallocatechin

EGCG; (-)-epigallocatechin gallate

GC; (+)-gallocatechin

GCG; (-)-gallocatechin gallate

Ki; inhibition constant

mTOR; mammalian target of rapamycin

NF-κB; nuclear factor kappa-light-chain-enhancer of activated B cells

nM; nanomolar

p85/p110kin; phosphatidylinositol-4,5-bisphosphate 3-kinase

PCa; prostate cancer

PI3K; phosphatidylinositol 3-kinase

Rb; retinoblastoma protein

ROS; reactive oxygen species

RTK; receptor tyrosine kinase

S6K1; ribosomal protein S6 kinase beta-1

TCM; traditional Chinese medicine

Abstract

As the most abundant bioactive polyphenol in green tea, epigallocatechin gallate (EGCG) is a promising natural product that should be utilized in the discovery and development of potential drug leads. Due to its association with chemoprevention, EGCG may find a role in the development of therapeutics for prostate cancer. Natural products have long been employed as a scaffold for drug design, as their already noted bioactivity can help accelerate the development of novel treatments. Green tea and the EGCG contained within have become associated with chemoprevention, and both *in vitro* and *in vivo* studies have correlated EGCG to inhibiting cell growth and increasing the metabolic stress of cancer cells, possibly giving merit to its long utilized therapeutic use in traditional therapies. There is accumulating evidence to suggest that EGCG's role as an inhibitor of the PI3K/Akt/mTOR signaling cascade, acting upon major axis points within cancer survival pathways. The purpose of this review is to examine the research conducted on tea along with EGCG in the areas of the treatment of and/or prevention of cancer. This review discusses *Camellia sinensis*, as well as the bioactive phytochemical compounds contained within. Clinical uses of tea are explored, and possible pathways for activity are discussed before examining the evidence for EGCG's potential for acting on these processes. EGCG is identified as being a possible lead phytochemical for future drug design investigations.

EGCG; Cancer; PI3K/Akt/mTOR; Prostate Cancer; Natural Products

1.0 Introduction

There are multiple strategies when it comes to drug design, including *de novo* design, structure-based, target-based screening, pharmacophore searching; however, one of the longest standing approaches is the study of natural products. Isolation of bioactive components within natural products can lead to a stand-alone treatment or present a structural basis for a more efficient novel drug design. Green tea is one such natural product and has been traditionally administered for therapeutic use. Large cohort studies have hinted at a positive correlation between green tea consumption and cancer chemoprevention in men diagnosed with prostate cancer [1-6]. It has been discovered that one of green tea's most prominent bioactive component, the flavanol (-)-epigallocatechin gallate (EGCG), is likely the source of this activity [3, 7-12]. EGCG has been noted to influence key enzymes in the PI3K/Akt/mTOR pathway, which is commonly dysregulated in the development of prostate cancer, and could potentially act in a similar form to the synthetic inhibitors being developed against this pathway [13]. Despite its potential, work still needs to be done to identify whether green tea or EGCG can be recommended as a chemopreventative.[13]. Much of the large cohort evidence struggles to differentiate between the effect of consuming green tea and lifestyle choices [14]. Thus although there are multiple claims and evidence to suggest the benefit of EGCG for cancer therapy, more research is needed in both the therapeutic mechanisms of actions and the clinical benefit. By reviewing literature in these areas, the relevance of this natural product may be brought to light.

2.0 Approach

This study utilized a series of medical databases, inclusive of PubMed, EMBASE, MedLine, and SciFinder for articles published in the past 20 years to obtain a viable and comprehensive depiction of our current understanding of EGCG and its potential involvement in minimizing the deregulated of biochemical pathways observed in cancers. Search strategies began with using keywords such as “epigallocatechin gallate” AND “prostate cancer”, or more generally “green tea” AND “metastasis”. As data were collected and the interacting pathways better comprehended, the search requests expanded to more expansively investigate the involved PI3K/Akt/mTOR pathway, history, and previous association of green tea as a chemopreventive medicine, and studies investigating the modern approach to targeting the metabolic pathways of cancer.

3. Green Tea. Source and Bioactivity.

3.1 Botanical Source

EGCG is most abundantly found in green tea; however, it is also present in black and oolong teas, along with trace amounts found in miscellaneous fruit and vegetables [15]. All three of the major tea varieties including black, oolong, and green, are sourced from the *Camellia sinensis* plant, which grows globally in warm and humid climates [16]. China, Indonesia, Sri Lanka, and southern India have a year-round harvesting and growing season, whereas areas such as northern-eastern

India and northern China have a shorter season due to the greater seasonal variations [17]. The *Camellia Sinensis* is harvested by hand, with the “flush,” consisting of the top leaves connected to the bud and part of the stem making up the basis of tea [18]. It is during the processing of this flush where the black, green, and oolong tea varieties differ (Figure 1). For green tea, the flushes are withered and rolled, then either steamed or pan-roasted to inactivate the polyphenol oxidases within the plant [19]. From here, green tea is relatively stable during storage until seeping. This varies from the processing of black and oolong tea, as they lack the primary steaming step performed in green tea, and consequentially have a lower proportion of bioactive components in the final product [20-22].

3.2 Active Components in Green Tea

Amongst the wide variety of bioactive components in green tea, the polyphenols are the most abundant (Figure 2). Compromising around 40% of green tea’s dry mass, these compounds are colorless and water-soluble, contributing to the bitterness of the final product [20, 23]. Other compounds including the stimulatory methylxanthines, caffeine, theobromine, and theophylline are also present in tea, along with L-theanine, tannins, gallic acid, oxalic acid, pectin, fluoride, minerals and vitamins such as B1, B2, C, and E which can be found at varying concentrations, the most predominant category are the flavonoids [24, 25]. Characterized by their 2-phenylbenzopyran ring, variations in the C-ring saturation and oxidation status of flavonoids divide the classifications up into eight different groups, in which the flavan-3-ols are the most abundant (Figure 3).

Compared to the darker black and oolong teas which have most of their flavanols converted into their theaflavins and thearubigins counterparts during oxidation, green tea maintains a far higher proportion of the more bioactive flavanols (Table 1) [10, 26]. Such flavonoids include quercetin, kaempferol, and myricetin and the flavones apigenin and luteolin, with the largest class being the catechins [27]. By mass, epigallocatechin gallate (EGCG) is the most predominant (7–74 mg/g), followed by epicatechin gallate (ECG) (1–41 mg/g), epigallocatechin (EGC) (0–36.5 mg/g), epicatechin (EC) (0.1–9.5 mg/g) and catechin (C) (0–5.8 mg/g) [28-30] (Figure 4). However, depending on the variety, brand and location of harvest, these concentrations may vary [31].

3.3 Bioactive Role

Catechins are hydroxy and gallate substitutions of the flavan-3-ol structure, each with relative bioactive effects [32]. Chemotherapeutically, the gallocylated catechins, GC, EGC, GCG, and EGCG are noted to possess the most chemotherapeutically active role [33-37]. The combined use of green tea catechins has been associated with antioxidant activity, chemoprevention, anti-viral, anti-inflammatory and anti-diabetic activity [38-41]. However, with the trihydroxyl groups at carbons 3', 4', and 5' on the B-ring, and a gallate moiety esterified at carbon 3' on the C-ring, EGCG presents with the greatest anti-proliferative and pro-apoptotic activity against cancer cells compared to the other catechins [3, 7-12].

Studies show extracting EGCG from tea is most effective at 80^{o}C using a 50% v/v ethanol solution as this prevented epimerization of the catechin, however, if using

fresh leaves, then the extraction should use 75% v/v ethanol to compensate for the higher moisture content [42]. A later 2014 study investigating various extraction solvents, including ethanol, methanol, and water at different time intervals, concluded that a 40-minute extraction with ethanol maintained the greatest proportion of the catechins [43].

3.4 Clinical Uses

Records of the production and attributed health benefits of tea have dated back to the *Cha Jing (Tea Bible)* by the Lu Yu of the Tang Dynasty, often with a focus towards its anti-inflammatory action [44]. Such traditional Chinese medicines are still appreciated due to their theoretical approach and long-documented history [45]. Nowadays, many commercially available drugs derive inspiration from natural products, such as the chemotherapeutics topotecan and docetaxel which are synthetic alterations of the natural products camptothecin (*Camptothec acuminate*) and paclitaxel (*Taxus brevifolia*), along with Vincristine (*Catharanthus roseus*) which is a natural product (often synthetically generated) from the Madagascar periwinkle (Figure 5) [46]. EGCG's association with chemoprevention has prompted investment towards furthering its potential clinical application with two studies initiated in March 2018 to investigate its effect at minimizing the chemotherapeutic damage done in patients undergoing lung or breast cancer treatments [47, 48].

4. Prostate Cancer & Current Treatments

From 2015, 3300 deaths per year were attributed to prostate cancer, making it one of the leading causes of cancer-related mortality, accounting for 16% of Australia's male cancer expenditure [49, 50]. With the major risk factor being age, patients are left with few options to decrease their susceptibility towards the disease. Consequently, greater reliance is placed upon detection and treatment [51]. If surgery or radiotherapy fails to remove the cancer growth, androgen deprivation therapy (ADT), primarily bicalutamide (trade name Casodex), serves as the first-line chemotherapeutic [49]. However, this treatment is only palliative, acting to suppress the androgen driven growth in the early stages. Within 14-30 months, ADTs typically become redundant as the cells mutate into an androgen-independent state known as castration-resistant prostate cancer (CRPCa) [49]. Whether or not CRPCa is initially metastatic, 60% of men develop the metastatic disease within five years, with most developing it within three [52].

From here, docetaxel (tradename 'Taxotere') is the preferred chemotherapeutic, and it is associated with extremely high rates of chemoresistance and only extends the nine months' lifespan by an average three months [49, 53-55]. Since 2010, alternative treatments including immunology, cabazitaxel, enzalutamide, and abiraterone acetate have been trailed, extending the life expectancy by up to 5 months [23, 56]. However, these have been associated with a poorer quality of life than docetaxel. Some of the more common drug-based treatment options in Australia are tabulated below (Table 3).

4.1 Green tea and Prostate Cancer

The need for intervention, which can reduce the incidence of metastasis of Prostate Cancer (PCa) without severely hindering the quality of life, is going to be crucial to address this global health issue. In both Japanese and Chinese populations, there is a lower incidence of many cancers, including PCa, primarily attributed to their diet of soy, low fat, and high fiber as means of chemoprevention. Furthermore, their high intake of green tea has a strong positive correlation to chemoprevention [1-6]. Daily consumption of 10 or more cups a day is seen to increase the age of onset and decrease metastasis of a variety of cancers, including PCa [57-59]. Although not PCa, studies using squamous cell carcinomas cells show that the therapeutic index of 10 μM can be reached with regular consumption of green tea [60]. Using a preparation known as polyphenol E, it was found that the maximum tolerable dose of green tea was 4.2 g/m^2 (equivalent to 20-30 cups of green tea) when tested on metachronous colorectal cells [61, 62].

The primary side effects, including polydipsia and urinary frequency, were suspected to be due to the caffeine content [57, 63-65]. However, with or without caffeine present, there was no significant difference in green tea's ability to inhibit angiogenesis *in vivo [66]*. Studies observing green tea's influence over PCa cell survival show a decrease in proliferation of androgen insensitive cells due to the bioactive components in green tea [6].

4.2 Bioavailability

The primary concern regarding the use of EGCG and other green tea preparations clinically was their low bioavailability [67]. The non-gallated green tea catechins undergo glucuronidation and sulfation *in vivo*, preventing their chemopreventive activity [68]. This observed in patients following a 6-week trial of oral green tea consumption, where 50% of EGCG in the prostate tissue appeared in its methylated form, consequentially decreasing the chemopreventive activity in the cells [69]. However, this may be combatted by the combined use of EGCG and quercetin (another polyphenol found in tea) [70]. Quercetin was seen to inhibit the catechol-*O*-methyltransferase and the multidrug-resistant proteins responsible for the methylation of EGCG and to improve EGCG's chemopreventive activity [70].

5.0 PI3K/AKT/MTOR PATHWAY IN CANCER

To better understand EGCG's potential clinical benefit, it is fitting to examine the likely intracellular signaling pathways affected by EGCG. It is unclear whether EGCG's activity is pro or antioxidant [36, 71, 72], much of EGCG's chemotherapeutic action is attributed to its influence over the PI3K/Akt/mTOR pathway. Defined by the key proteins; phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR), this pathway is a key regulator of metabolism, cell cycle, and preventing apoptosis; thus its hyperactivation is greatly involved in promoting the hallmarks of cancer [37, 73]. Many various carcinomas and prostate cancers observe the dysregulation of the PI3K/Akt/mTOR pathway, and this mutation is often a characteristic of chemoresistant cancer types [74].

This pathway is typically activated in response to the binding of hormonal or mitogenic ligands to a receptor tyrosine kinase, phosphorylating the intracellular subunit and activating the p85 and p110 kinase receptor units of the PI3K heterodimer [75]. Activation induces the addition of ATP to PIP_2 in the cell membrane, forming the PIP_3 signaling molecule, which in turn activates the PH subunit of Akt, recruiting the protein to the cell membrane (Figure 6). This is followed by the phosphorylation of phosphoinositide-dependent protein kinase-1 at the T308 residue, activating the complex [76]. Akt goes onto activate a number of intracellular signaling processes, each holding influencing cell survival, proliferation, and growth, primarily mediated through the two mTOR multiprotein complexes mTORC1 and mTORC2 [77, 78].

5.1 Pro survival and acceleration of growth

Pro-survival and growth signaling are vital to cancer progression. With control over the cell cycle and suppression of apoptosis, overactivation of the PI3K/Akt/mTOR pathway can promote cancer cell survival [79]. The activated Akt phosphorylates and inactivates glycogen synthase kinase-3 beta, preventing the activation of tumor suppressor p53 and degradation of cyclin D [80]. Akt also induces the degradation of p53 by inhibiting the transduction of nuclear-localized E3 ubiquitin ligase [81]. Now remaining active in the nucleus, CD1 binds and activates the cyclin-dependent kinase (CDK) proteins [82]. CDK4 and CDK6 inhibit the tumor suppressor retinoblastoma protein (Rb), preventing the inhibitor of transcription factors G2F and enabling the progression from G_1 to S-phase [82]. This amplified through mTORC1's

activation of ribosomal protein S6 kinase beta-1, F-box only protein 4, and inhibition of N-eukaryotic initiator factor, thus enhancing the stability of genes involved in S-phase entry [83]. Akt further ensures the activity of CDKs by inhibiting $p21^{Cip1/Waf}$ and $p27^{Kip1}$ [84, 85]. Direct phosphorylation of p21 also inhibits proliferating cell nuclear antigen, a suppressor of DNA replication [86]. Thus, in a multifactorial mechanism, the activation of the Akt pathway promotes and protects the progression through the cell cycle. Studies have observed that the cell cycle can be arrested at the G_1 phase through the inhibition of PI3K [87].

Another vital aspect of cell survival is the prevention of apoptosis. Through the breakdown of forkhead box O3 (FOXO3), Akt prevents the activation of p27, p21 p15, and p19, along with other proapoptotic genes such as BH3-only protein, Fas ligand and the p53 upregulated modulator of apoptosis [88]. Studies of primary chronic lymphatic leukemia B cells show that the constitutively active Akt increases expression and stability of the induced myeloid leukemia cell differentiation protein Mcl-1, the X-linked inhibitor of apoptosis protein and antiapoptotic B-cell lymphoma-extra large proteins, thus contributing to the inhibition of apoptosis & extending the longevity of diseased cells [78]. Furthermore, the cytochrome C induced apoptotic signaling pathway is inhibited by Akt at caspase 9, thereby promoting cell survival during cellular stress typical of the cancer environment.

5.2 Glycolysis

Another key hallmark of cancer is the switch towards anaerobic metabolism, described as the Warburg Effect [89]. This avoids the reliance on oxygen for energy production and is often correlated with tumor aggressiveness as it equips the cells with a rapid source of energy and intermediates for growth [90-93]. Targeting enzymes that promote the Warburg effect, such as the PI3K/Akt/mTOR pathway, act as a promising strategy to target the metabolic adaptations of cancer cells [94-97].

By phosphorylating the AS160 substrate on the glucose transporter type 4 receptor, AKT prompts its translocation to the cell surface and increases the cell's intake of glucose [98]. Downstream from the mTOR axis, there is the activation of other metabolism modulations that act to promote energy production and consumption within the cell [99]. PI3K phosphorylation and inhibition of FOXO1 and (downstream) CREB regulated transcription coactivator 2 inhibiting the fasting regulation of gluconeogenesis [100]. Storage of this excess glycogen is promoted through the inhibition of the glycogen synthase GSK3β, which indirectly lowers the levels of c-Myc (noted in leukemic blast cells) [101]. Overall this prevents the inhibition of the hypoxic induced gene, promoting the Warburg Effect [102].

6.0 Targeting PI3K/Akt/mTOR

A genetic study of 218 prostate cancer tumors showed that 42% of primary growths and 100% of metastasizes displayed a genomic dysregulation of the PI3K/Akt/mTOR pathway [13], thus targeting key axis points within this pathway might be vital in

reducing the aggressiveness CRPCa. A meta-analysis in 2018 suggested that PI3K/Akt/mTOR pathway inhibitors can significantly improve the survival of patients with advanced solid tumors [74]. With a range of synthetic inhibitors being proposed, including dual mTORC1/2, dual PI3K/mTOR, Pan-PI3K, isoform-specific PI3K, and second-generation Akt inhibitors (Table 4), the therapeutic demand for a range of PI3K/Akt/mTOR inhibitors is evident.

6.1 Evidence for EGCGs role

EGCG itself acts as a competitive inhibitor (Ki 380 nM) of the common class 1 isomers of PI3K (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ), preventing the initial phosphorylation of Akt [103-108]. The binding mode of EGCG is noted to be similar to the PI3K inhibitor LY294002 [37]. It should be noted that within the LNCaP and PC-3 PCa cell lines, EGCG had no significant effect on the phosphorylation of PI3K at the Ser437 residue. The lack of the phosphatase and tensin homolog allele was suspected to cause the non-response [37]. EGCG also inhibits mTOR (Ki of 320 ± 24 nM [37], aligning itself in a similar category to the synthetic dual PI3K/Akt/mTOR inhibitors. These non-selective inhibitors display more promising effects as both pre-clinically and clinically, they are better equipped at overcoming the compensatory feedback mechanisms [37, 103-105].

Including its activity against the central PI3K/Akt/mTOR axis points, EGCG also interferes with the signaling cascade downstream from mTOR to reactivate the apoptotic signaling. Similar to other chemopreventive natural products such as curcumin, caffeinic acid, and capsaicin, EGCG is inhibitory against the transcription

369 factor; nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [109].
370 NF-κB is redox-responsive, and is highly implicated with the cancer cell proliferation
371 and survival [110-112]. Although not specifically in PCa, when the squamous cell
372 carcinomas cell line, A431 was treated with doses of 30-80 μM of EGCG, the EGCG
373 was seen to suppress the activation of NF-κB, to which there is substantial evidence
374 of crosstalk between the two pathways [113] [114]. Depleting the levels of NF-κB in
375 both the nucleus and cytoplasm, cancer cells were no longer protected against
376 apoptosis, resulting in cell death [115]. Comparing the responsive dose of EGCG
377 required to inhibit NF-κB displayed an evident selectivity towards the cancerous
378 A431 cell line over the non-cancerous normal human epidermal keratinocytes [109].
379 Furthermore, with the correlation between NF-κB expression and PCa resistance
380 against Docetaxel, the inhibition of NF-κB (via BAY11-7082 inhibitor), appeared to
381 reverse this resistance, and maybe the key to improving the efficacy of PCa drugs
382 [116].
383
384 As a catechin, EGCG has a single-electron reduction potential enabling it to act as a
385 scavenger for reactive oxygen species (ROS), and its pro-oxidant nature strongly
386 contributes to pro-apoptotic activity. EGCG is susceptible to oxidation by H_2O_2 [36,
387 117, 118]. The then oxidized EGCG forms a cytotoxic o-quinone, which later reacts
388 with glutathione to form various ROS [118, 119]. These ROS are suspected to
389 downregulate Bcl-2 and Mcl-1 [36, 120]. When EGCG is administered in combination
390 with arsenic trioxide (Trisenox®), a natural product based chemotherapeutic used in
391 acute promyelocytic leukemia, the production of ROS was greater than seen with
392 either used alone [36]. EGCG also displays some selectivity to cancerous cells, with
393 apoptosis induced in the cancerous A431 cell line, but not normal epidermal

keratinocyte counterparts [109]. Thus, the combined increase in ROS and depletion of NF-kB, EGCG is seen to counteract the prosurvival signaling enacted by PI3K/Akt/mTOR hyperactivation.

7.0 Discussion and Conclusion

There a deficit in our collective knowledge in the area of EGCG's role in the occurrence and treatment of cancer, as well as that of tea products in this same area, and this is indicative of the future work that might be done to address this. Due to EGCG being considered a pan assay interference compound, it can be assumed that other pathways are affected beyond PI3K/Akt/mTOR since its structural properties are conducive to broad interactions [121, 122]. Thus, there is a concern with its use to guide synthetic drug design. EGCG also has poor stability, it rapidly oxidizes in solution, and is rapidly metabolized in vivo [123-125]. Even so, the evidence provided in laboratory and clinical studies gives encouraging support for the further investigation of this phytochemical and its botanical source. Further study may take the form of clinical trials to assess the use of EGCG or tea products as adjunct natural therapies alongside traditional chemotherapy, or another promising area of work may be computational analysis for guided drug design, with EGCG as a lead compound. Although there is the potential for nonspecific interactions of such compounds when examined via in vitro assay, in vivo evidence encourages research to continue in this area.

Overcoming the metabolic adaptations of metastatic prostate cancer continues to be a major hurdle in producing effective treatments without severely hindering the

patient's quality of life. Due to the multifactorial nature of many cancers, in particular, CRPCa, single-target drugs are often redundant due to crosstalk within the prosurvival cascades, such as the PI3K/Akt/mTOR pathway. However, natural product EGCG may hold the solution. Acknowledged for its tolerability and chemotherapeutic activity against a variety of cancers, EGCG acts upon a range of targets within the PI3K/Akt/mTOR cascade to promote the selective apoptosis of cancer cells. With a growing risk of many late-stage cancers, investigating tolerable options such as EGCG may be essential for cancer treatment going forward. Whether effective on its own or to be utilized as adjuvant therapy, EGCG shows potential as a chemopreventative or sensitizer and may have the potential to lead further synthetic drug design.

8.0 Acknowledgments

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10.0 Figures

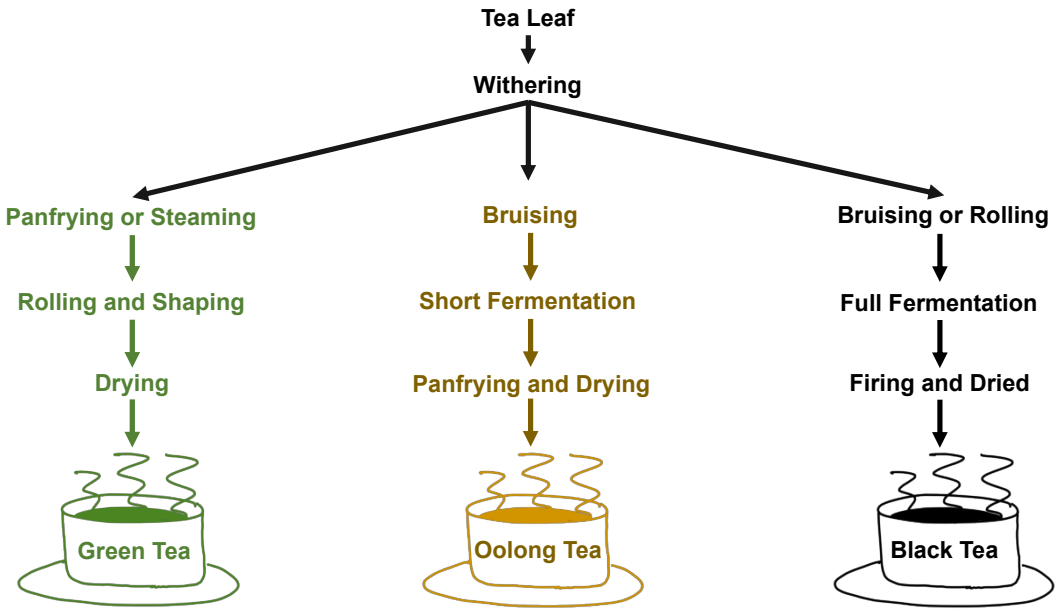


Figure 1: Generalized processing protocol for Green, Oolong and Black Tea. Primary differences in the catechin content of each tea variety result from the variation in treatment during the processing of the *Camellia sinensis* flush.

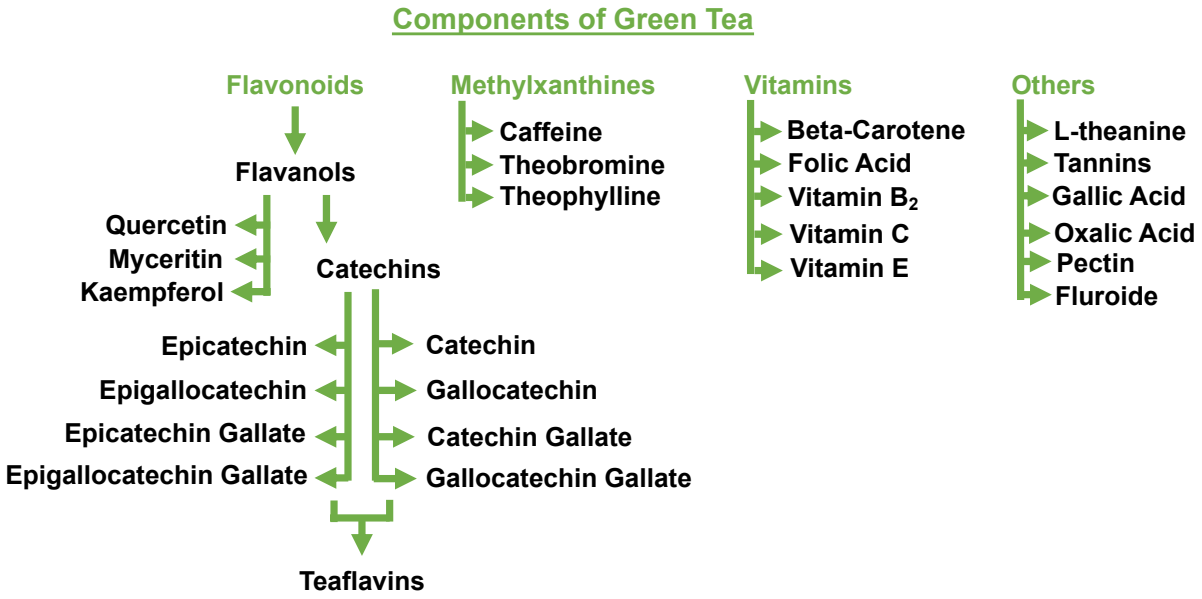


Figure 2: Key bioactive components of green tea, broadly categorized into flavonoids, methylxanthines, vitamins and other.

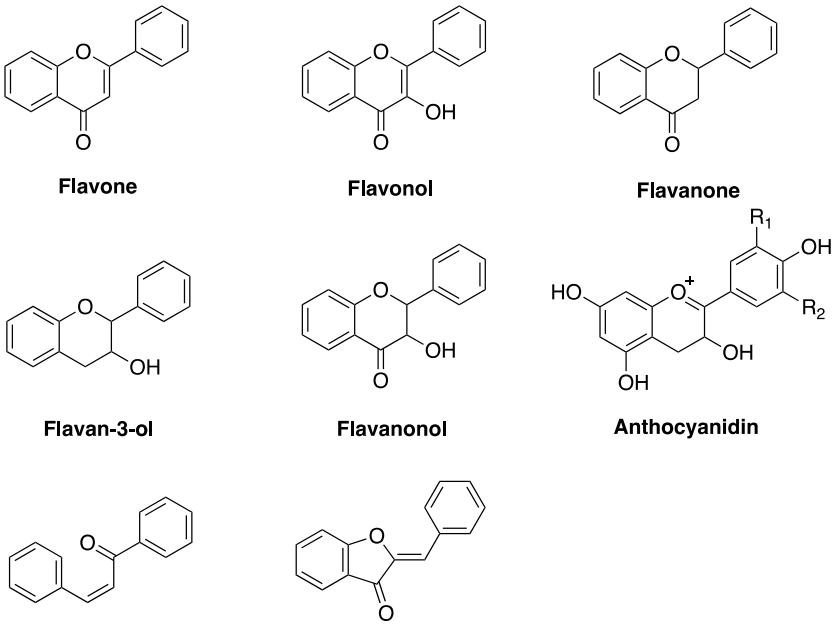
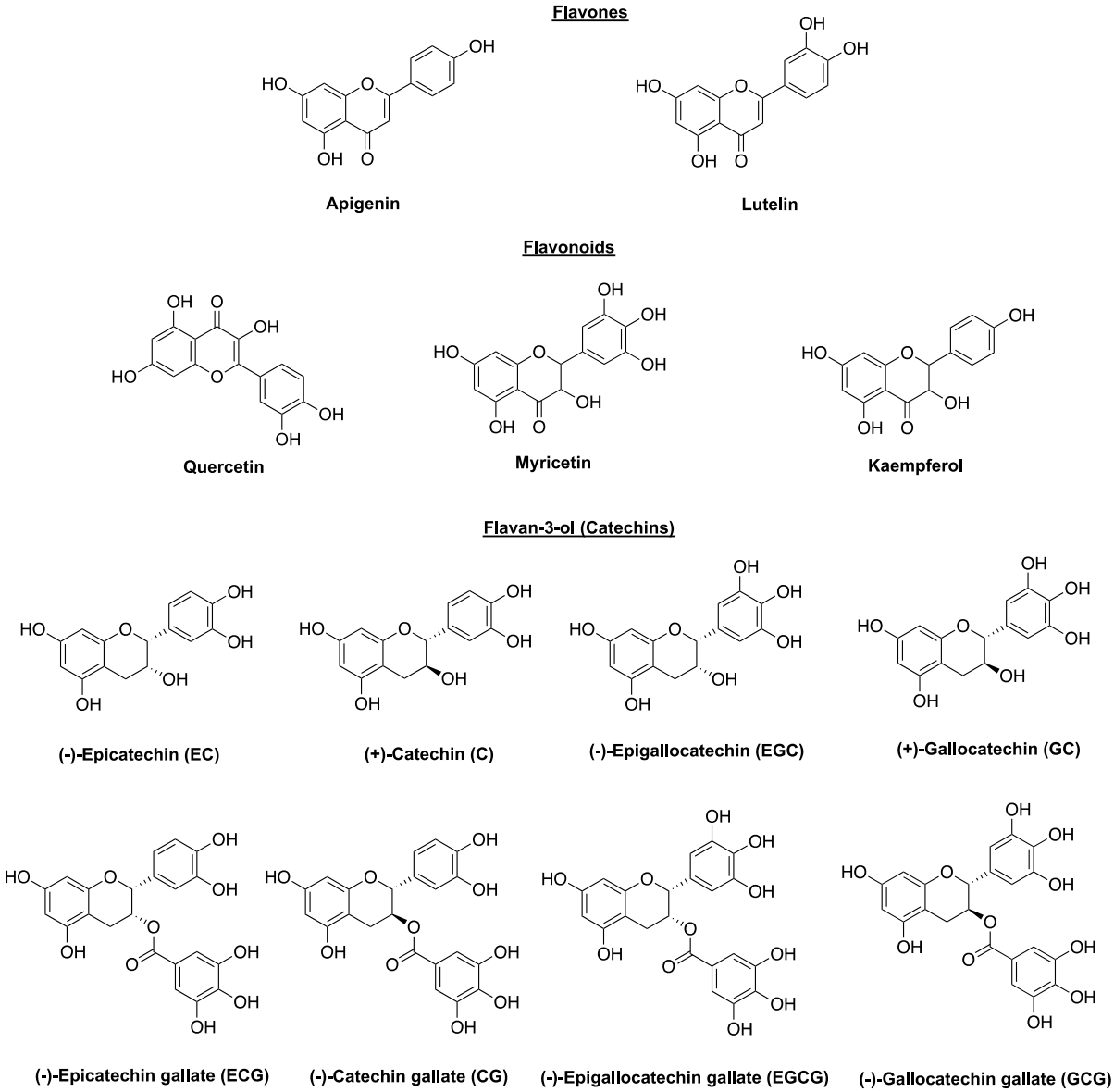


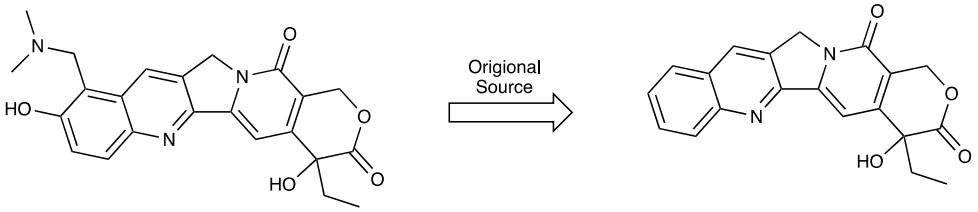
Figure 3: Names and structures of the 2-phenylbenzopyrans (flavonoids), in which flavan-3-ol is the most predominant



853

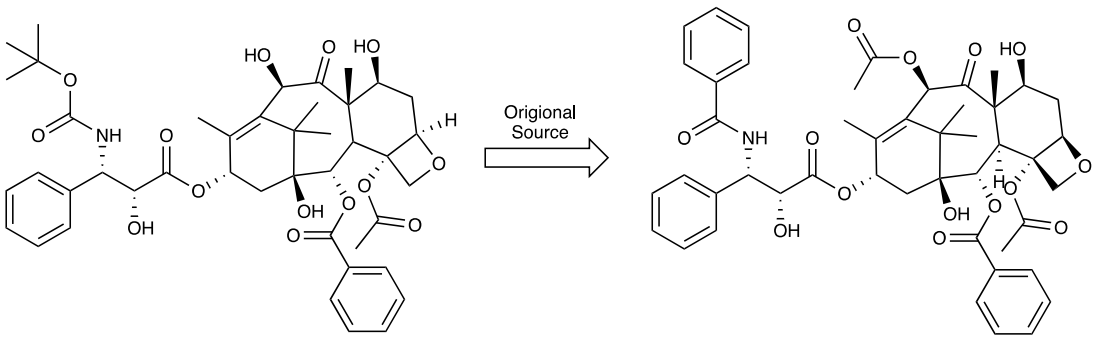
854 **Figure 4: Structures, names, and abbreviations of the major flavonols found in green**

855 **tea**



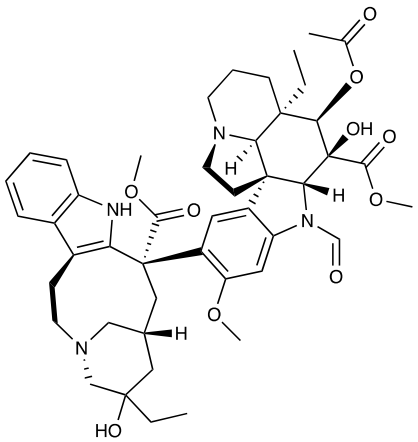
Topotecan (Hycamtin)
Lung cancer, ovarian cancer
GlaxoSmithKline, October 2007

Camptothecin (CPT)
Bark and stem of *Camptothec acuminate* (Happy Tree)



Docetaxel (DTX, DXL, Taxotere)
Breast, ovarian, lung, bladder, prostate, melanoma, esophageal
Sanofi-Aventis June 1998
(also sold as Docefrez by Sun Pharma Global and Zytax by Zydus.)

Paclitaxel (PTX or Taxol)
Bark of the Pacific yew tree
Taxus brevifolia



Vincristine (Oncovin)
Rosy Periwinle *Catharanthus roseus*
Acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer
Eli Lilly and Company. July 1963

856

857 **Figure 5: Structures of semi-synthetic and natural products used in chemotherapy**

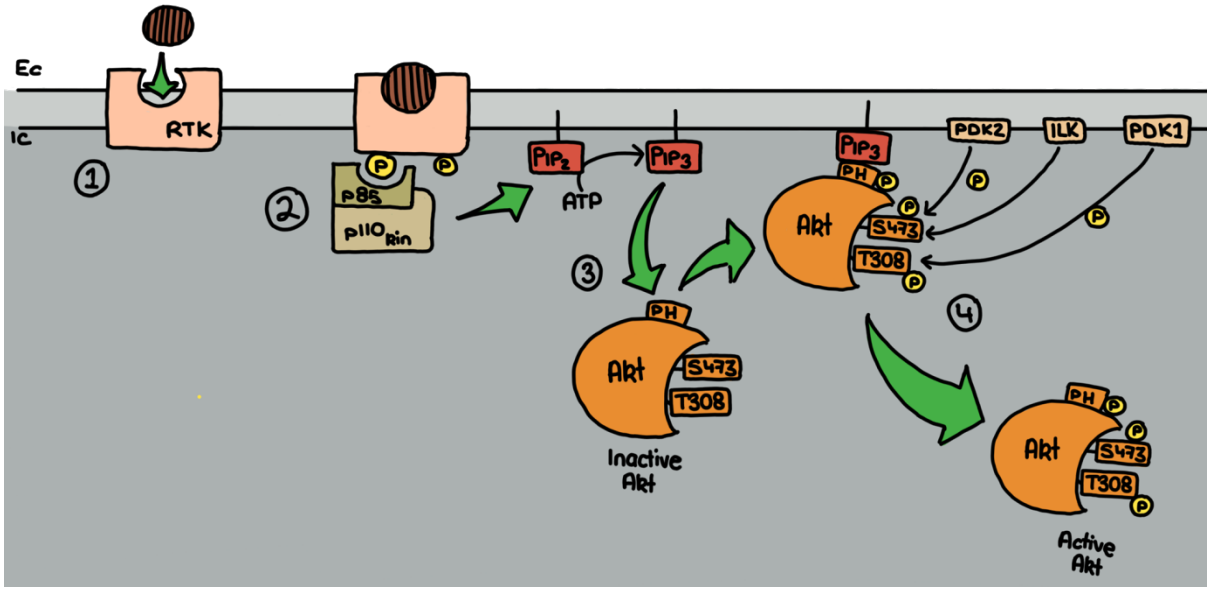


Figure 6: Activation of PI3K and Akt mediated through (a) mitogenic activation at the receptor tyrosine kinase (RTK) resulting in the (2) phosphorylation and binding of the PI3K intracellular unit (3) conversion of PIP2 to PIP3 and activation of the Ph subunit on Akt inducing the translocation to the cell membrane (4) phosphorylation and activation of Akt. Abbreviations: receptor tyrosine kinase (RTK), Phosphatidylinositol-4,5-bisphosphate 3-kinase (p85/p110kin), Phosphatidylinositol 4,5-bisphosphate (PIP), Pyruvate Dehydrogenase Kinase (PDK) and Integrin-linked kinase (ILK).

866

867 **11.0 Tables**

868

Table 1: Proportion of Catechins present in Tea	
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Non-Fermented (Green)	8.0–14.4
Partially Fermented (Oolong)	4.14–4.92
Fermented (Black)	0.24–0.51

Table 2: EGCG's association as a chemopreventive with a range of cancers.

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	Prevent reoccurrence	[33]
	Fewer side effects	[126]
Colon	Chemoprevention	[57, 62, 127, 128]
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	Reduced adenocarcinoma multiplicity (Polyphenol E*)	[57]
	Increase phosphorylation of cJun	[130, 131]
Epidermal	Increase phosphorylation of Erk1/2	[131]
	Increase PCNA	[131]
	G_0/G_1 halt in A431 (not non-cancerous NHEK)	[11]
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**polyphenol E is a concentrated catechin preparation; ** GTP refers to a combination of green tea proteins;*

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Table 3: Eligibility criteria and common side effects for current PCa treatments.

	Drug	Brand Name (Manufacturer)	Adverse Reactions	Eligibility
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Others	Cabazitaxel	Jevtana (Sanofi-Aventis)	Severe neutropenia Thrombocytopenia Anorexia Diarrhea Constipation Skin Rash Arthralgia Fatigue Peripheral neuropathy Peripheral neuropathy	Post-docetaxel CRPCa. Must be in combination with prednisone or prednisolone

	Nausea and vomiting Diarrhea

Note that this table is not fully comprehensive and the most current Australian data can be found at the EviQ [132-140]

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		LY294002	
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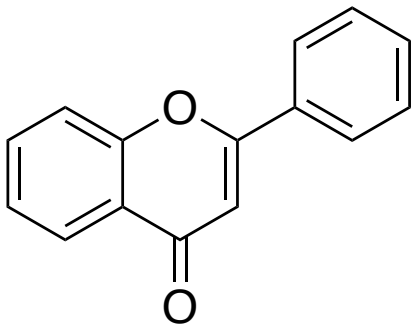
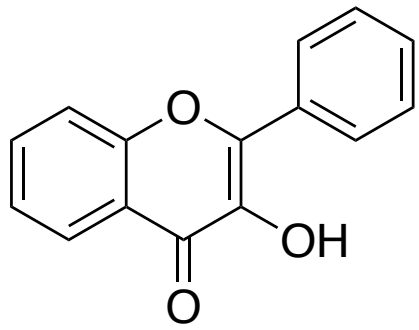
PI3K		BKM 120	Buparlisib
	p110 Isoform-specific	GSK 2636771	
	PI3K Inhibitors	AZD 8186	
		GSK2141795	Uprosertib
AKT	Akt	GDC-0068	Ipatasertib
		AZD5363	
	mTORC1 &	AZD 8055	
mTORC	mTORC2 Dual Inhibitor	INK 128	
	MTORC1	Everolimus	

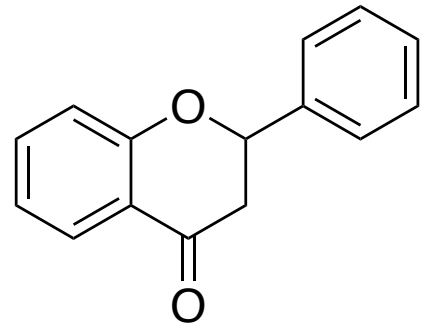
873



Flavone



Flavonol



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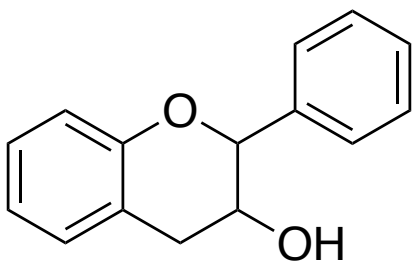
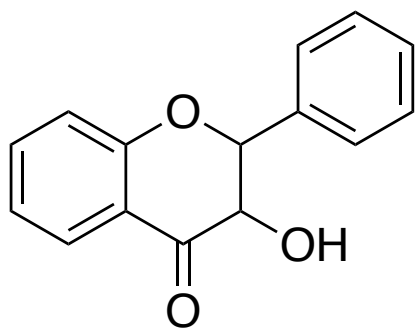
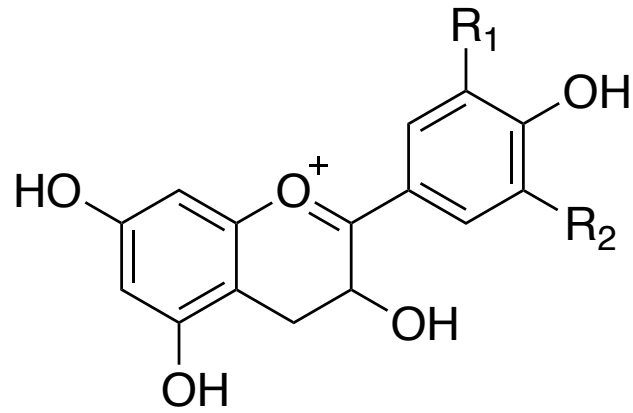


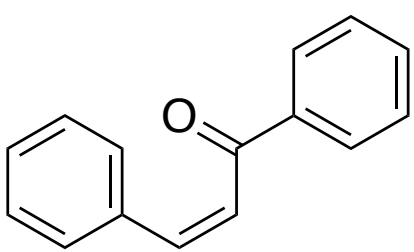
Flavan-3-ol



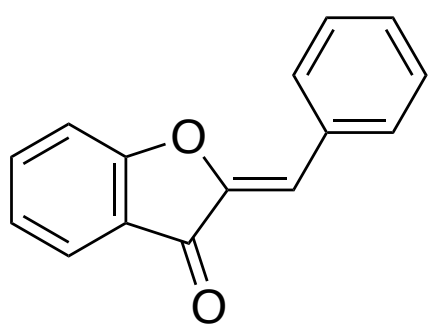
Flavanonol



Anthocyanidin

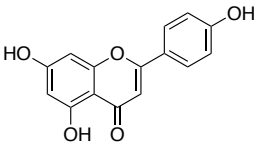


Chalcone

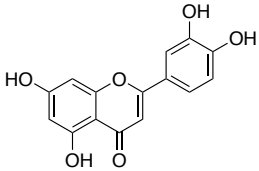


Aurone

Flavones

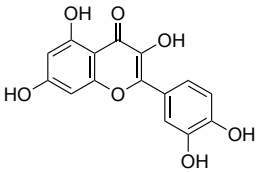


Apigenin

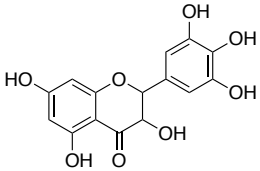


Lutelin

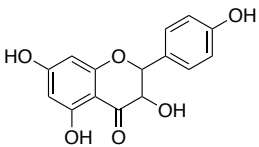
Flavonoids



Quercetin

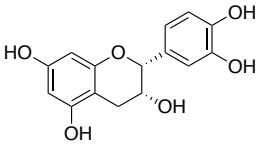


Myricetin

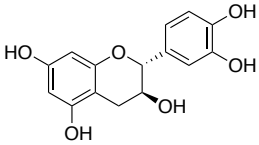


Kaempferol

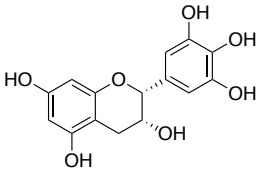
Flavan-3-ol (Catechins)



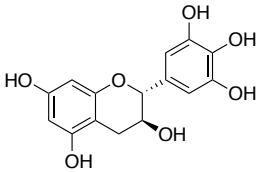
(-)-Epicatechin (EC)



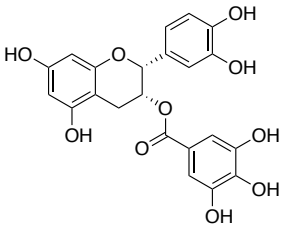
(+)-Catechin (C)



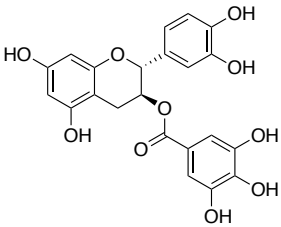
(-)-Epigallocatechin (EGC)



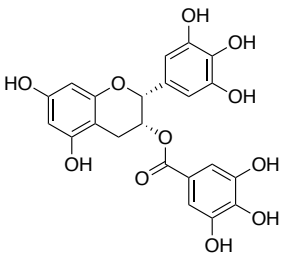
(+)-Gallocatechin (GC)



(-)-Epicatechin gallate (ECG)



(-)-Catechin gallate (CG)



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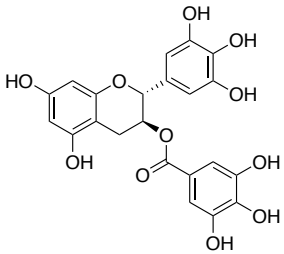

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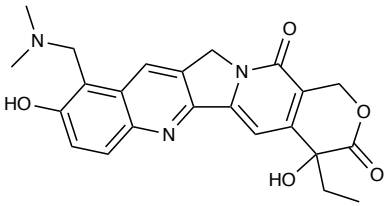
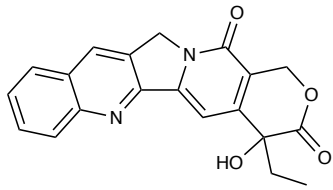
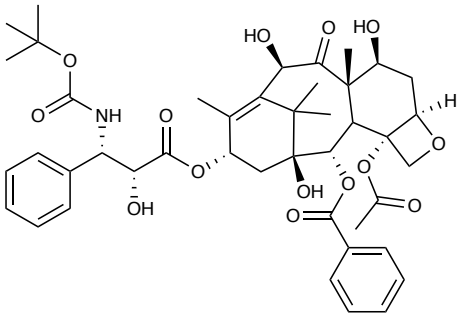


Topotecan (Hycamtin)
Lung cancer, ovarian cancer
GlaxoSmithKline, October 2007

Origional Source

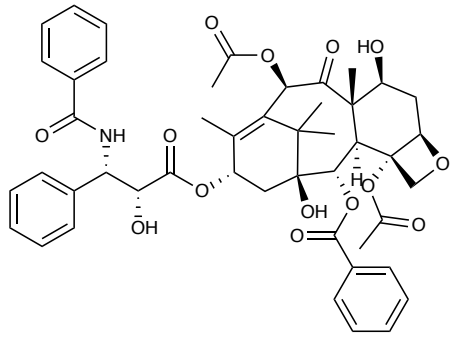


Camptothecin (CPT)
Bark and stem of *Camptothec acuminate* (Happy Tree)

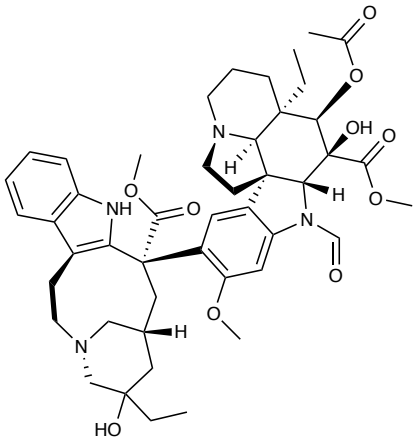


Docetaxel (DTX, DXL, Taxotere)
Breast, ovarian, lung, bladder, prostate, melanoma, esophageal
Sanofi-Aventis June 1998
(also sold as Docefrez by Sun Pharma Global and Zytax by Zydus.)

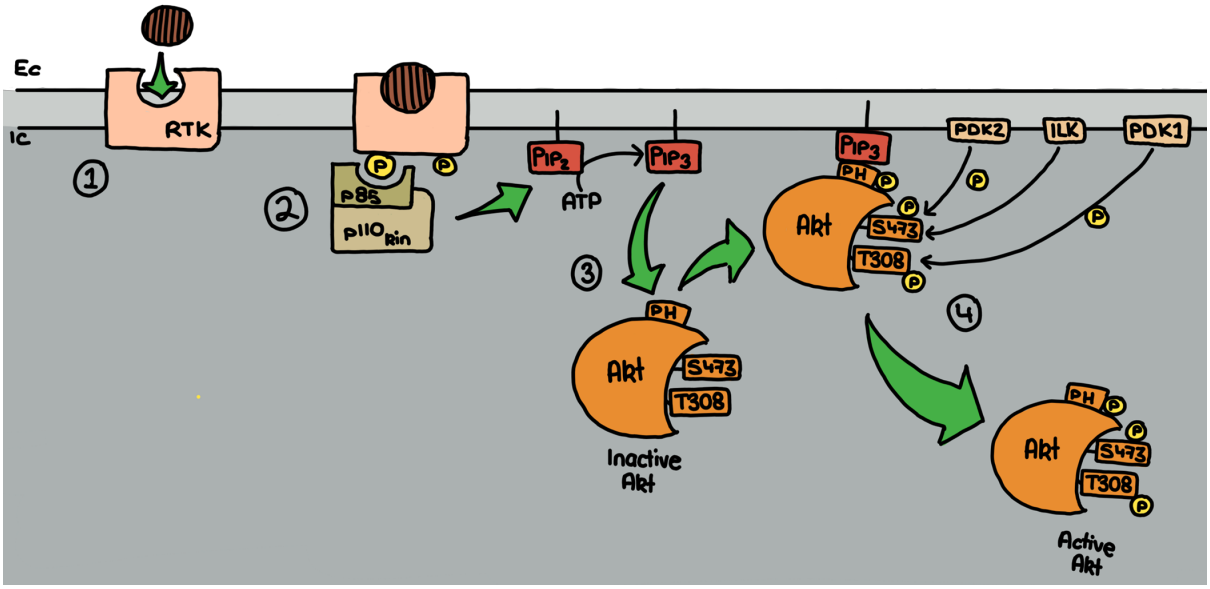
Origional Source



Paclitaxel (PTX or Taxol)
Bark of the Pacific yew tree
Taxus brevifolia



Vincristine (Oncovin)
Rosy Periwinle *Catharanthus roseus*
Acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer
Eli Lilly and Company. July 1963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IC
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2
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PIP3
PH
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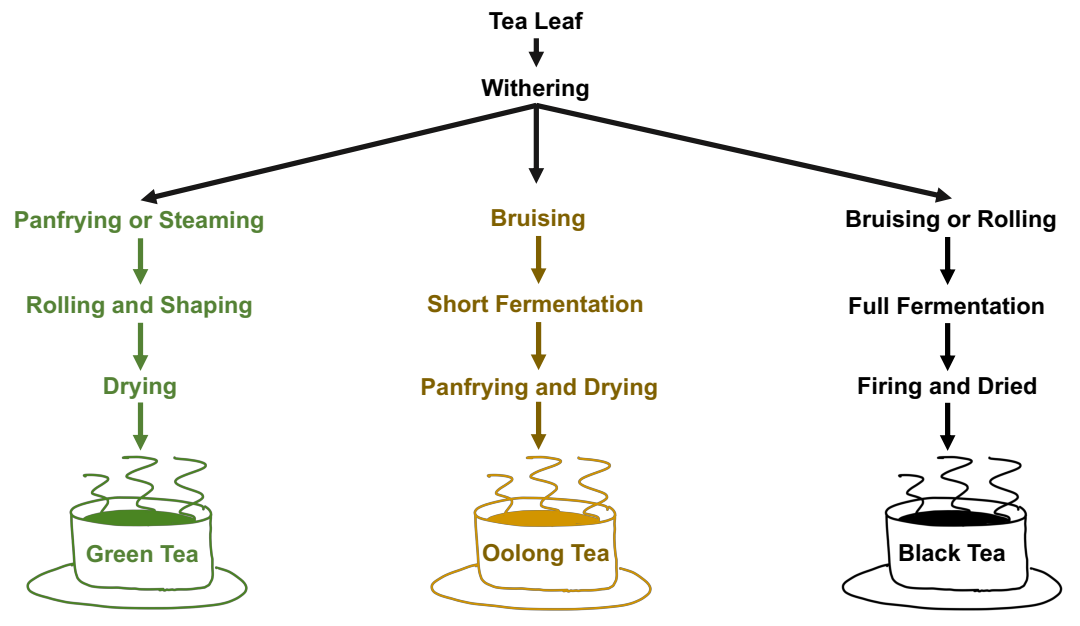
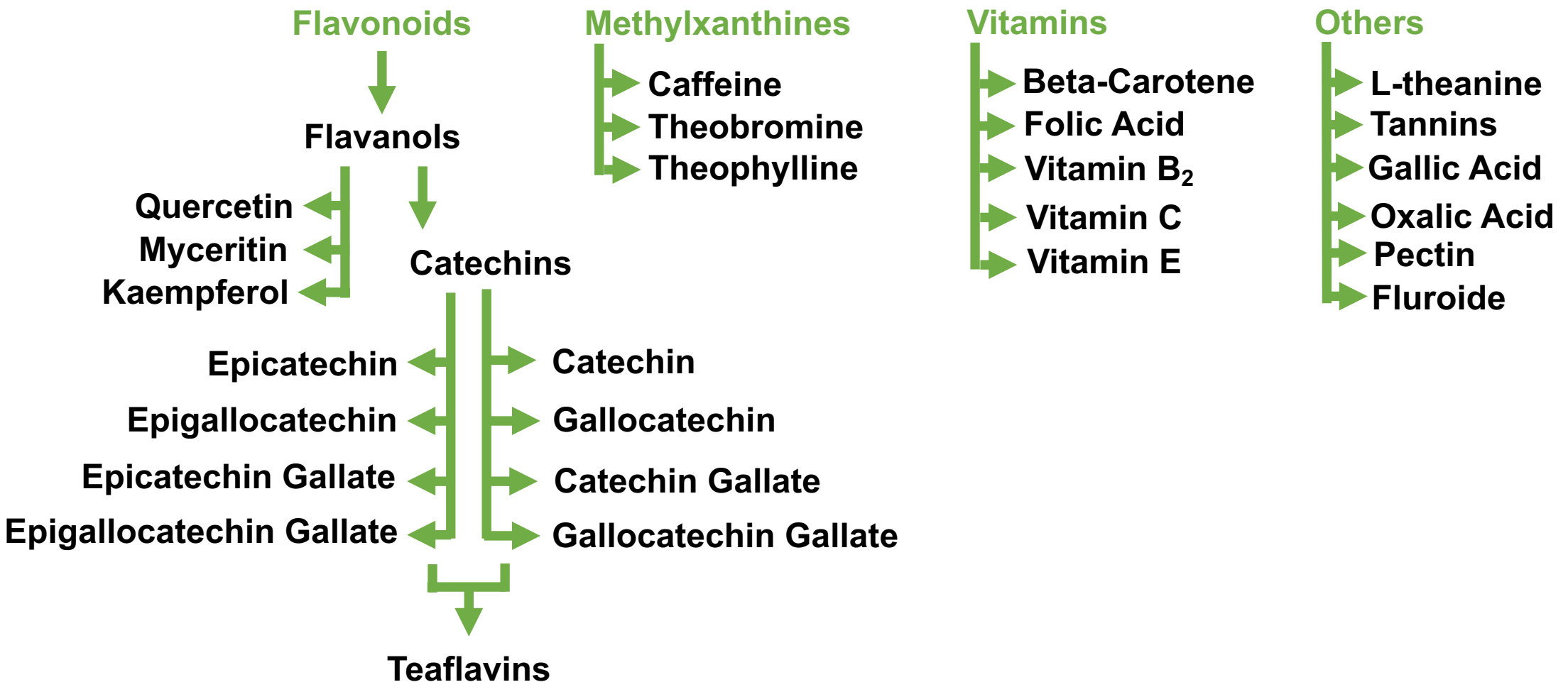

Tea Leaf
Withering
Panfrying or Steaming
Rolling and Shaping
Drying
Green Tea
Bruising
Short Fermentation
Panfrying and Drying
Oolong Tea
Bruising or Rolling
Full Fermentation
Firing and Dried
Black Tea

Components of Green Tea



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Diarrhea

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		GSK2141795	Uprosertib
AKT	Akt	GDC-0068	Ipatasertib
		AZD5363	
	mTORC1 &	AZD 8055	
mTORC	mTORC2 Dual Inhibitor	INK 128	
	MTORC1	Everolimus	