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**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

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

3

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16

17 **List of Abbreviations**

18

19 ADT; androgen deprivation therapy

20 Akt; protein kinase B

21 ATP; adenosine triphosphate

22 C; (+)-catechin

23 CDK; cyclin-dependent kinase

24 CG; (-)-catechin gallate

25 CLL; chronic lymphatic leukemia

26 CRPCa; castration-resistant prostate cancer

27 CRTC2; CREB regulated transcription coactivator 2

28 EC; (-)-epicatechin

29 ECG; (-)-epicatechin gallate

30 EGC; (-)-epigallocatechin

31 EGCG; (-)-epigallocatechin gallate

32 GC; (+)-gallocatechin

33 GCG; (-)-gallocatechin gallate

34  $K_i$ ; inhibition constant

35 mTOR; mammalian target of rapamycin

36 NF- $\kappa$ B; nuclear factor kappa-light-chain-enhancer of activated B cells

37 nM; nanomolar

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

39 PCa; prostate cancer

40 PI3K; phosphatidylinositol 3-kinase

41 Rb; retinoblastoma protein

- 42 ROS; reactive oxygen species
- 43 RTK; receptor tyrosine kinase
- 44 S6K1; ribosomal protein S6 kinase beta-1
- 45 TCM; traditional Chinese medicine

46 **Abstract**

47

48 As the most abundant bioactive polyphenol in green tea, epigallocatechin gallate  
49 (EGCG) is a promising natural product that should be utilized in the discovery and  
50 development of potential drug leads. Due to its association with chemoprevention,  
51 EGCG may find a role in the development of therapeutics for prostate cancer.

52 Natural products have long been employed as a scaffold for drug design, as their  
53 already noted bioactivity can help accelerate the development of novel treatments.

54 Green tea and the EGCG contained within have become associated with  
55 chemoprevention, and both *in vitro* and *in vivo* studies have correlated EGCG to  
56 inhibiting cell growth and increasing the metabolic stress of cancer cells, possibly  
57 giving merit to its long utilized therapeutic use in traditional therapies. There is  
58 accumulating evidence to suggest that EGCG's role as an inhibitor of the  
59 PI3K/Akt/mTOR signaling cascade, acting upon major axis points within cancer  
60 survival pathways. The purpose of this review is to examine the research conducted  
61 on tea along with EGCG in the areas of the treatment of and/or prevention of cancer.

62 This review discusses *Camellia sinensis*, as well as the bioactive phytochemical  
63 compounds contained within. Clinical uses of tea are explored, and possible  
64 pathways for activity are discussed before examining the evidence for EGCG's  
65 potential for acting on these processes. EGCG is identified as being a possible lead  
66 phytochemical for future drug design investigations.

67

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

## 69 **1.0 Introduction**

70

71 There are multiple strategies when it comes to drug design, including *de novo*

72 design, structure-based, target-based screening, pharmacophore searching;

73 however, one of the longest standing approaches is the study of natural products.

74 Isolation of bioactive components within natural products can lead to a stand-alone

75 treatment or present a structural basis for a more efficient novel drug design. Green

76 tea is one such natural product and has been traditionally administered for

77 therapeutic use. Large cohort studies have hinted at a positive correlation between

78 green tea consumption and cancer chemoprevention in men diagnosed with prostate

79 cancer [1-6]. It has been discovered that one of green tea's most prominent

80 bioactive component, the flavanol (-)-epigallocatechin gallate (EGCG), is likely the

81 source of this activity [3, 7-12]. EGCG has been noted to influence key enzymes in

82 the PI3K/Akt/mTOR pathway, which is commonly dysregulated in the development of

83 prostate cancer, and could potentially act in a similar form to the synthetic inhibitors

84 being developed against this pathway [13]. Despite its potential, work still needs to

85 be done to identify whether green tea or EGCG can be recommended as a

86 chemopreventative.[13]. Much of the large cohort evidence struggles to differentiate

87 between the effect of consuming green tea and lifestyle choices [14]. Thus although

88 there are multiple claims and evidence to suggest the benefit of EGCG for cancer

89 therapy, more research is needed in both the therapeutic mechanisms of actions and

90 the clinical benefit. By reviewing literature in these areas, the relevance of this

91 natural product may be brought to light.

92

93

## 94 **2.0 Approach**

95

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

107

108

## 109 **3. Green Tea. Source and Bioactivity.**

110

### 111 **3.1 Botanical Source**

112

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



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

129

### 130 **3.2 Active Components in Green Tea**

131

132 Amongst the wide variety of bioactive components in green tea, the polyphenols are  
133 the most abundant (Figure 2). Comprising around 40% of green tea’s dry mass,  
134 these compounds are colorless and water-soluble, contributing to the bitterness of  
135 the final product [20, 23]. Other compounds including the stimulatory  
136 methylxanthines, caffeine, theobromine, and theophylline are also present in tea,  
137 along with L-theanine, tannins, gallic acid, oxalic acid, pectin, fluoride, minerals and  
138 vitamins such as B1, B2, C, and E which can be found at varying concentrations, the  
139 most predominant category are the flavonoids [24, 25]. Characterized by their 2-  
140 phenylbenzopyran ring, variations in the C-ring saturation and oxidation status of  
141 flavonoids divide the classifications up into eight different groups, in which the flavan-  
142 3-ols are the most abundant (Figure 3).

143

144 Compared to the darker black and oolong teas which have most of their flavanols  
145 converted into their theaflavins and thearubigins counterparts during oxidation, green  
146 tea maintains a far higher proportion of the more bioactive flavanols (Table 1) [10,  
147 26]. Such flavonoids include quercetin, kaempferol, and myricetin and the flavones  
148 apigenin and luteolin, with the largest class being the catechins [27]. By mass,  
149 epigallocatechin gallate (EGCG) is the most predominant (7–74 mg/g), followed by  
150 epicatechin gallate (ECG) (1–41 mg/g), epigallocatechin (EGC) (0–36.5 mg/g),  
151 epicatechin (EC) (0.1–9.5 mg/g) and catechin (C) (0–5.8 mg/g) [28-30] (Figure 4).  
152 However, depending on the variety, brand and location of harvest, these  
153 concentrations may vary [31].

154

### 155 **3.3 Bioactive Role**

156

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

166

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

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

174

### 175 **3.4 Clinical Uses**

176

177 Records of the production and attributed health benefits of tea have dated back to  
178 the *Cha Jing (Tea Bible)* by the Lu Yu of the Tang Dynasty, often with a focus  
179 towards its anti-inflammatory action [44]. Such traditional Chinese medicines are still  
180 appreciated due to their theoretical approach and long-documented history [45].

181 Nowadays, many commercially available drugs derive inspiration from natural  
182 products, such as the chemotherapeutics topotecan and docetaxel which are  
183 synthetic alterations of the natural products camptothecin (*Camptothec acuminata*)  
184 and paclitaxel (*Taxus brevifolia*), along with Vincristine (*Catharanthus roseus*) which  
185 is a natural product (often synthetically generated) from the Madagascar periwinkle  
186 (Figure 5) [46]. EGCG's association with chemoprevention has prompted investment  
187 towards furthering its potential clinical application with two studies initiated in March  
188 2018 to investigate its effect at minimizing the chemotherapeutic damage done in  
189 patients undergoing lung or breast cancer treatments [47, 48].

190

191

192

193

#### 194 **4. Prostate Cancer & Current Treatments**

195

196 From 2015, 3300 deaths per year were attributed to prostate cancer, making it one  
197 of the leading causes of cancer-related mortality, accounting for 16% of Australia's  
198 male cancer expenditure [49, 50]. With the major risk factor being age, patients are  
199 left with few options to decrease their susceptibility towards the disease.

200 Consequently, greater reliance is placed upon detection and treatment [51]. If  
201 surgery or radiotherapy fails to remove the cancer growth, androgen deprivation  
202 therapy (ADT), primarily bicalutamide (trade name Casodex), serves as the first-line  
203 chemotherapeutic [49]. However, this treatment is only palliative, acting to suppress  
204 the androgen driven growth in the early stages. Within 14-30 months, ADTs typically  
205 become redundant as the cells mutate into an androgen-independent state known as  
206 castration-resistant prostate cancer (CRPCa) [49]. Whether or not CRPCa is initially  
207 metastatic, 60% of men develop the metastatic disease within five years, with most  
208 developing it within three [52].

209

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

218

#### 219 **4.1 Green tea and Prostate Cancer**

220

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

234

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

241

242

243

## 244 **4.2 Bioavailability**

245

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

256

## 257 **5.0 PI3K/AKT/MTOR PATHWAY IN CANCER**

258

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

269

270 This pathway is typically activated in response to the binding of hormonal or  
271 mitogenic ligands to a receptor tyrosine kinase, phosphorylating the intracellular  
272 subunit and activating the p85 and p110 kinase receptor units of the PI3K  
273 heterodimer [75]. Activation induces the addition of ATP to PIP<sub>2</sub> in the cell  
274 membrane, forming the PIP<sub>3</sub> signaling molecule, which in turn activates the PH  
275 subunit of Akt, recruiting the protein to the cell membrane (Figure 6). This is followed  
276 by the phosphorylation of phosphoinositide-dependent protein kinase-1 at the T308  
277 residue, activating the complex [76]. Akt goes onto activate a number of intracellular  
278 signaling processes, each holding influencing cell survival, proliferation, and growth,  
279 primarily mediated through the two mTOR multiprotein complexes mTORC1 and  
280 mTORC2 [77, 78].

281

## 282 **5.1 Pro survival and acceleration of growth**

283

284 Pro-survival and growth signaling are vital to cancer progression. With control over  
285 the cell cycle and suppression of apoptosis, overactivation of the PI3K/Akt/mTOR  
286 pathway can promote cancer cell survival [79]. The activated Akt phosphorylates and  
287 inactivates glycogen synthase kinase-3 beta, preventing the activation of tumor  
288 suppressor p53 and degradation of cyclin D [80]. Akt also induces the degradation of  
289 p53 by inhibiting the transduction of nuclear-localized E3 ubiquitin ligase [81]. Now  
290 remaining active in the nucleus, CD1 binds and activates the cyclin-dependent  
291 kinase (CDK) proteins [82]. CDK4 and CDK6 inhibit the tumor suppressor  
292 retinoblastoma protein (Rb), preventing the inhibitor of transcription factors G2F and  
293 enabling the progression from G<sub>1</sub> to S-phase [82]. This amplified through mTORC1's

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

302

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

314

315

316

317

318



## 319 **5.2 Glycolysis**

320

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

327

328 By phosphorylating the AS160 substrate on the glucose transporter type 4 receptor,  
329 AKT prompts its translocation to the cell surface and increases the cell's intake of  
330 glucose [98]. Downstream from the mTOR axis, there is the activation of other  
331 metabolism modulations that act to promote energy production and consumption  
332 within the cell [99]. PI3K phosphorylation and inhibition of FOXO1 and (downstream)  
333 CREB regulated transcription coactivator 2 inhibiting the fasting regulation of  
334 gluconeogenesis [100]. Storage of this excess glycogen is promoted through the  
335 inhibition of the glycogen synthase GSK3 $\beta$ , which indirectly lowers the levels of c-  
336 Myc (noted in leukemic blast cells) [101]. Overall this prevents the inhibition of the  
337 hypoxic induced gene, promoting the Warburg Effect [102].

338

## 339 **6.0 Targeting PI3K/Akt/mTOR**

340

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

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

350

### 351 **6.1 Evidence for EGCGs role**

352

353 EGCG itself acts as a competitive inhibitor ( $K_i$  380 nM) of the common class 1  
354 isomers of PI3K (PI3K $\alpha$ , PI3K $\beta$ , PI3K $\gamma$ , and PI3K $\delta$ ), preventing the initial  
355 phosphorylation of Akt [103-108]. The binding mode of EGCG is noted to be similar  
356 to the PI3K inhibitor LY294002 [37]. It should be noted that within the LNCaP and  
357 PC-3 PCa cell lines, EGCG had no significant effect on the phosphorylation of PI3K  
358 at the Ser437 residue. The lack of the phosphatase and tensin homolog allele was  
359 suspected to cause the non-response [37]. EGCG also inhibits mTOR ( $K_i$  of  $320 \pm$   
360 24 nM [37], aligning itself in a similar category to the synthetic dual PI3K/Akt/mTOR  
361 inhibitors. These non-selective inhibitors display more promising effects as both pre-  
362 clinically and clinically, they are better equipped at overcoming the compensatory  
363 feedback mechanisms [37, 103-105].

364

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

369 factor; nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) [109].  
370 NF- $\kappa$ B 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  $\mu$ M of EGCG, the EGCG  
373 was seen to suppress the activation of NF- $\kappa$ B, to which there is substantial evidence  
374 of crosstalk between the two pathways [113] [114]. Depleting the levels of NF- $\kappa$ B 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- $\kappa$ B 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- $\kappa$ B expression and PCa resistance  
380 against Docetaxel, the inhibition of NF- $\kappa$ B (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<sub>2</sub>O<sub>2</sub> [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<sup>®</sup>), 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

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

397

## 398 **7.0 Discussion and Conclusion**

399

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

416

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

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

430

431

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433

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435 interest.

436

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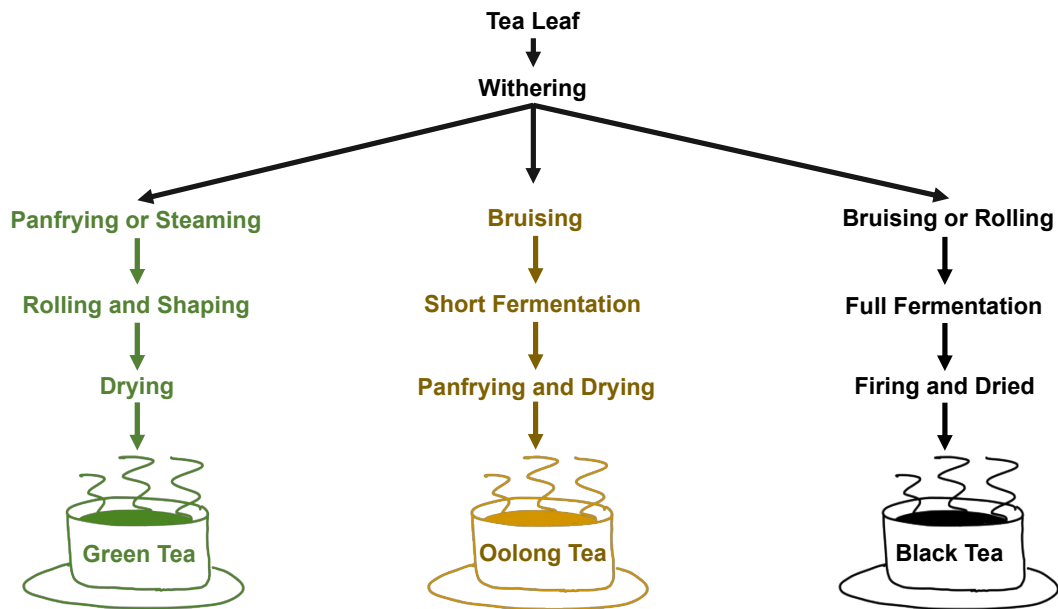
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835

836 10.0 Figures



837

838 **Figure 1: Generalized processing protocol for Green, Oolong and Black Tea. Primary**

839 **differences in the catechin content of each tea variety result from the variation in**

840 **treatment during the processing of the *Camellia sinensis* flush.**

841

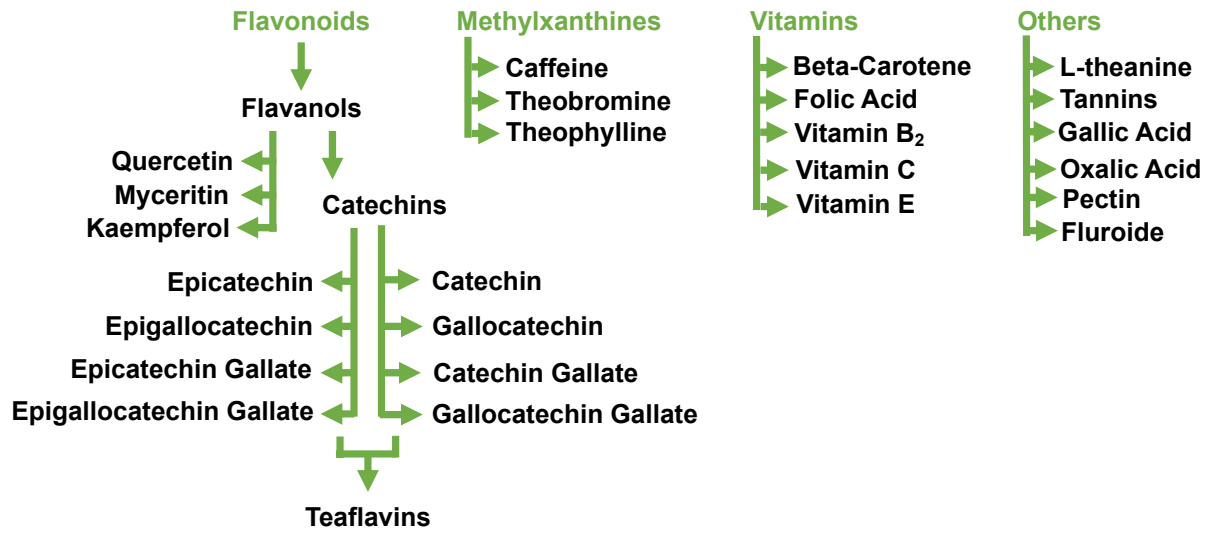
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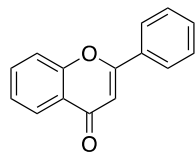
### Components of Green Tea



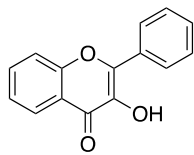
846 **Figure 2: Key bioactive components of green tea, broadly categorized into flavonoids,**  
847 **methylxanthines, vitamins and other.**

848

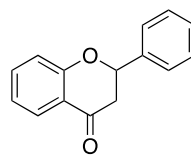




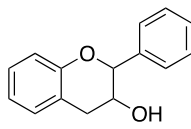
Flavone



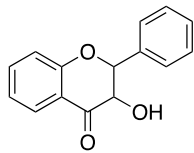
Flavonol



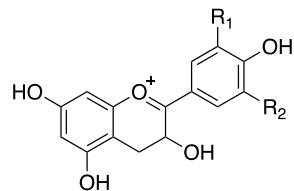
Flavanone



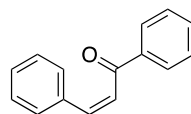
Flavan-3-ol



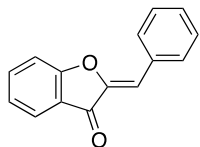
Flavanonol



Anthocyanidin



Chalcone



Aurone

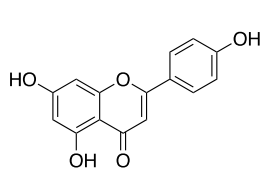
849

850 **Figure 3: Names and structures of the 2-phenylbenzopyrans (flavonoids), in which**

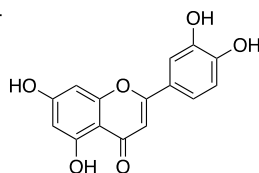
851 **flavan-3-ol is the most predominant**

852

**Flavones**

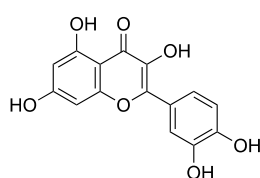


**Apigenin**

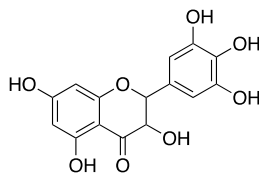


**Lutelin**

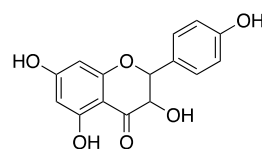
**Flavonoids**



**Quercetin**

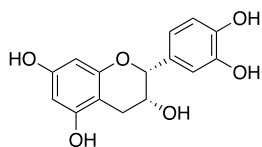


**Myricetin**

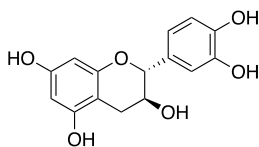


**Kaempferol**

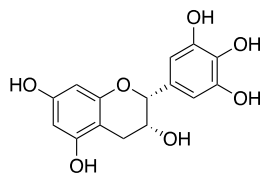
**Flavan-3-ol (Catechins)**



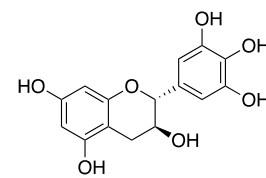
**(-)-Epicatechin (EC)**



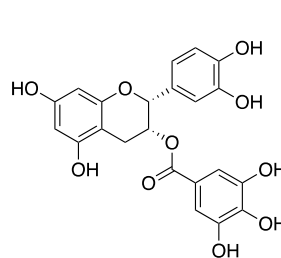
**(+)-Catechin (C)**



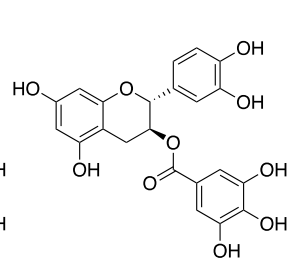
**(-)-Epigallocatechin (EGC)**



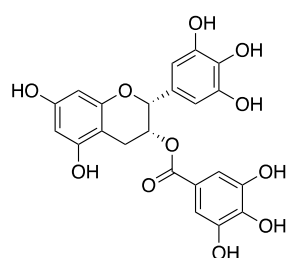
**(+)-Gallocatechin (GC)**



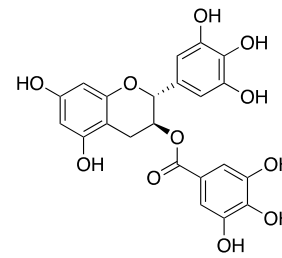
**(-)-Epicatechin gallate (ECG)**



**(-)-Catechin gallate (CG)**



**(-)-Epigallocatechin gallate (EGCG)**

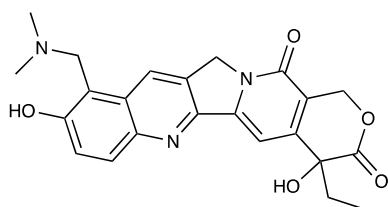


**(-)-Gallocatechin gallate (GCG)**

853

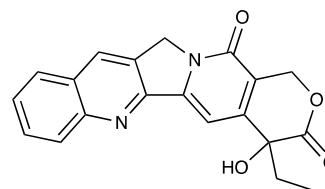
854 **Figure 4: Structures, names, and abbreviations of the major flavonols found in green**

855 **tea**

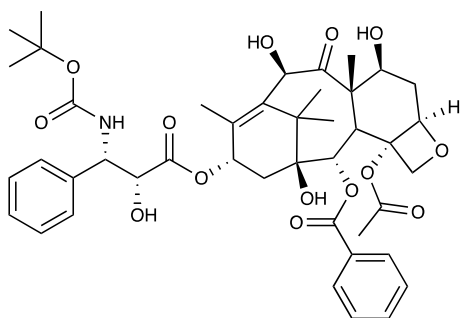


**Topotecan (Hycamtin)**  
Lung cancer, ovarian cancer  
GlaxoSmithKline, October 2007

Original Source  
→

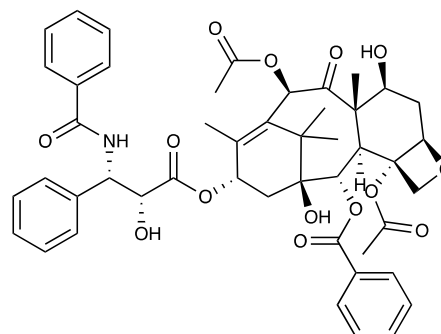


**Camptothecin (CPT)**  
Bark and stem of *Camptothec acuminata* (Happy Tree)

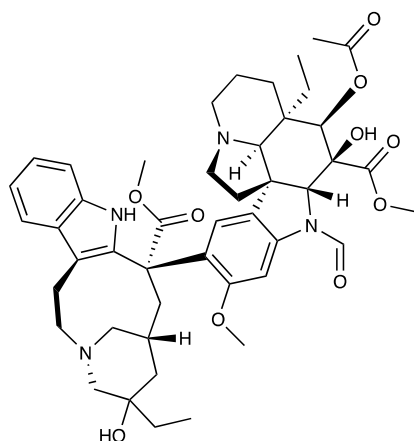


**Docetaxel (DTX, DXL, Taxotere)**  
Breast, ovarian, lung, bladder, prostate, melanoma, esophageal  
Sanofi-Aventis June 1998  
(also sold as Docefrez by Sun Pharma Global and Zytax by Zydus.)

Original Source  
→



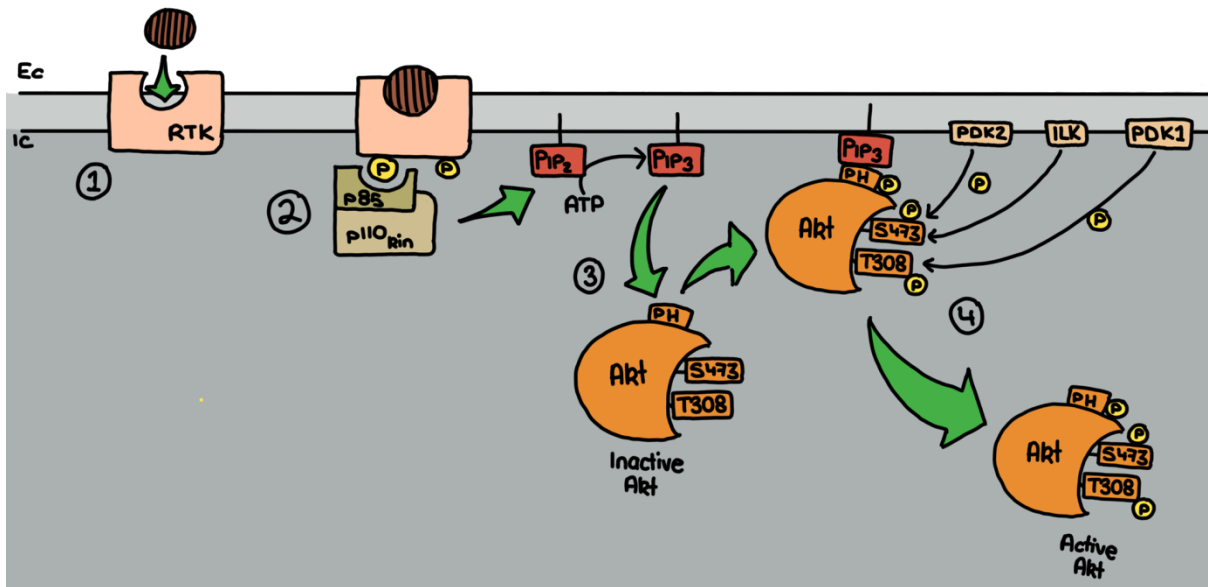
**Paclitaxel (PTX or Taxol)**  
Bark of the Pacific yew tree  
*Taxus brevifolia*



**Vincristine (Oncovin)**  
Rosy Periwinkle *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**



858

859 **Figure 6: Activation of PI3K and Akt mediated through (a) mitogenic activation at the**  
 860 **receptor tyrosine kinase (RTK) resulting in the (2) phosphorylation and binding of the**  
 861 **PI3K intracellular unit (3) conversion of PIP<sub>2</sub> to PIP<sub>3</sub> and activation of the Ph subunit**  
 862 **on Akt inducing the translocation to the cell membrane (4) phosphorylation and**  
 863 **activation of Akt. Abbreviations: receptor tyrosine kinase (RTK), Phosphatidylinositol-**  
 864 **4,5-bisphosphate 3-kinase (p85/p110 $\alpha$ kin), Phosphatidylinositol 4,5-bisphosphate (PIP),**  
 865 **Pyruvate Dehydrogenase Kinase (PDK) and Integrin-linked kinase (ILK).**



867 **11.0 Tables**

868 **Table 1: Proportion of Catechins present in Tea**

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<b>Fermentation</b>	<b>% Flavanols</b>
Non-Fermented (Green)	8.0–14.4
Partially Fermented (Oolong)	4.14–4.92
Fermented (Black)	0.24–0.51

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

<b>Cancer</b>	<b>Effect of EGCG</b>	<b>Source</b>
<b>Prostate</b>	Cellular apoptosis	[109]
	Reduced risk	[36]
<b>Lymphoma (mouse)</b>	Cellular apoptosis	[109]
<b>Keratinocytes</b>	Cellular apoptosis	[109]
<b>Bladder Carcinoma</b>	Reduced Risk	[36]
	Chemoprevention	[4, 5]
	Prevent reoccurrence	[33]
	Fewer side effects	[126]
<b>Colon</b>	Chemoprevention	[57, 62, 127, 128]
	Cellular apoptosis	[10]
	Chemoprevention	[57]
	Inhibit tumour development (mouse/rat)	[57]
<b>Lung</b>	Controversial association with efficacy	[4]
	Apoptosis via triggering H <sub>2</sub> O <sub>2</sub> production (H661)	[118]
	Inhibit proliferation	[37]
<b>Breast</b>	Chemoprevention	[129]
	Inhibit proliferation	[37]
<b>Lymphatic</b>	Elevate ROS production during apoptosis	[36]
	Cellular apoptosis (mouse LY5178)	[109]
	Reduced adenocarcinoma incidence (Polyphenol E*)	[57]
	Reduced adenocarcinoma multiplicity (Polyphenol E*)	[57]
	Increase phosphorylation of cJun	[130, 131]
<b>Epidermal</b>	Increase phosphorylation of Erk1/2	[131]
	Increase PCNA	[131]
	G <sub>0</sub> /G <sub>1</sub> halt in A431 (not non-cancerous NHEK)	[11]
	Constitutively expression of NF-kB	[109]
	Apoptotic cell death	[109]
<b>(Inflammation)</b>	Protect against collagen-induced arthritis (GTP**)	[109]
<b>Esophageal</b>	Chemopreventive	[4, 57]
<b>Stomach</b>	Chemopreventive	[4, 57]
<b>Intestine</b>	Chemopreventive	[4, 57]

*\*polyphenol E is a concentrated catechin preparation; \*\* GTP refers to a combination of green tea proteins;*

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

	<b>Drug</b>	<b>Brand Name (Manufacturer)</b>	<b>Adverse Reactions</b>	<b>Eligibility</b>
<b>GnRH Agonist / Antagonist</b>	Goserelin	Zoladex (AstraZeneca Pharmaceuticals)	Hot flushes Tumor flare Hyperglycaemia Hyperlipidemia Hypercholesterolemia Reduced libido	locally advanced or metastatic hormone-sensitive prostate cancer
	Triptorelin	Decapeptyl (Ferring Pharmaceuticals)	Hot flushes Tumor flare Hyperglycaemia Hyperlipidemia Hypercholesterolaemia Reduced libido Depression	locally advanced or metastatic hormone-sensitive prostate cancer
	Degarelix	Firmagon (Ferring Pharmaceuticals)	Hot flushes Arthralgia Fatigue Constipation Reduced libido Gynaecomastia Fatigue Constipation Nausea Drowsiness	Locally advanced or metastatic prostate cancer
	Bicalutamide	Casodex (AstraZeneca Pharmaceuticals)	Constipation Dizziness Hot flushes Abdominal pain Fluid retention Hepatotoxicity Anorexia	locally advanced or metastatic CRPCa in combination with LHRH agonist
	Cyproterone Acetate	Sandoz (Sandoz Pty Ltd)	Hot flushes Fatigue Depression Swelling Bone weakening Weight fluctuations Dry skin	Locally advanced inoperable prostate cancer in combination with radiation therapy Locally advanced or metastatic castrate-resistant prostate cancer in combination with LHRH agonist Short term prevention of tumor flare associated with the initiation of an LHRH agonist
	Abiraterone	Zytiga (Janssen Biotech)	Hypertension Fluid retention Hypokalaemia Vomiting and Diarrhoea	Post-docetaxel CRPCa. secondary hormonal therapeutic. Must be in combination with prednisone or prednisolone, and no other chemotherapy
	Enzalutimide	Xtandi (Astellas Pharma US)	Hypertension Anxiety Fatigue Seizures	Post-docetaxel CRPCa. Available for clinical trials secondary hormonal therapeutic. Cannot use with abiraterone.



**Others**

Flutamide	Eulexin (Schering-Plough)	Hot Flashes Urine Discolouration Loss of sexual interest Diarrhea Nausea Vomiting Enlargement of male breasts Skin sensitivity Impotence Rectal bleeding	Locally advanced or metastatic castrate resistant prostate cancer. Used in combination with LHRH agonist throughout treatment.  Short term prevention of tumour flare
Radium-223	Xofigo (Bayer)	Nausea Vomiting Diarrhea Swelling	Asymptomatic bone metastasis. Bone metastasis
Sipuleucel-T	Provenge (Dendreon Pharmaceuticals)	Fatigue Fever Chills Nausea Vomiting Neutropenia Thrombocytopenia Oral Mucositis	Asymptomatic or minimally metastatic CRPCa
Docetaxel	Taxotere (Phyton Biotech)	Diarrhea Skin rash Peripheral neuropathy Palmar-plantar Erythrodysesthesia Arthralgia Ocular changes Fatigue Fluid retention Nausea Hair loss Mouth ulcers	Diagnosed CRPCa (standard treatment)
Mitoxantrone	Novantrone (Pfizer)	Neutropenia Thrombocytopenia Oral Mucositis Anorexia Arthralgia Fatigue Severe neutropenia Thrombocytopenia Anorexia	Diagnosed CRPCa
Cabazitaxel	Jevtana (Sanofi-Aventis)	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

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870 Note that this table is not fully comprehensive and the most current Australian data can be found at the EviQ  
871 [132-140]  
872

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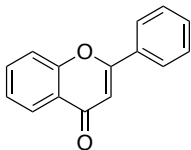
**Table 4: PI3K/Akt/mTOR pathway inhibitors**

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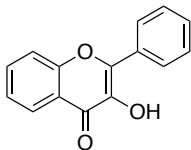
<b>Target</b>		<b>Name</b>	<b>Tradename</b>
<b>Dual PI3K/ mTOR</b>		LY3023414	
		LY294002	
	Pan-class I Inhibitors	PX 866	Sonolisib
<b>PI3K</b>		BKM 120	Buparlisib
	p110 Isoform-specific	GSK 2636771	
	PI3K Inhibitors	AZD 8186	
		GSK2141795	Uprosertib
<b>AKT</b>	Akt	GDC-0068	Ipatasertib
		AZD5363	
	mTORC1 &	AZD 8055	
<b>mTORC</b>	mTORC2 Dual	INK 128	
	Inhibitor		
	MTORC1	Everolimus	

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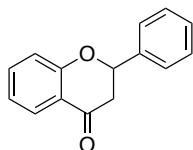
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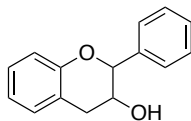
**Flavone**



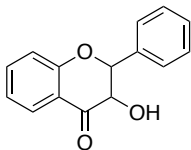
**Flavonol**



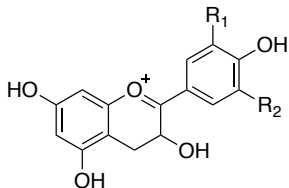
**Flavanone**



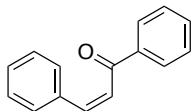
**Flavan-3-ol**



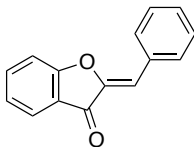
**Flavanonol**



**Anthocyanidin**

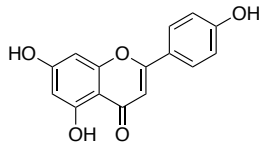


**Chalcone**

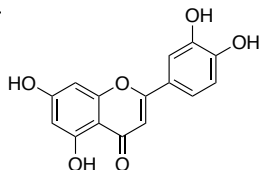


**Aurone**

## Flavones

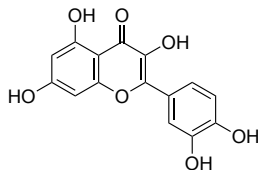


**Apigenin**

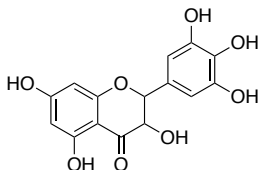


**Lutelin**

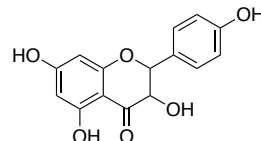
## Flavonoids



**Quercetin**

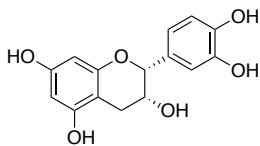


**Myricetin**

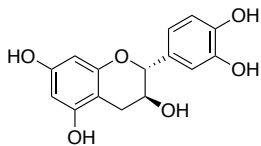


**Kaempferol**

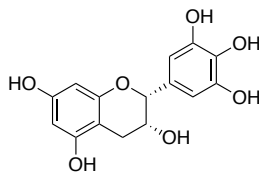
## Flavan-3-ol (Catechins)



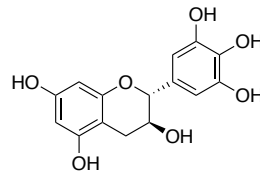
**(-)-Epicatechin (EC)**



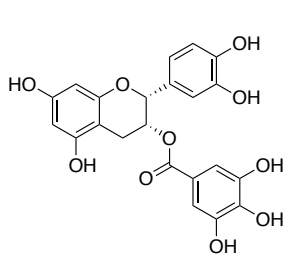
**(+)-Catechin (C)**



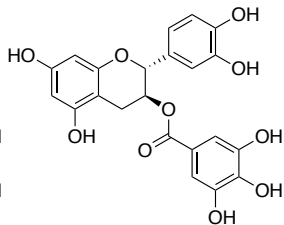
**(-)-Epigallocatechin (EGC)**



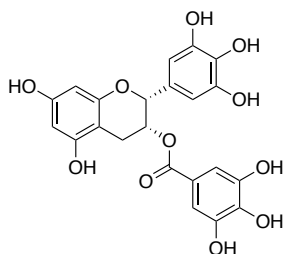
**(+)-Gallocatechin (GC)**



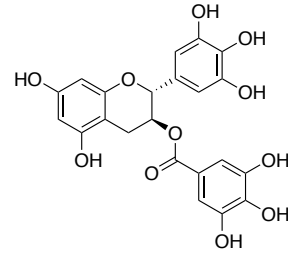
**(-)-Epicatechin gallate (ECG)**



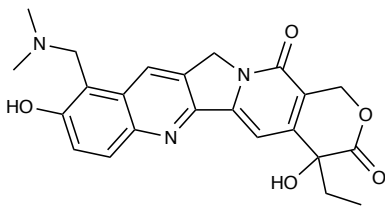
**(-)-Catechin gallate (CG)**



**(-)-Epigallocatechin gallate (EGCG)**

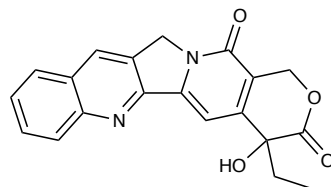


**(-)-Gallocatechin gallate (GCG)**

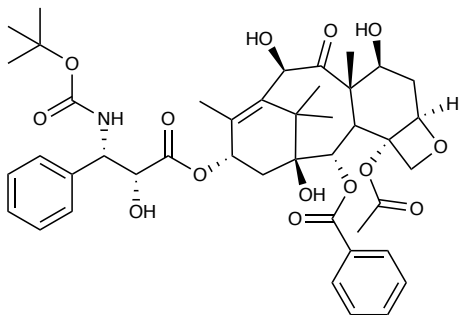


**Topotecan (Hycamtin)**  
Lung cancer, ovarian cancer  
GlaxoSmithKline, October 2007

Original  
Source  
→

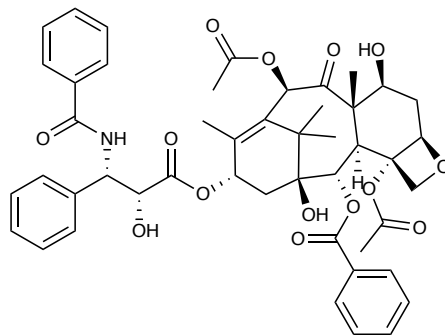


**Camptothecin (CPT)**  
Bark and stem of *Camptothec  
acuminata* (Happy Tree)

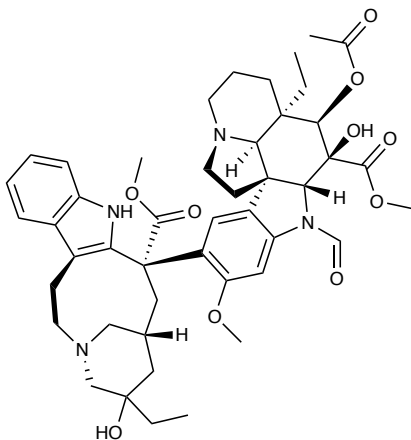


**Docetaxel (DTX, DXL, Taxotere)**  
Breast, ovarian, lung, bladder, prostate, melanoma, esophageal  
Sanofi-Aventis June 1998  
(also sold as Docefrez by Sun Pharma Global and Zytax by  
Zydus.)

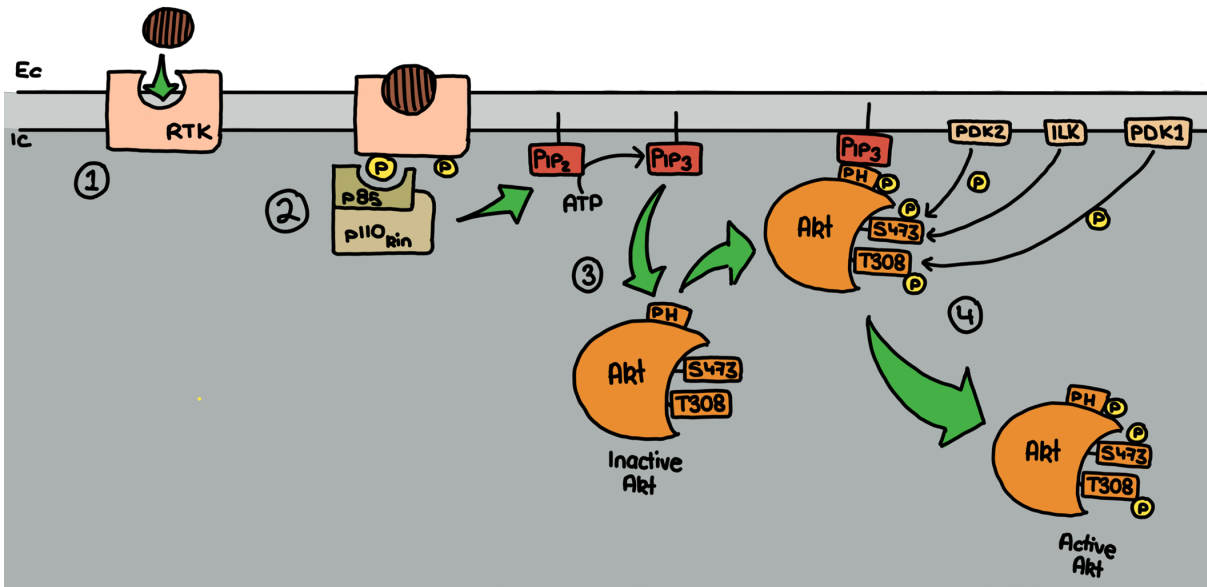
Original  
Source  
→



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



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



Tea Leaf



Withering

Panfrying or Steaming



Rolling and Shaping



Drying



Bruising



Short Fermentation



Panfrying and Drying



Bruising or Rolling



Full Fermentation

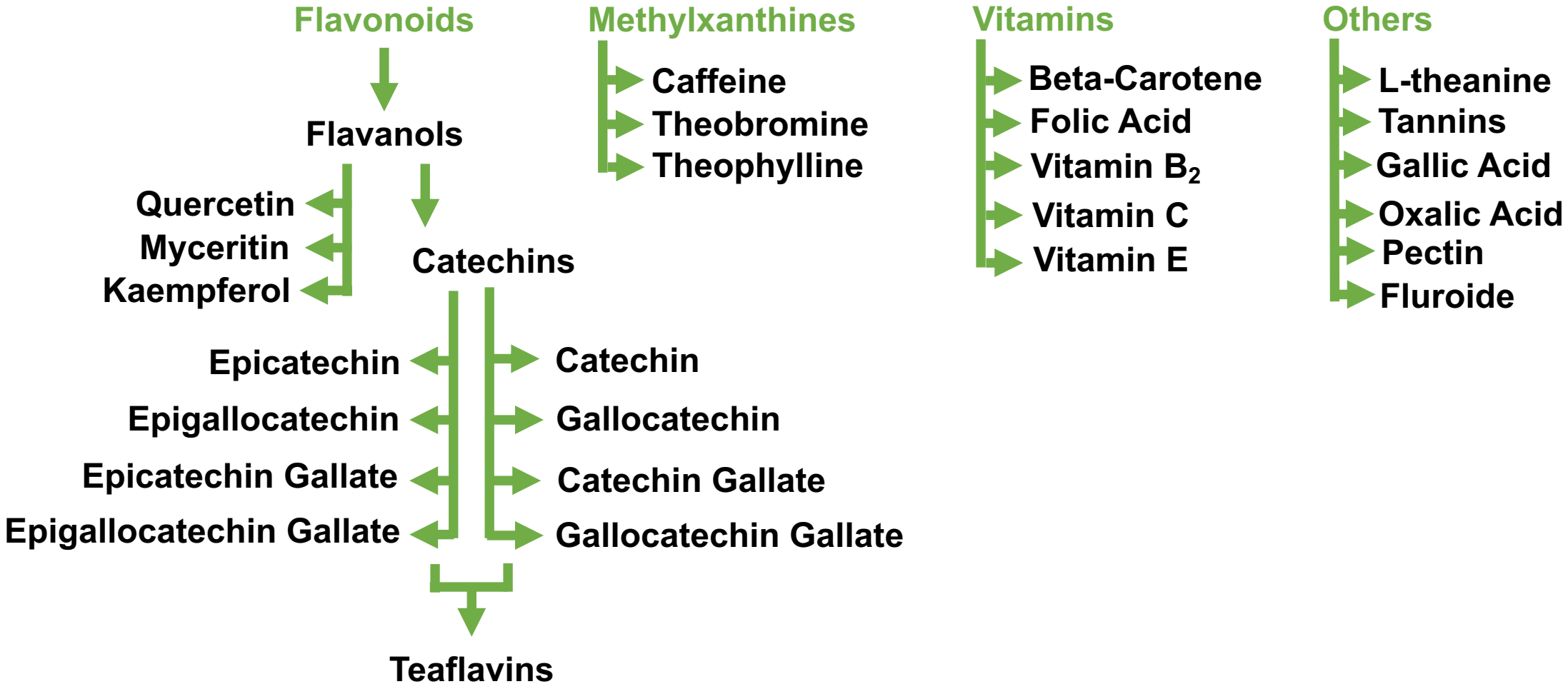


Firing and Dried





# Components of Green Tea



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**Table 1: Proportion of Catechins present in Tea**

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<b>Fermentation</b>	<b>% Flavanols</b>
Non-Fermented (Green)	8.0–14.4
Partially Fermented (Oolong)	4.14–4.92
Fermented (Black)	0.24–0.51

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

<b>Cancer</b>	<b>Effect of EGCG</b>	<b>Source</b>
<b>Prostate</b>	Cellular apoptosis	[109]
	Reduced risk	[36]
<b>Lymphoma (mouse)</b>	Cellular apoptosis	[109]
<b>Keratinocytes</b>	Cellular apoptosis	[109]
<b>Bladder Carcinoma</b>	Reduced Risk	[36]
<b>Colon</b>	Chemoprevention	[4, 5]
	Prevent reoccurrence	[33]
	Fewer side effects	[126]
	Chemoprevention	[57, 62, 127, 128]
<b>Lung</b>	Cellular apoptosis	[10]
	Chemoprevention	[57]
	Inhibit tumour development (mouse/rat)	[57]
	Controversial association with efficacy	[4]
<b>Breast</b>	Apoptosis via triggering H <sub>2</sub> O <sub>2</sub> production (H661)	[118]
	Inhibit proliferation	[37]
	Chemoprevention	[129]
<b>Lymphatic</b>	Inhibit proliferation	[37]
	Elevate ROS production during apoptosis	[36]
	Cellular apoptosis (mouse LY5178)	[109]
	Reduced adenocarcinoma incidence (Polyphenol E*)	[57]
	Reduced adenocarcinoma multiplicity (Polyphenol E*)	[57]
<b>Epidermal (Inflammation)</b>	Increase phosphorylation of cJun	[130, 131]
	Increase phosphorylation of Erk1/2	[131]
	Increase PCNA	[131]
	G <sub>0</sub> /G <sub>1</sub> halt in A431 (not non-cancerous NHEK)	[11]
	Constitutively expression of NF-kB	[109]
	Apoptotic cell death	[109]
<b>Esophageal</b>	Protect against collagen-induced arthritis (GTP**)	[109]
<b>Stomach</b>	Chemopreventive	[4, 57]
<b>Intestine</b>	Chemopreventive	[4, 57]

*\*polyphenol E is a concentrated catechin preparation; \*\* GTP refers to a combination of green tea proteins;*

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

	<b>Drug</b>	<b>Brand Name (Manufacturer)</b>	<b>Adverse Reactions</b>	<b>Eligibility</b>
<b>GnRH Agonist / Antagonist</b>	Goserelin	Zoladex (AstraZeneca Pharmaceuticals)	Hot flushes Tumor flare Hyperglycaemia Hyperlipidemia Hypercholesterolemia Reduced libido	locally advanced or metastatic hormone-sensitive prostate cancer
	Triptorelin	Decapeptyl (Ferring Pharmaceuticals)	Hot flushes Tumor flare Hyperglycaemia Hyperlipidemia Hypercholesterolaemia Reduced libido	locally advanced or metastatic hormone-sensitive prostate cancer
	Degarelix	Firmagon (Ferring Pharmaceuticals)	Depression Hot flushes Arthralgia Fatigue Constipation Reduced libido Gynaecomastia	Locally advanced or metastatic prostate cancer
	Bicalutamide	Casodex (AstraZeneca Pharmaceuticals)	Fatigue Constipation Nausea Drowsiness Constipation Dizziness Hot flushes Abdominal pain Fluid retention Hepatotoxicity Anorexia	locally advanced or metastatic CRPCa in combination with LHRH agonist
	Cyproterone Acetate	Sandoz (Sandoz Pty Ltd)	Hot flushes Fatigue Depression Swelling Bone weakening Weight fluctuations Dry skin	Locally advanced inoperable prostate cancer in combination with radiation therapy Locally advanced or metastatic castrate-resistant prostate cancer in combination with LHRH agonist Short term prevention of tumor flare associated with the initiation of an LHRH agonist
	Abiraterone	Zytiga (Janssen Biotech)	Hypertension Fluid retention Hypokalaemia Vomiting and Diarrhoea	Post-docetaxel CRPCa. secondary hormonal therapeutic. Must be in combination with prednisone or prednisolone, and no other chemotherapy
	Enzalutimide	Xtandi (Astellas Pharma US)	Hypertension Anxiety Fatigue Seizures	Post-docetaxel CRPCa. Available for clinical trials secondary hormonal therapeutic. Cannot use with abiraterone.

**Others**

Flutamide	Eulexin (Schering-Plough)	Hot Flashes Urine Discolouration Loss of sexual interest Diarrhea Nausea Vomiting Enlargement of male breasts Skin sensitivity Impotence Rectal bleeding	Locally advanced or metastatic castrate resistant prostate cancer. Used in combination with LHRH agonist throughout treatment.
Radium-223	Xofigo (Bayer)	Nausea Vomiting Diarrhea Swelling	Asymptomatic bone metastasis. Bone metastasis
Sipuleucel-T	Provenge (Dendreon Pharmaceuticals)	Fatigue Fever Chills Nausea Vomiting Neutropenia Thrombocytopenia Oral Mucositis	Asymptomatic or minimally metastatic CRPCa
Docetaxel	Taxotere (Phyton Biotech)	Diarrhea Skin rash Peripheral neuropathy Palmar-plantar Erythrodysesthesia Arthralgia Ocular changes Fatigue Fluid retention Nausea Hair loss Mouth ulcers	Diagnosed CRPCa (standard treatment)
Mitoxantrone	Novantrone (Pfizer)	Neutropenia Thrombocytopenia Oral Mucositis Anorexia Arthralgia Fatigue Severe neutropenia Thrombocytopenia Anorexia Diarrhea	Diagnosed CRPCa
Cabazitaxel	Jevtana (Sanofi-Aventis)	Constipation Skin Rash Arthralgia Fatigue Peripheral neuropathy Peripheral neuropathy Nausea and vomiting	Post-docetaxel CRPCa. Must be in combination with prednisone or prednisolone

## Diarrhea

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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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**Table 4: PI3K/Akt/mTOR pathway inhibitors**

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<b>Target</b>		<b>Name</b>	<b>Tradename</b>
<b>Dual PI3K/ mTOR</b>		LY3023414	
		LY294002	
	Pan-class I Inhibitors	PX 866	Sonolisib
<b>PI3K</b>		BKM 120	Buparlisib
	p110 Isoform-specific	GSK 2636771	
	PI3K Inhibitors	AZD 8186	
		GSK2141795	Uprosertib
<b>AKT</b>	Akt	GDC-0068	Ipatasertib
		AZD5363	
	mTORC1 &	AZD 8055	
<b>mTORC</b>	mTORC2 Dual	INK 128	
	Inhibitor		
	MTORC1	Everolimus	

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