Enhanced Chemopreventive Effect by Combining Quercetin and Green tea in Prostate Cancer

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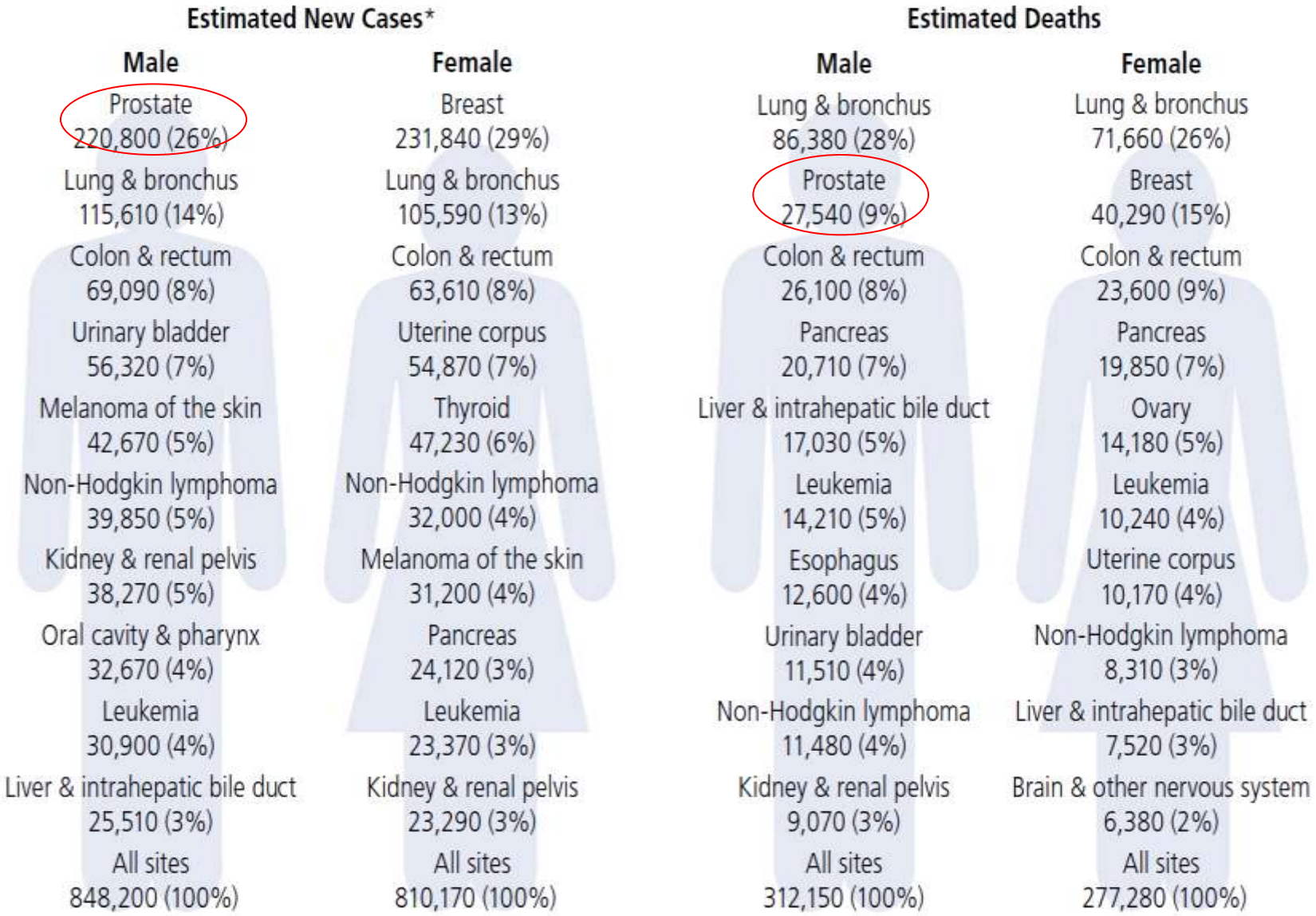
Leading Sites of New Cancer Cases and Deaths – 2015 Estimates



*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

(Cancer Facts & Figures 2015)

Probability (%) of Developing Invasive Cancer during Selected Age Intervals by Sex, US, 2009-2011*

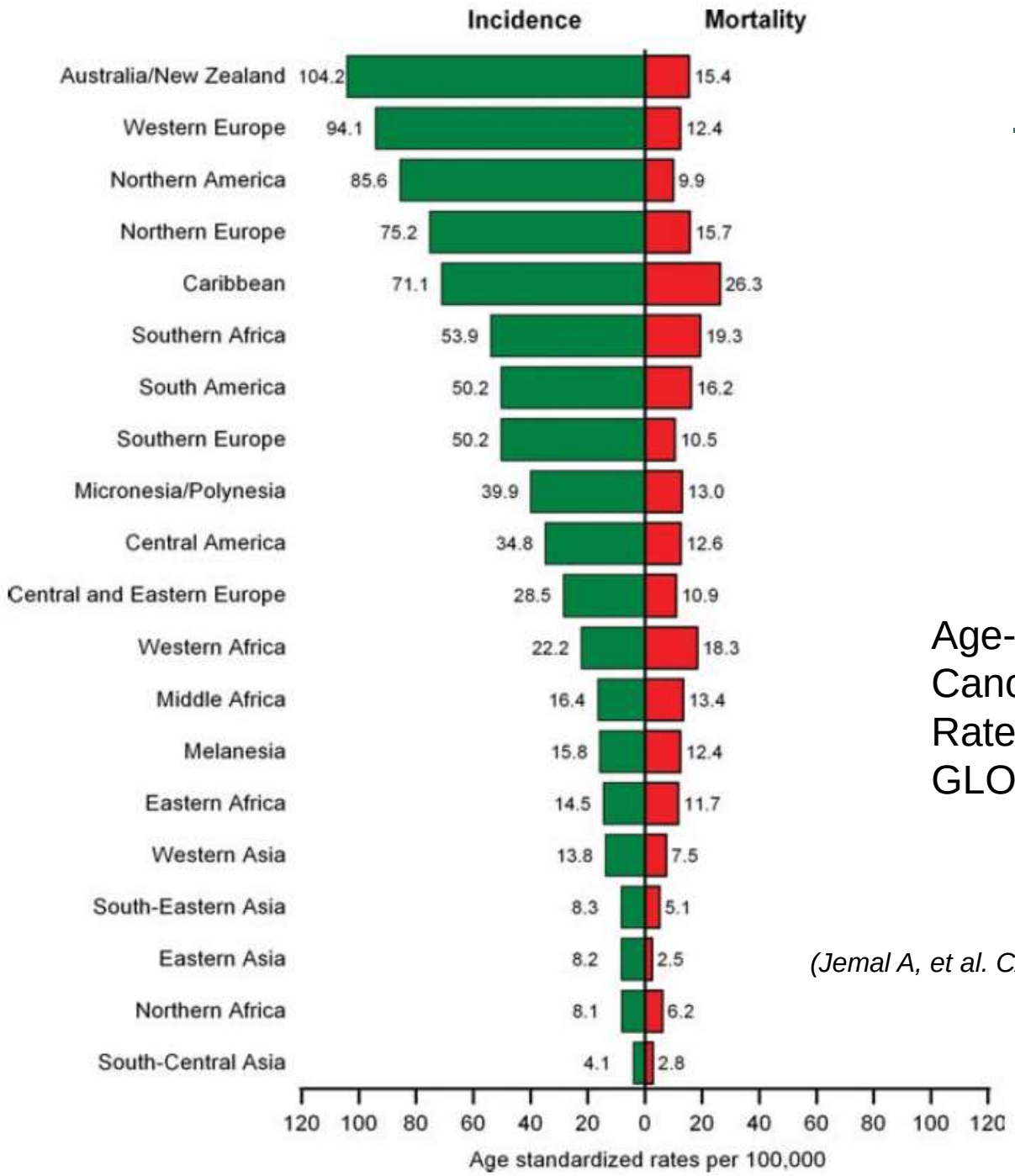
		Birth to 49	50 to 59	60 to 69	70 and Older	Birth to Death
All sites†	Male	3.4 (1 in 29)	6.7 (1 in 15)	15.1 (1 in 7)	36.0 (1 in 3)	43.3 (1 in 2)
	Female	5.4 (1 in 19)	6.0 (1 in 17)	10.0 (1 in 10)	26.4 (1 in 4)	37.8 (1 in 3)
Breast	Female	1.9 (1 in 53)	2.3 (1 in 44)	3.5 (1 in 29)	6.7 (1 in 15)	12.3 (1 in 8)
Colon & rectum	Male	0.3 (1 in 300)	0.7 (1 in 148)	1.3 (1 in 80)	3.9 (1 in 26)	4.8 (1 in 21)
	Female	0.3 (1 in 326)	0.5 (1 in 193)	0.9 (1 in 112)	3.5 (1 in 28)	4.5 (1 in 22)
Kidney & renal pelvis	Male	0.2 (1 in 468)	0.3 (1 in 292)	0.6 (1 in 157)	1.3 (1 in 76)	2.0 (1 in 49)
	Female	0.1 (1 in 752)	0.2 (1 in 586)	0.3 (1 in 321)	0.7 (1 in 134)	1.2 (1 in 84)
Leukemia	Male	0.2 (1 in 419)	0.2 (1 in 598)	0.4 (1 in 271)	1.3 (1 in 75)	1.7 (1 in 59)
	Female	0.2 (1 in 516)	0.1 (1 in 968)	0.2 (1 in 464)	0.9 (1 in 117)	1.2 (1 in 84)
Lung & bronchus	Male	0.2 (1 in 578)	0.7 (1 in 140)	2.0 (1 in 49)	6.6 (1 in 15)	7.4 (1 in 13)
	Female	0.2 (1 in 541)	0.6 (1 in 173)	1.6 (1 in 64)	4.9 (1 in 20)	6.2 (1 in 16)
Melanoma of the skin‡	Male	0.3 (1 in 294)	0.4 (1 in 240)	0.8 (1 in 129)	2.1 (1 in 47)	3.0 (1 in 34)
	Female	0.5 (1 in 207)	0.3 (1 in 323)	0.4 (1 in 246)	0.9 (1 in 112)	1.9 (1 in 53)
Non-Hodgkin lymphoma	Male	0.3 (1 in 366)	0.3 (1 in 347)	0.6 (1 in 173)	1.8 (1 in 55)	2.4 (1 in 42)
	Female	0.2 (1 in 543)	0.2 (1 in 483)	0.4 (1 in 233)	1.4 (1 in 72)	1.9 (1 in 52)
Prostate	Male	0.3 (1 in 304)	2.3 (1 in 44)	6.3 (1 in 16)	10.9 (1 in 9)	15.0 (1 in 7)
Uterine cervix	Female	0.3 (1 in 358)	0.1 (1 in 840)	0.1 (1 in 842)	0.2 (1 in 565)	0.6 (1 in 154)
Uterine corpus	Female	0.3 (1 in 367)	0.6 (1 in 170)	0.9 (1 in 109)	1.3 (1 in 76)	2.7 (1 in 37)

*For those who are free of cancer at the beginning of each age interval. †All sites excludes basal cell and squamous cell skin cancers and in situ cancers except urinary bladder. ‡Statistic is for whites.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.1. Statistical Research and Applications Branch, National Cancer Institute, 2014. srab.cancer.gov/devcan.

Please note: The probability of developing cancer for additional sites, as well as the probability of cancer death, can be found in Supplemental Data at cancer.org/research/cancerfactsstatistics/index.

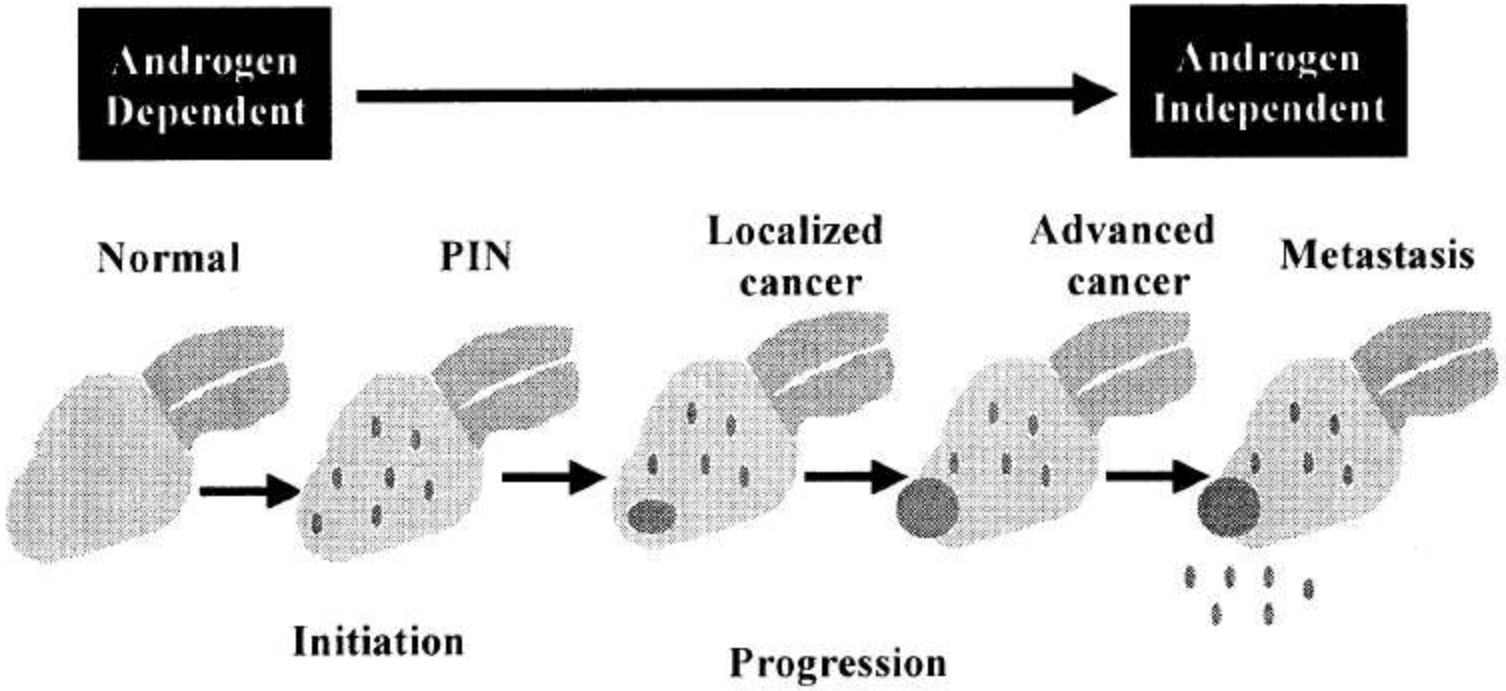
(Cancer Facts & Figures 2015)



Age-Standardized Prostate Cancer Incidence and Mortality Rates by World Area. Source: GLOBOCAN 2008.

(Jemal A, et al. CA CANCER J CLIN 2011;61:69–90)

Prostate cancer

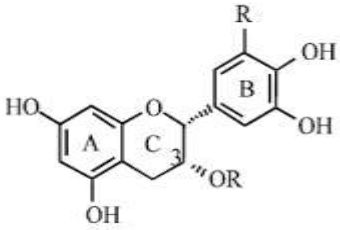


Prostate cancer: Science and clinical practice. Edited by: J Mydlo & C Godec. 2013)

Tea

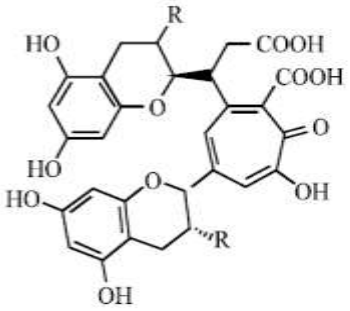
- From the plant *Camellia sinensis*

- **Green tea (GT):**
  - Not fermented
  - Polyphenol monomer (EC, EGC,ECG, EGCG)
- Oolong tea:
  - Partially fermented
- Black tea:
  - Fully fermented
  - Dimers and polymers (theaflavins, thearubigins)



EGCG: R = Galloyl; R' = OH
Epicatechin: R = R' = H
EGC: R = H; R' = OH
ECG: R = Galloyl; R' = H

Majorpolyphenols in green tea



Theaflavin: R = R' = OH
Theaflavin-3-gallate: R = Galloyl; R' = CH
Theaflavin-3, 3'-gallate: R = OH; R' = Galloyl
Theaflavin-3, 3'-digallate; R = R' = Galloyl

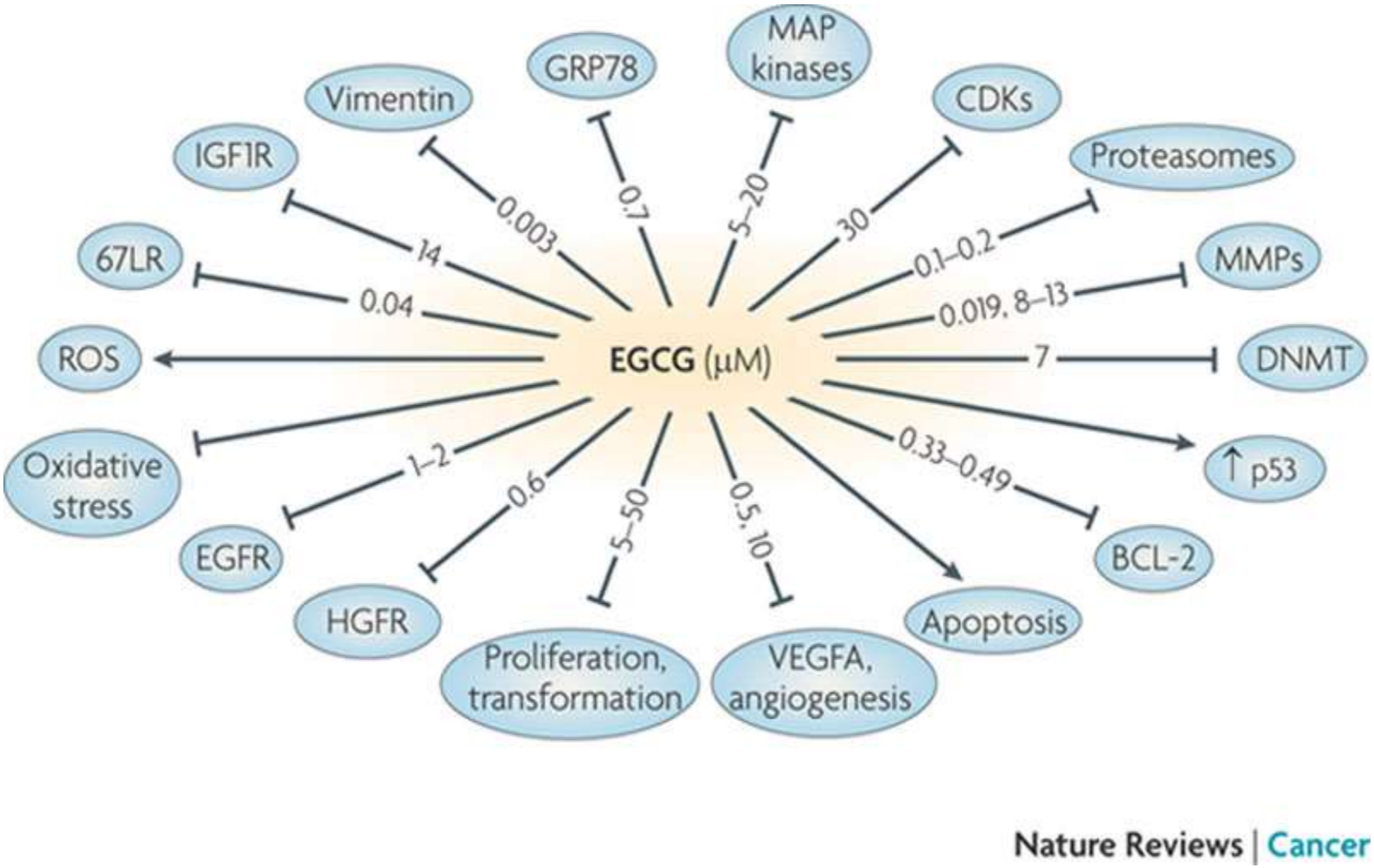
Thearubigins
The structures are not well defined
R = gallate or other groups

Majorpolyphenols in black tea

(Alipoor, et al. Asian J Clin Nutr. 2012, 4 (1): 1-15

GT and GT polyphenols

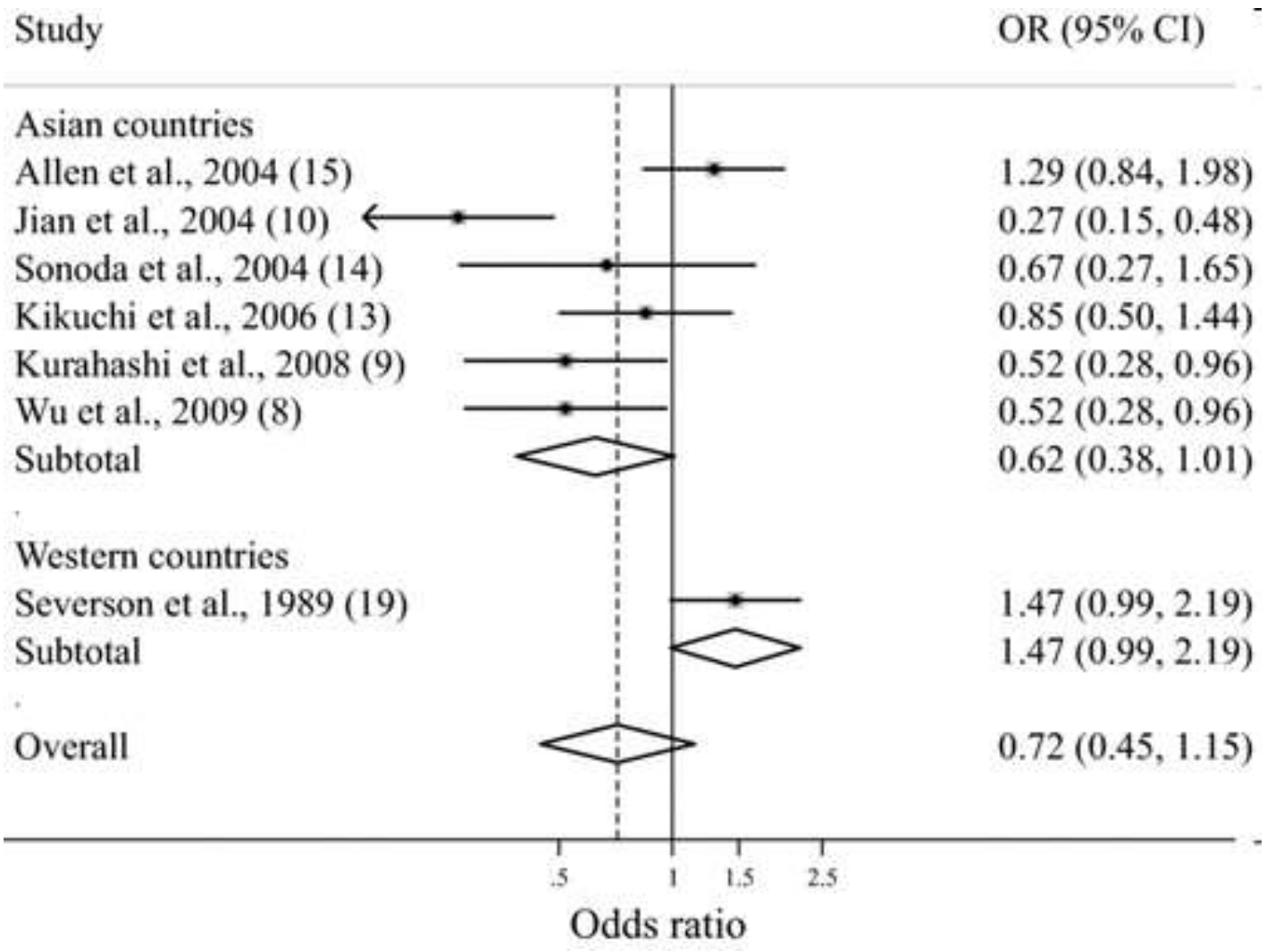
- Anti-carcinogenesis
  - Skin, lung, oral cavity, esophagus, stomach, intestine, colon, liver, pancreas, bladder, mammary gland, prostate
- Diabetes and obesity
- Cardiovascular diseases
- Neurodegenerative diseases
- Osteoporosis



Possible targets for the cancer preventive activity of (-)-epigallocatechin-3-gallate (EGCG).

(Yang CS, et al. Nature Reviews Cancer 2009, 9, 429-439)

Pooled odds ratio (OR) of GT consumption (highest versus non/lowest) and risk of prostate cancer



(Zheng J. et al. 2011 Nutr and Cancer 63(5):663-672)

Intervention studies: GT and prostate cancer

Tea, Country	Effect	Reference
GT extract, Italy, 600 mg	→ Reduced progression from HG-PIN to prostate cancer: Control 30% GTE 3%	Bettuzzi S et al. 2006
GT extract, USA, 800 mg EGCG (single arm)	→ Decreased serum PSA, HGF, VEGF in prostate cancer patients	McLarty J et al. 2009
GT extract, USA, 800 mg EGCG (placebo controlled)	→ A decreasing trend of PSA, in prostate cancer patients	Nguyen MM et al. 2012

A phase II clinical trial of tea in prostate cancer

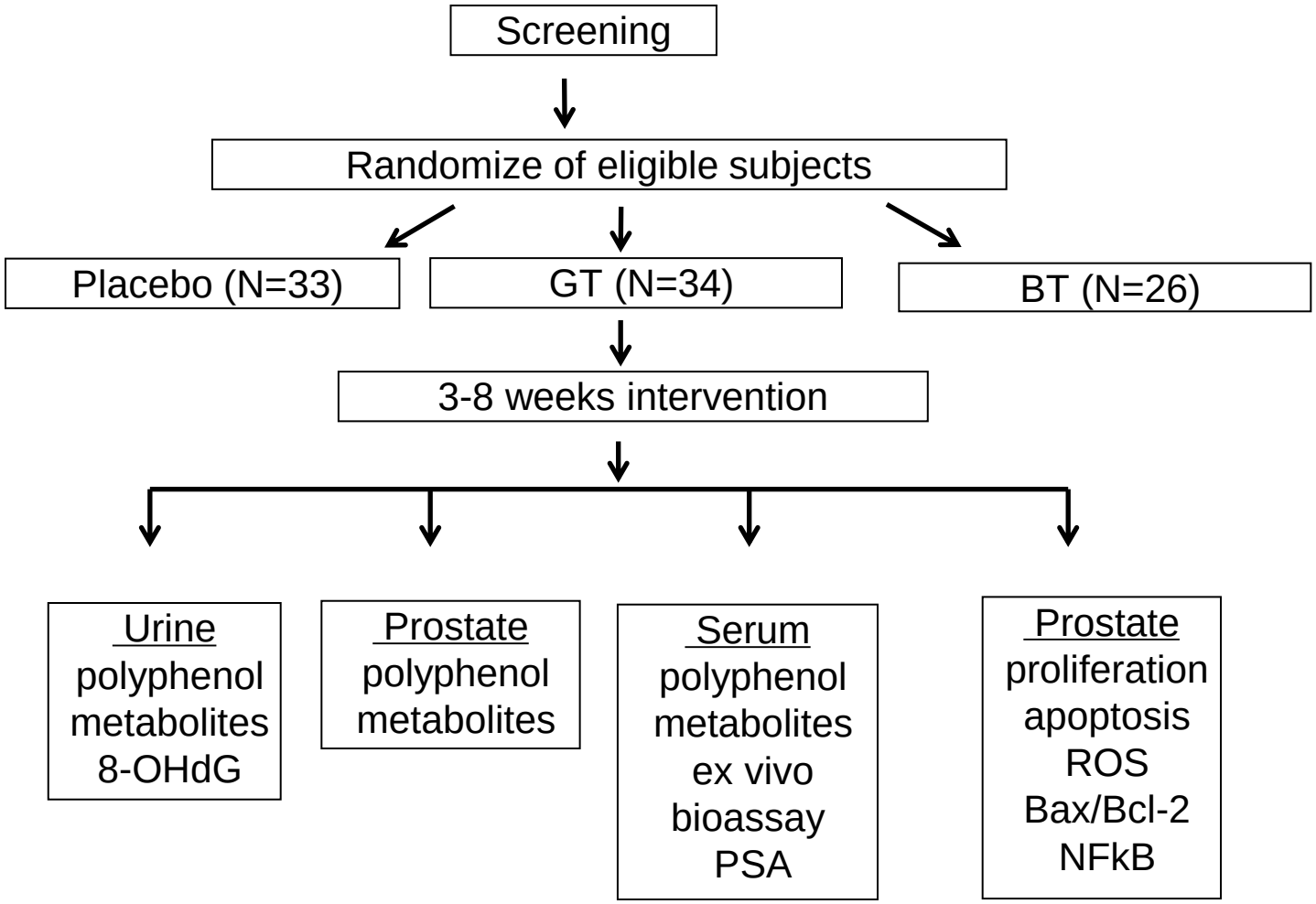
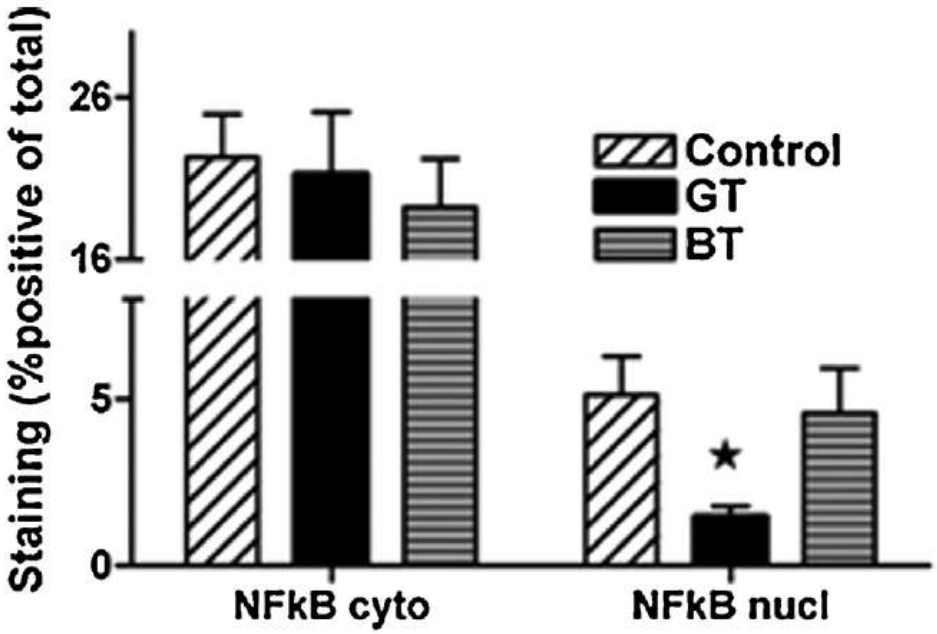


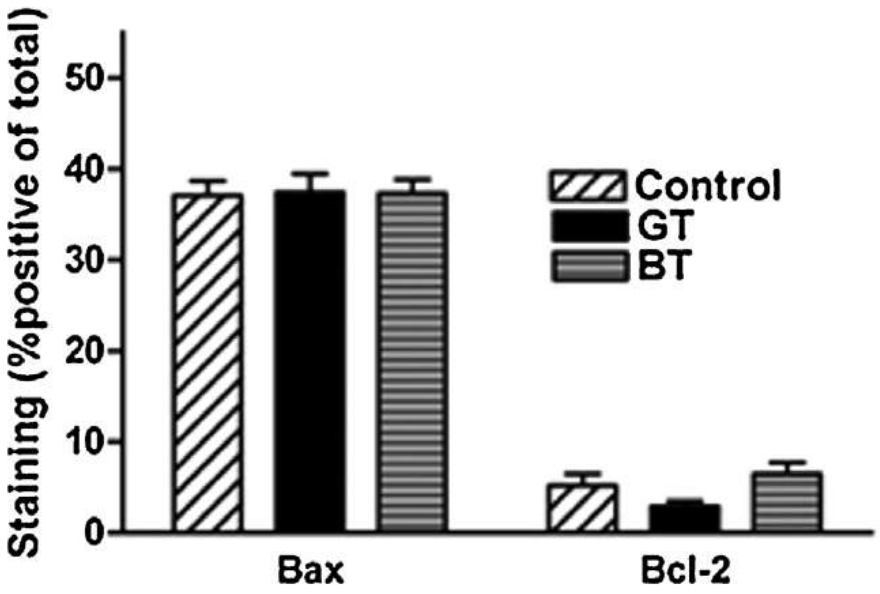
TABLE I. Baseline Characteristics of Study Population (mean ± s.d.)

	Water[a]	GT	BT	*P*-value
N	33	34	26	
Age	62.8 ± 6.2	62.1 ± 6.9	61.4 ± 7.4	0.93
Weight (kg)	86.6 ± 14.3	85.7 ± 12.2	89.9 ± 13.4	0.47
Height (cm)	175 ± 22	176 ± 21	175 ± 22	0.98
BMI (kg/m^2)	27.4 ± 4.9	27.2 ± 3.8	27.4 ± 3.6	0.98
Intervention (days)	29 ± 7.9	33 ± 23	31 ± 10	0.60
Compliance (%)	93 ± 12	95 ± 10	92 ± 13	0.75
Biopsy Gleason Score (%)				
6	14 (42)	18 (53)	13 (50)	0.74
7 (3 + 4)	15 (45)	11 (32)	9 (35)	
7 (4 + 3)	3 (9)	3 (9)	2 (8)	
>8	1 (3)	2 (6)	2 (8)	
Race/Ethnicity (%)				
Asian	0 (0)	1 (3)	3 (12)	0.14
Black	6 (18)	5 (15)	6 (23)	
Hispanic	3 (9)	1 (3)	4 (15)	
White	23 (70)	27 (80)	13 (50)	
Other	1 (3)	0 (0)	0 (0)	
Serum PSA (ng/mL)	9.9 ± 8.5	9.6 ± 5.2	9.2 ± 4.3	0.93

[a]green tea (GT), black tea (BT), body mass index (BMI), prostate-specific antigen (PSA)

(Henning. et al. 2015 Prostate 75:550-559)





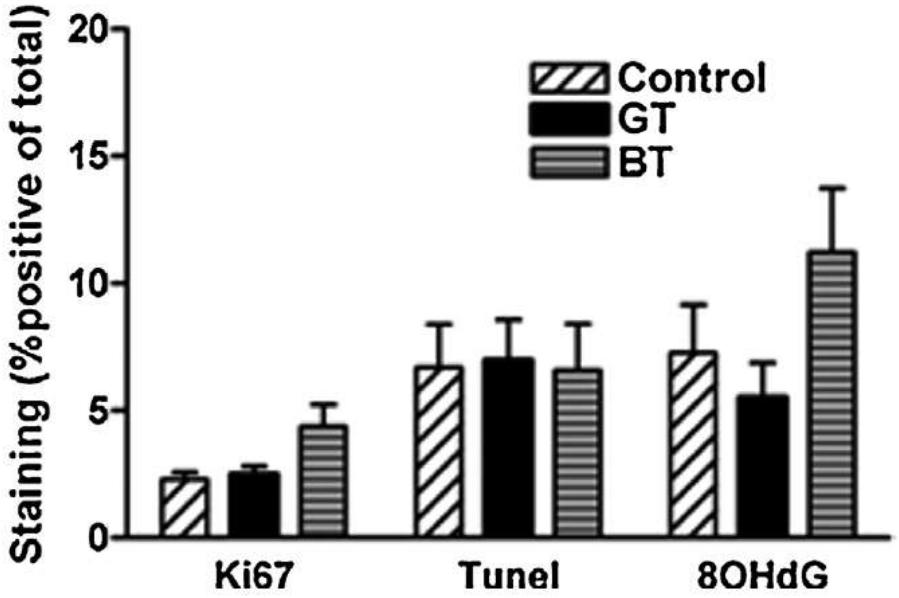


Fig. 1. Immunostaining of (A) Ki67, TUNEL and 8OHdG; (B) Bcl-2 and Bax; (C) nuclear and cytoplasmic NFκB in radical prostatectomy malignant epithelium from men consuming GT (29), BT (24) or water (30); mean ± std; $^{*}P < 0.05$.

(Henning. et al. 2015 Prostate 75:550-559)

TABLE III. Prostate Specific Antigen Concentrations in Serum Collected from Men Consuming GT, BT or Water Control Collected at Baseline and on the Morning of Radical Prostatectomy (Post-Intervention)

	Serum PSA (ng/mL)[a]		
	Water	GT	BT
PSA baseline	9.9 ± 8.5	9.6 ± 5.2	9.2 ± 4.3
PSA post-intervention	10.0 ± 9.0	$8.4 \pm 4.3^{*}$	9.6 ± 6.0

Data are presented as mean $\pm$ std; n = 30 (control), 30 (GT) and 23 (BT).

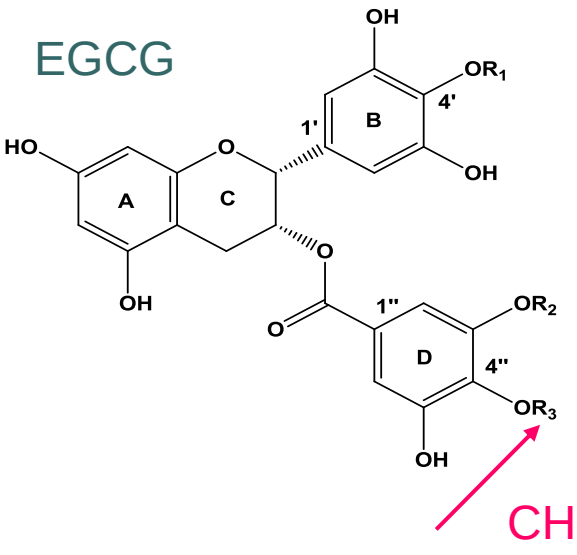
*PSA changes from pre to post were compared between the 3 groups using Analysis of Variance with pairwise contrasts, $P < 0.05$.

[a]green tea (GT), black tea (BT), prostate specific antigen (PSA).

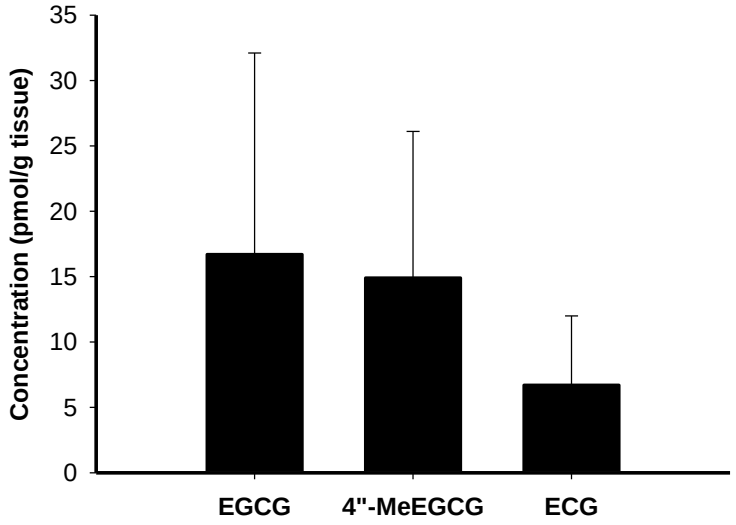
(Henning. et al. 2015 Prostate 75:550-559)

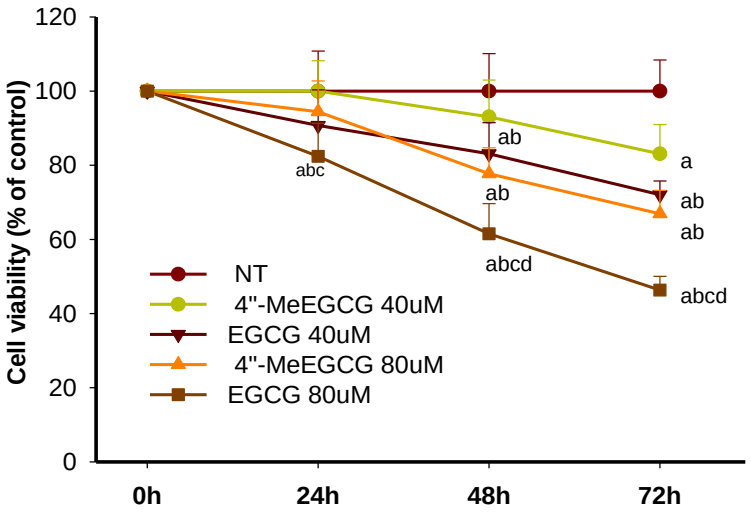
Limitations of GT in chemoprevention

- Low bioavailability of GT polyphenols
- Extensively methylation in vivo



Catechol-O-methyltransferase (COMT)

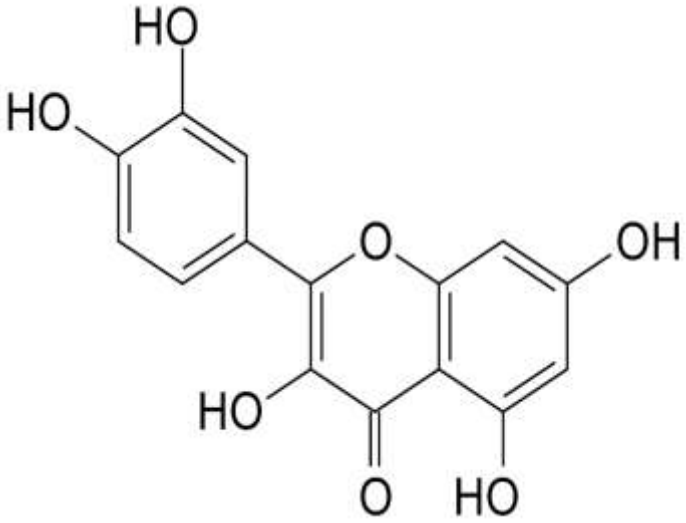




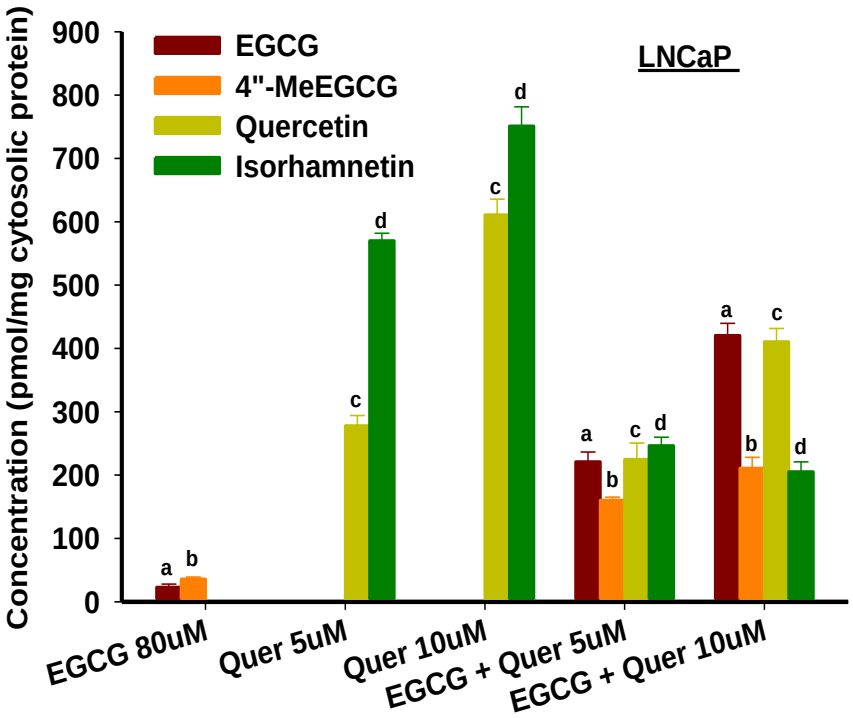
(Wang P, et al. 2010 Cancer Prev Res 3(8):985-93)

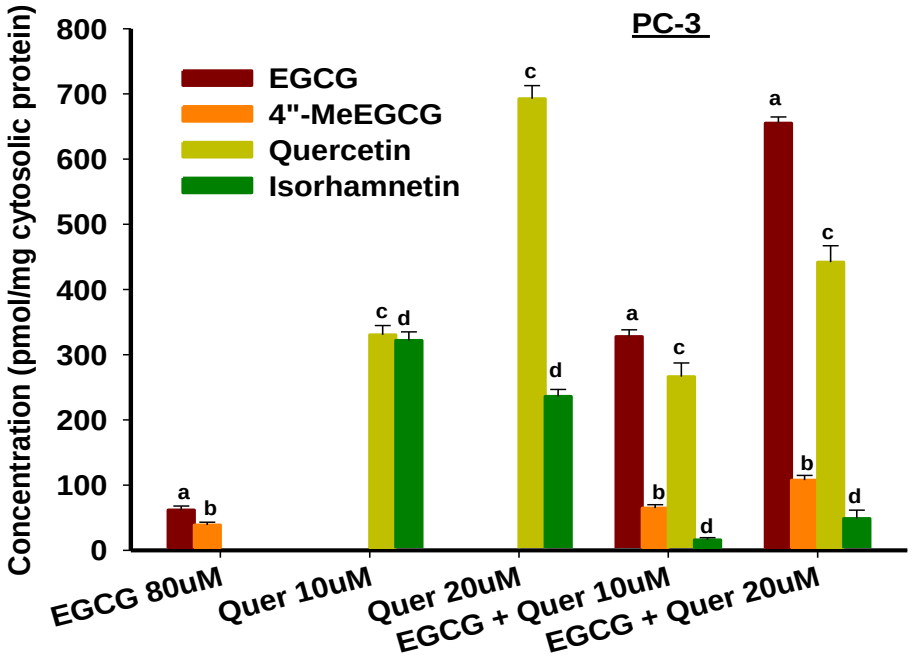
Quercetin (Q)

- A flavonoid commonly found in fruits and vegetables - red onions, apples, broccoli, berries, and tea
- A natural inhibitor of catechol-*O*-methyltransferase (COMT) and multidrug resistance-related proteins (MRPs)



Quercetin in combination with EGCG in vitro – cellular absorption

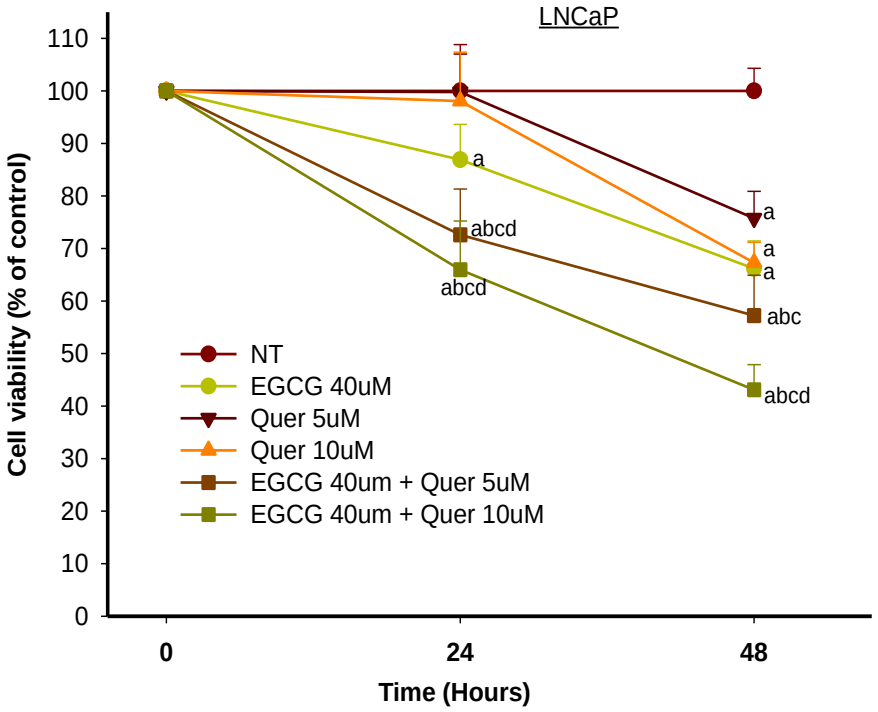


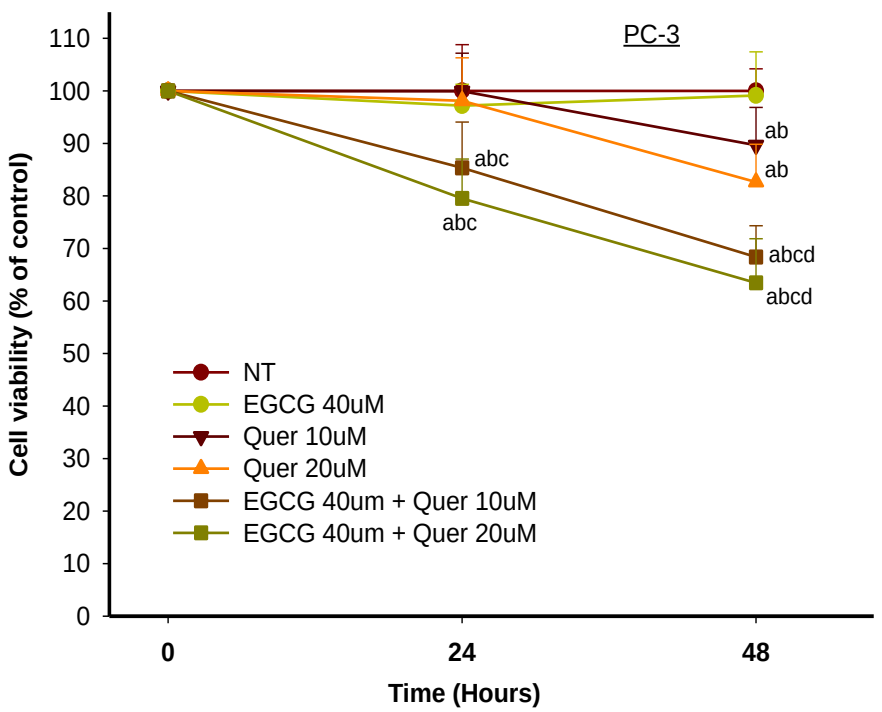


The groups with the same superscript letter represent significant difference between groups ($P<0.05$)

(Wang P, et al. 2012 Nutr Cancer 64(4): 580-587)

Quercetin in combination with EGCG in vitro – Antiproliferative effect

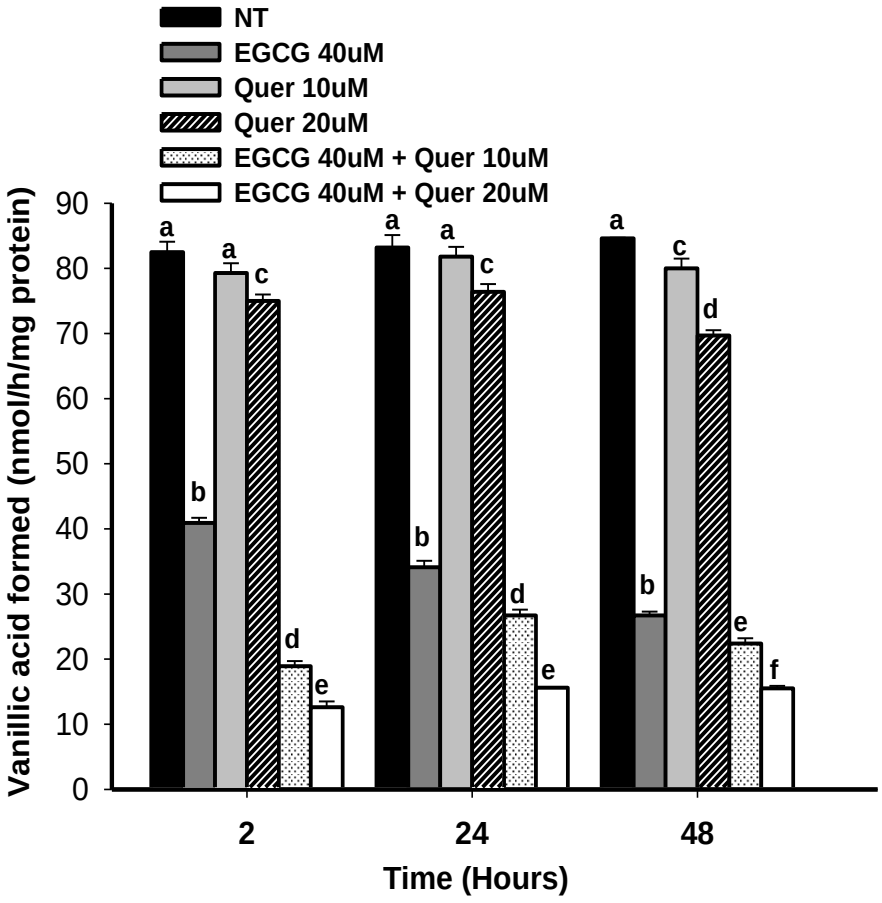


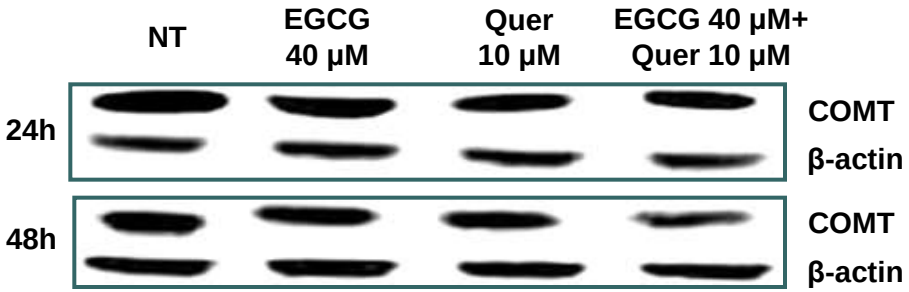


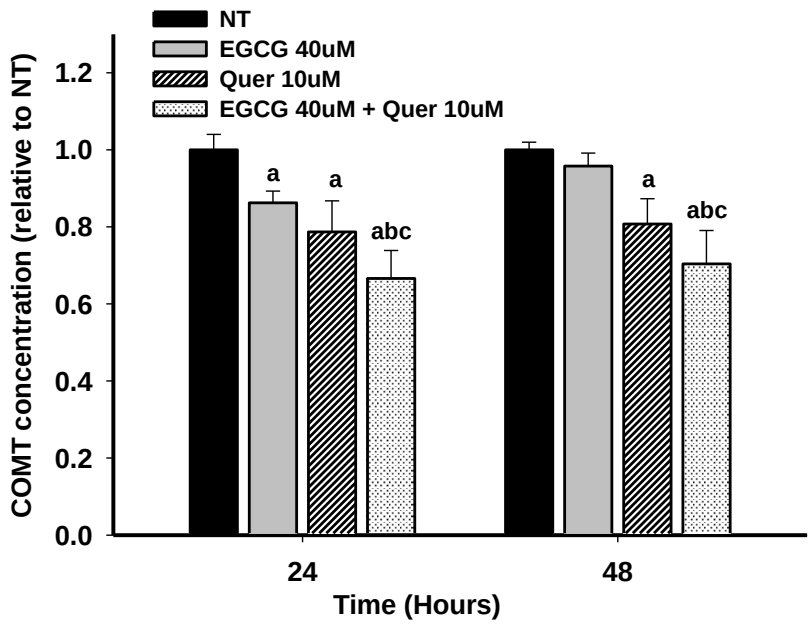
Compared to – a, control (NT); b, EGCG; c, Q 5umol/L; d, Q 10umol/L, $p<0.05$

(Wang P, et al. 2012 Nutr Cancer 64(4): 580-587)

Quercetin in combination with EGCG in vitro – COMT inhibition

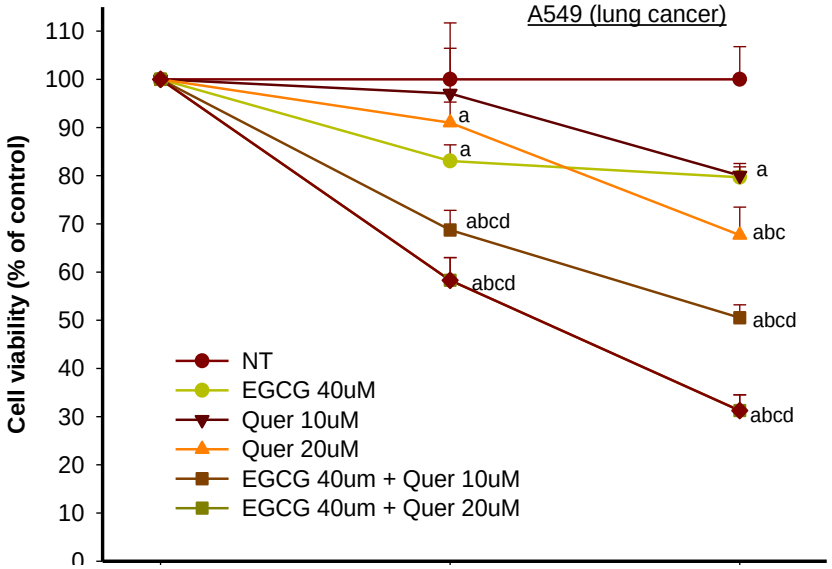


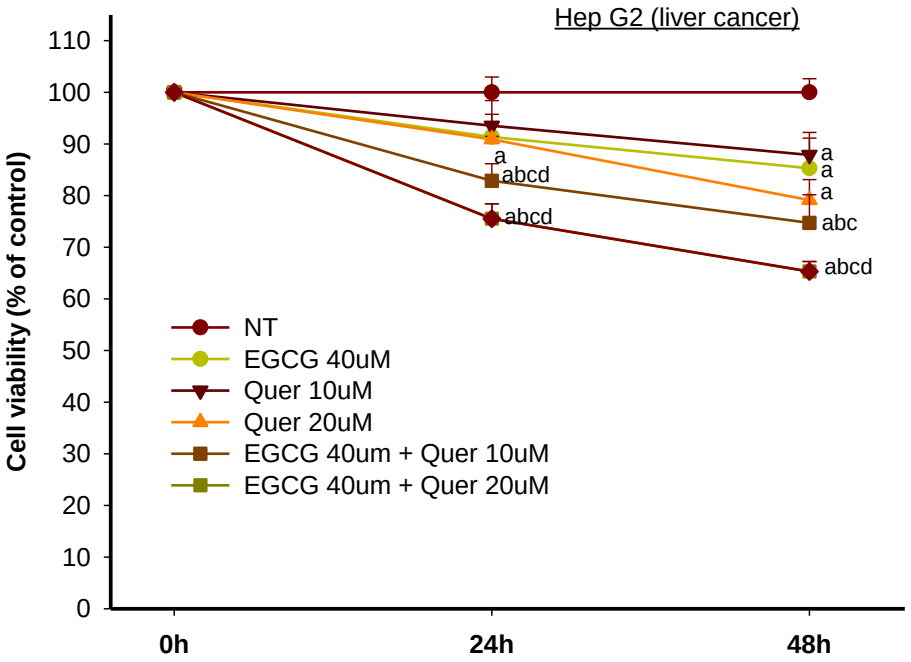


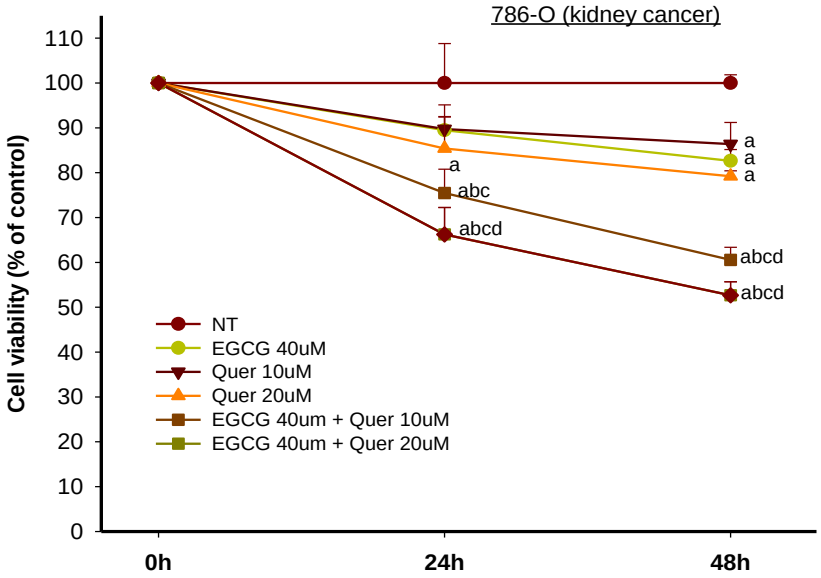


(Wang P, et al. 2012 Nutr Cancer 64(4): 580-587)

Increased anti-proliferative effect by EGCG + Q in lung, liver and kidney cancer cells

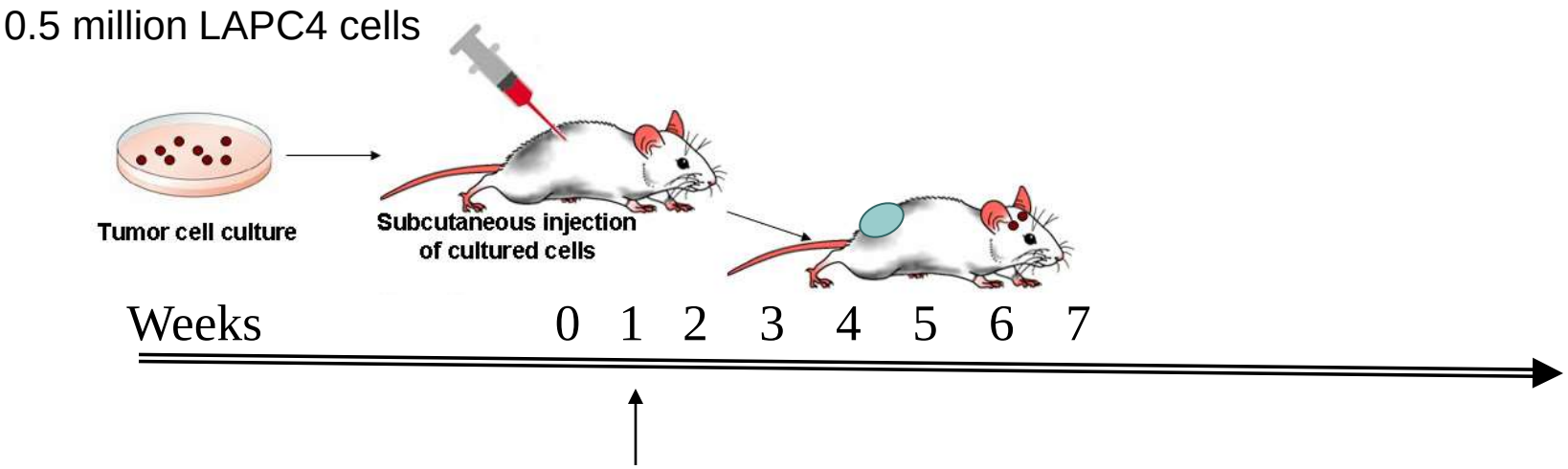






(Wang P, et al. 2012 Food Funct.3(6):635-42)

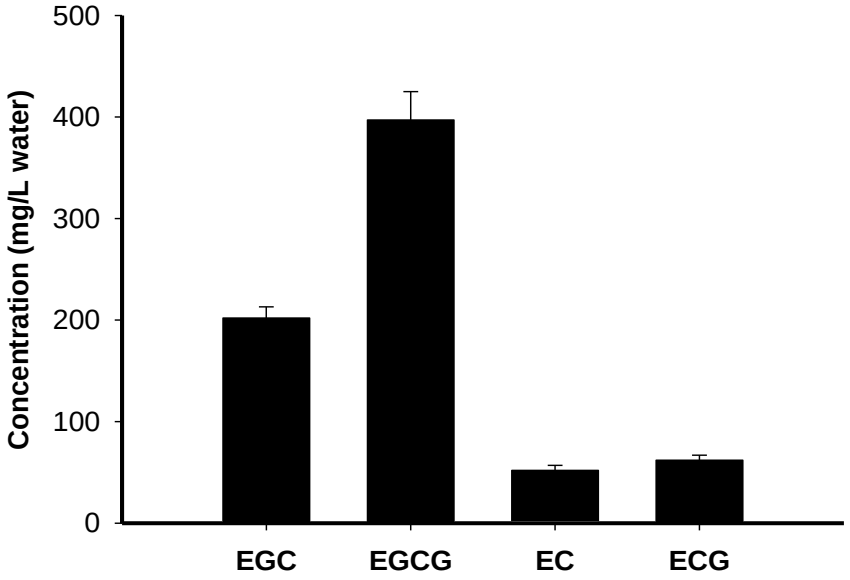
Xenograft SCID mouse model



When tumor was palpable - start of intervention

Quercetin in combination with GT in SCID mice

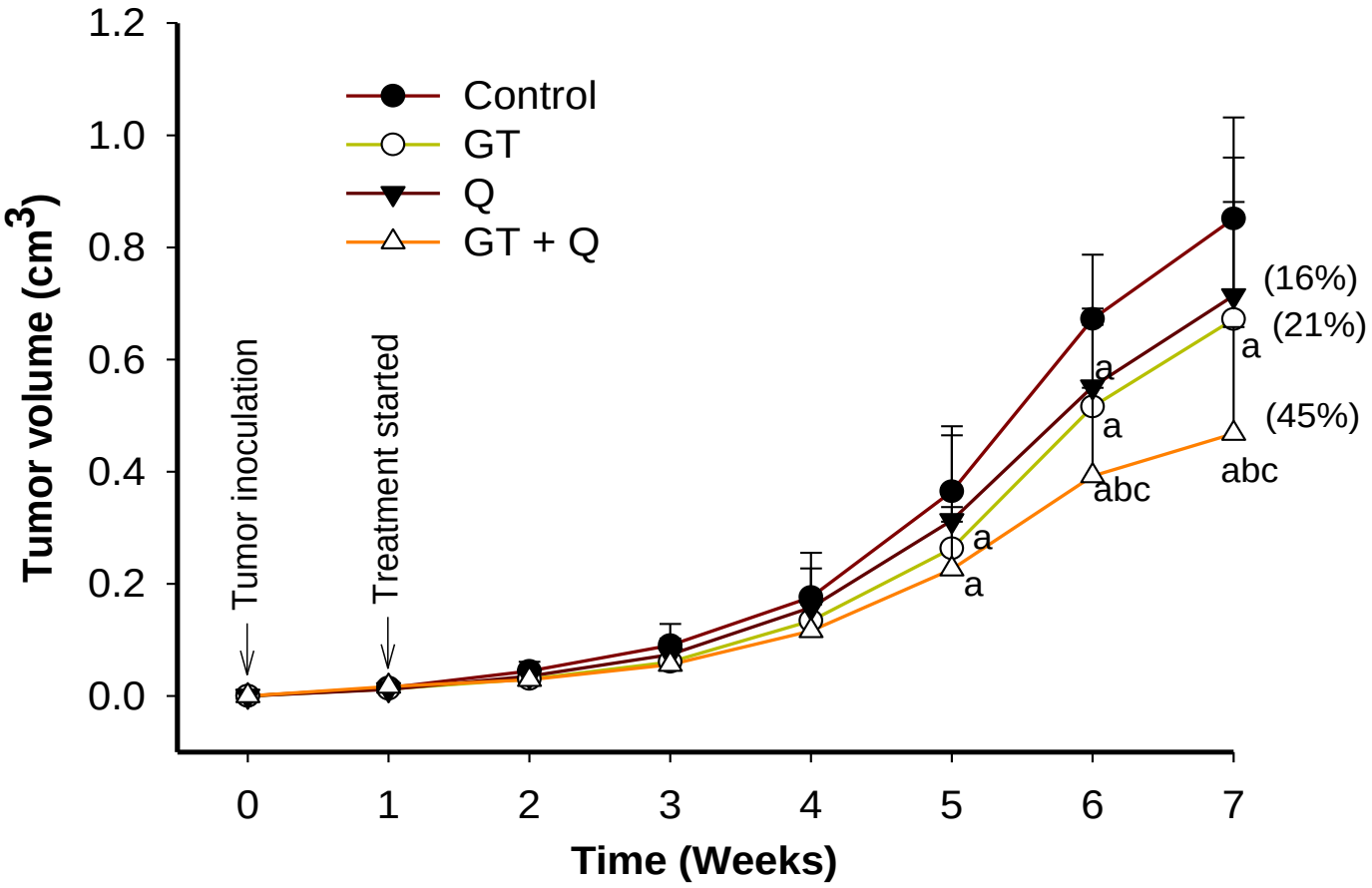
- GT (Celestial Seasonings, Boulder, CO): 1 tea bag brewed in 240 ml boiling water for 5min; 0.07% GT polyphenols



- Q (Sigma-Aldrich): 0.4% in diet

  AIN 93G+Quercetin

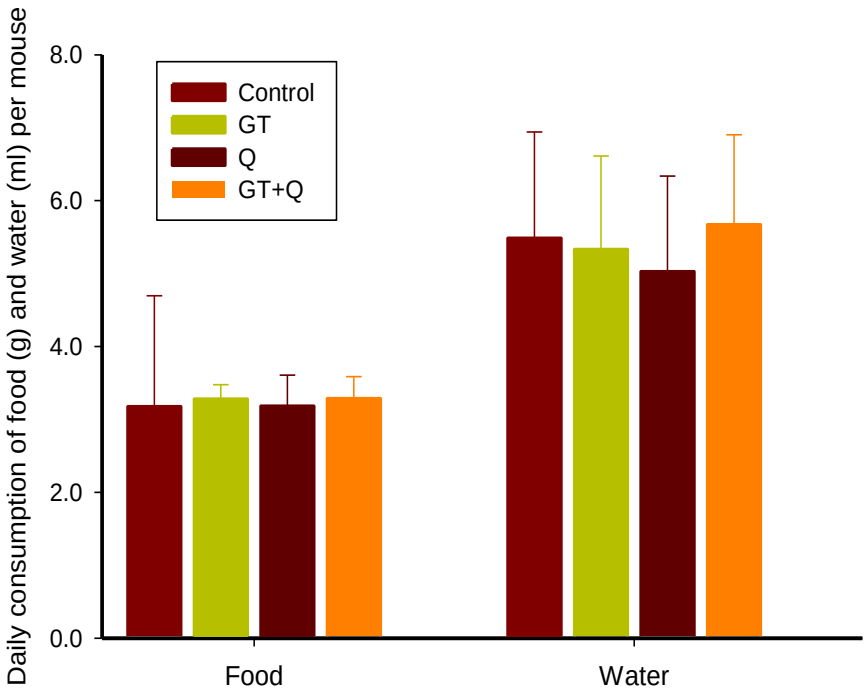
Xenograft tumor growth

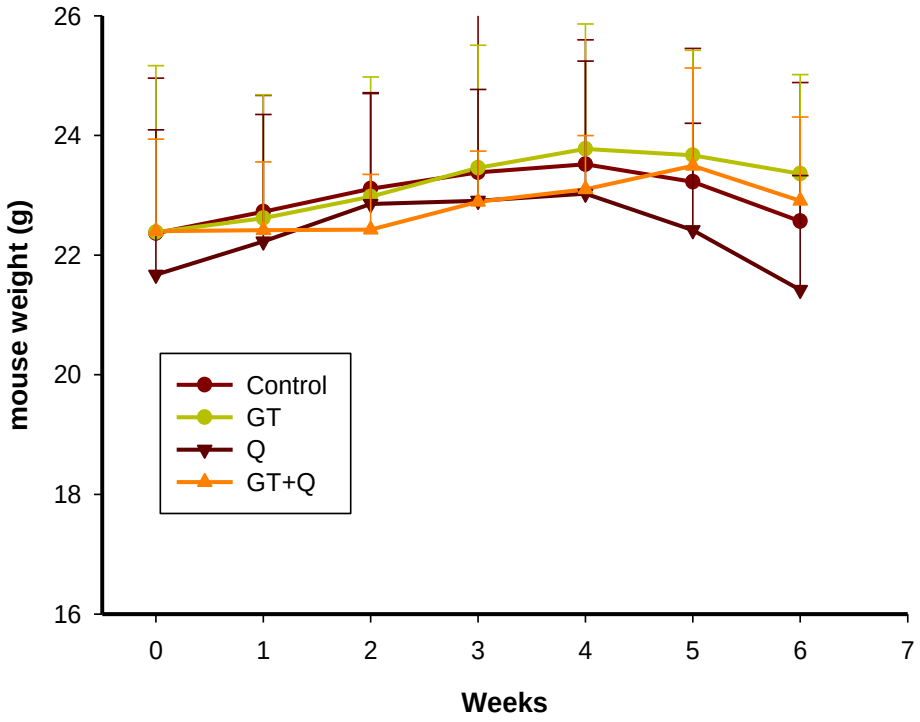


Compared to – a, control group; b, Q group; c, GT group, $p<0.05$

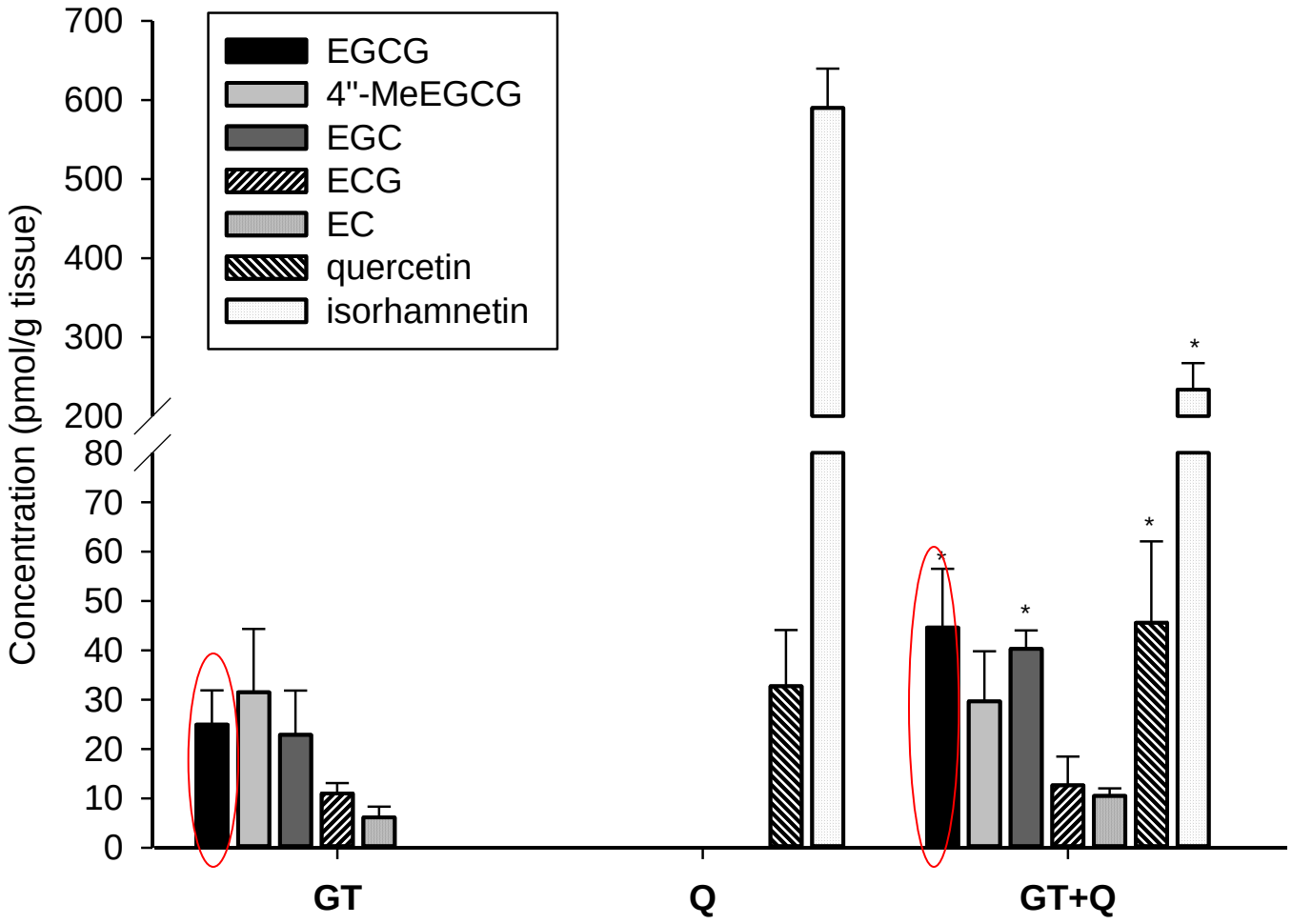
(Wang P, et al. 2014 J Nutr Biochem 25(1):73-80)

Food and water consumption and body weight



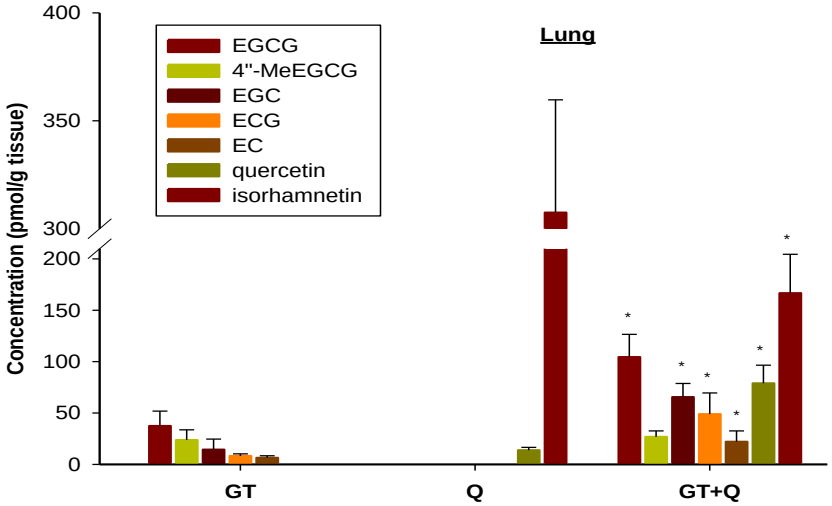


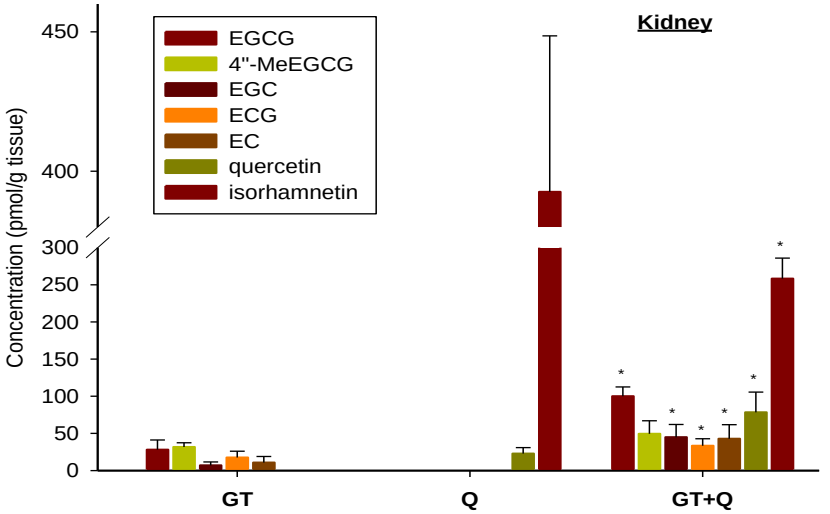
GT+Q increased the bioavailability and decreased methylation of GT polyphenols in tumor tissues

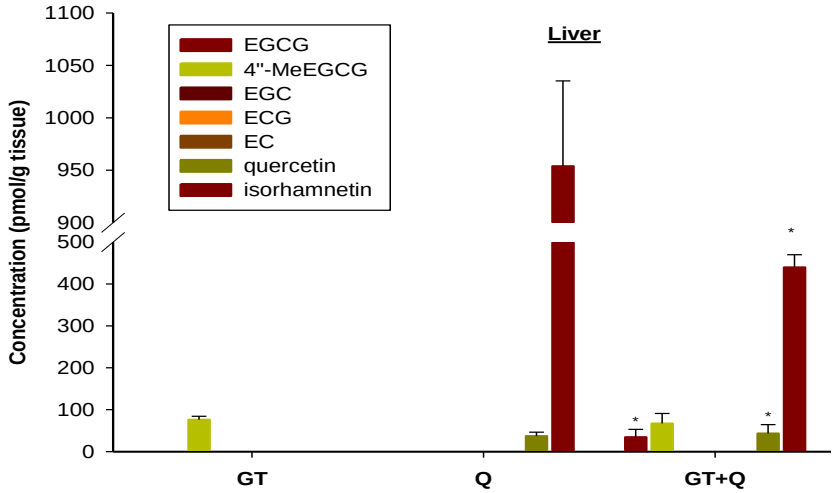


(Wang P, et al. 2014 J Nutr Biochem 25(1):73-80)

GT+Q increased the bioavailability and decreased methylation of GTPs in other tissues



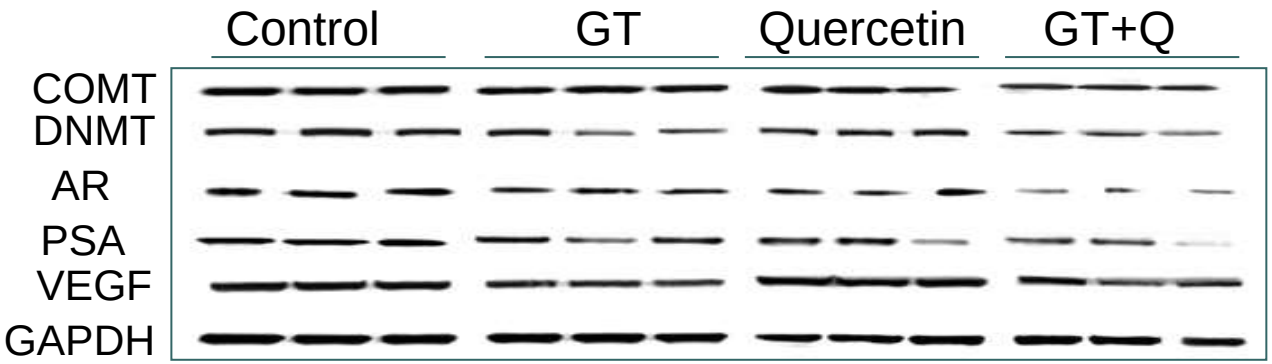


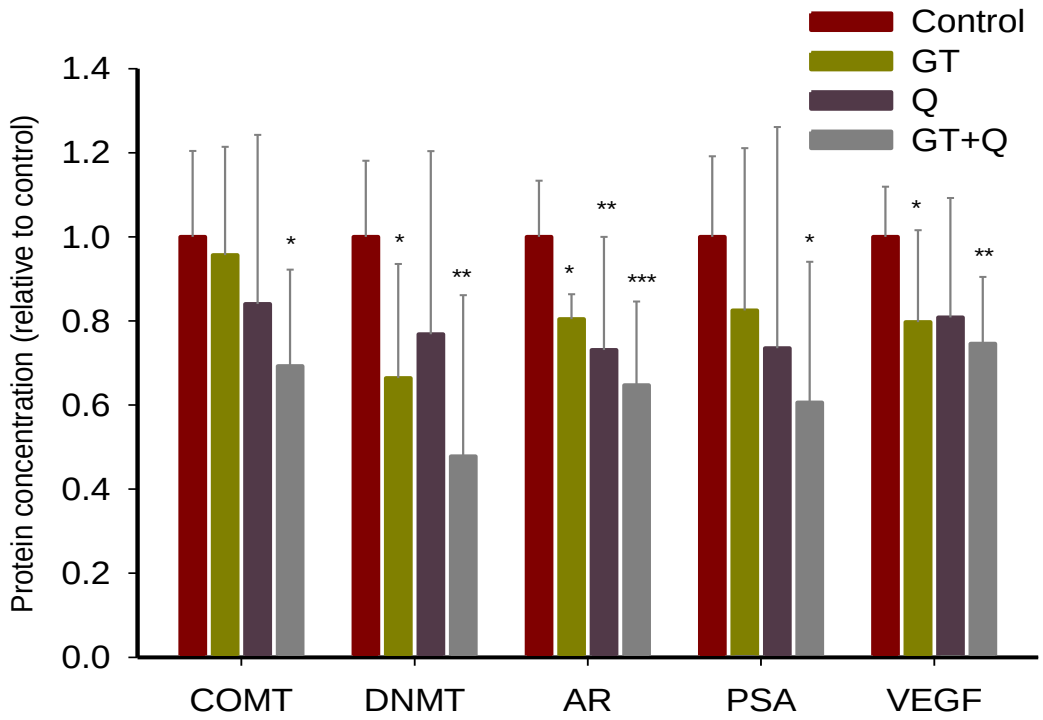


* compared to individual treatment, $p<0.05$

(Wang P, et al. 2012 Food & Function 3: 635-642)

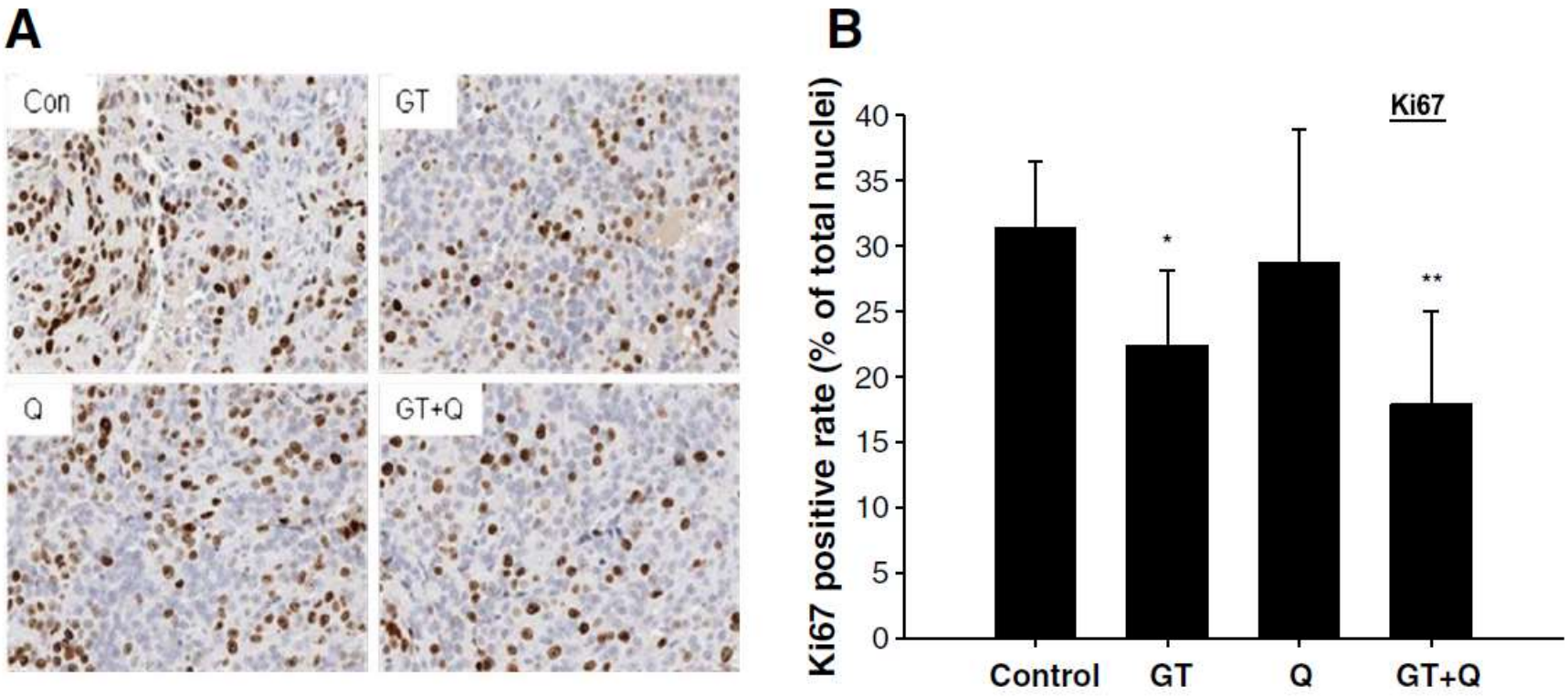
Modulation of protein marker expression





(Wang P, et al. 2014 J Nutr Biochem 25(1):73-80)

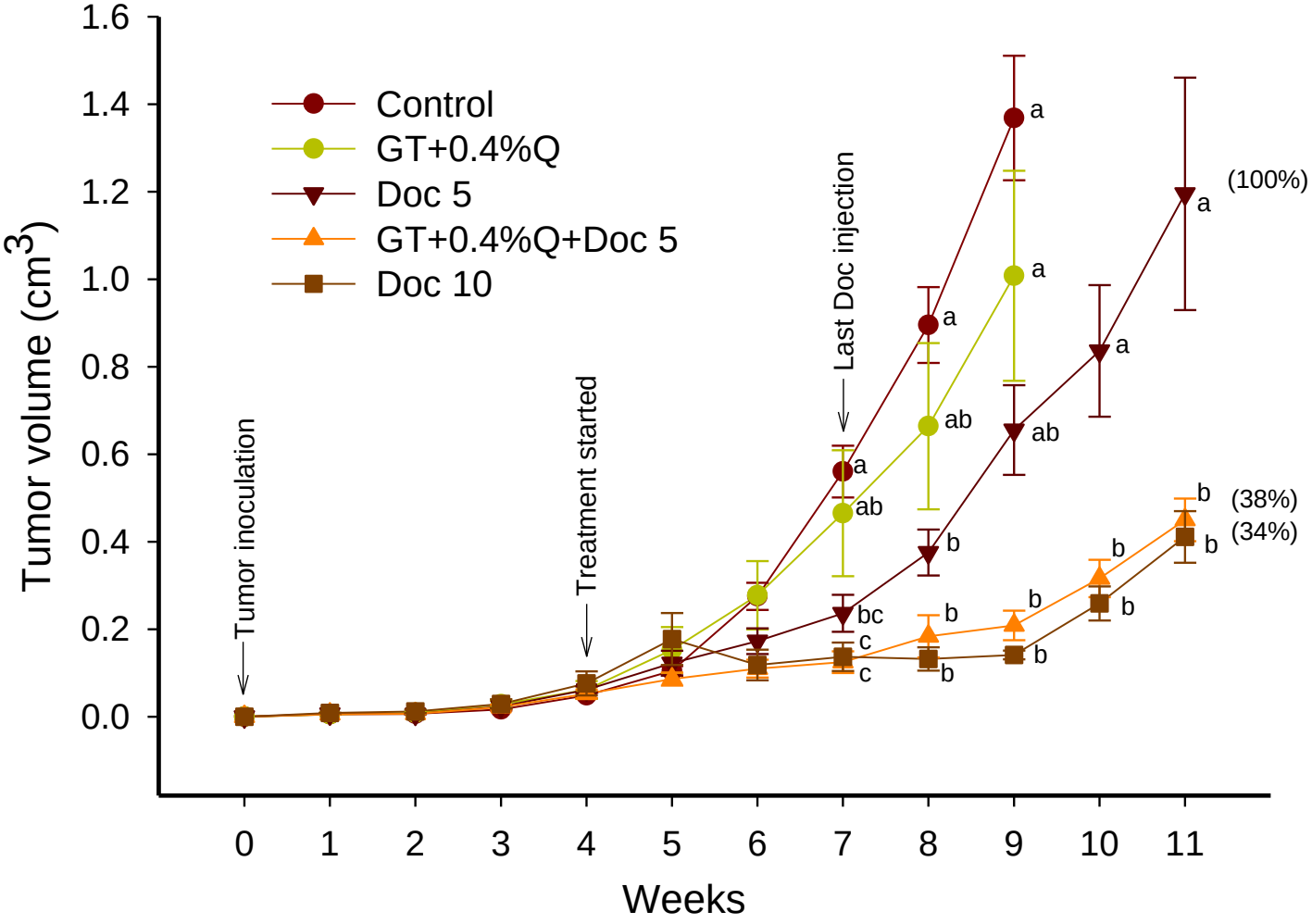
Inhibition of proliferation marker-Ki67



(Wang P, et al. 2014 J Nutr Biochem 25(1):73-80)

GT+Q in combination with drugs for chemotherapy of advanced prostate cancer

GT+Q+Docetaxel: Enhanced inhibition of PC-3 tumor growth



Data are presented as mean±SE. Different letters at each time point indicate statistically significant difference between groups, p<0.05 (manuscript submitted)

Summary and Conclusion

- Quercetin in combination with GT significantly enhances the anti-carcinogenic effect in vitro and in vivo

- The combined effect was associated with an increased bioavailability and decreased methylation of GT polyphenols

- These results warrant future studies to confirm the synergistic effect of the combination of GT and quercetin in humans

- In addition, this combination may improve clinical application in treatment of advanced prostate cancer by sensitizing tumor cells to chemotherapy

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