

Antioxidants and Cancer Therapy II: Quick Reference Guide

Davis W. Lamson, MS, ND, Matthew S. Brignall, ND

Abstract

The previous lengthy review concerning the effects of antioxidant compounds used concurrently with radiotherapy and chemotherapy has been reduced to a reference guide. There are only three presently known examples in which any agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy *in vivo*. The vast majority of both *in vivo* and *in vitro* studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action. (*Altern Med Rev* 2000;5(2):152-163)

Introduction

This guide is meant to be a companion to the previous review on effects of antioxidant supplementation during cancer therapy.¹ Widespread use of antioxidant compounds makes this an area of increasing interest to oncologists as well as other physicians; hence, the attempt to reduce the findings of a lengthy report to a manageable guide.

Reducing complicated interactions to a single sentence can be an oversimplification. In many instances the effect of an antioxidant compound with a certain therapeutic agent may be specific to a particular tumor type, or may vary with dosage of both antioxidant and chemotherapy. This guide is best used as a means of quickly identifying which antioxidants are likely to be indicated or contraindicated with a particular therapeutic agent. Please refer either to the earlier review (*Altern Med Rev* 1999;4(5):304-329) or the original research reports for more information on these interactions.

Many of these interactions have been studied only *in vitro*. While an *in vitro* result is often a predictor of *in vivo* response, this is not always the case. The interaction between the bioflavonoid tangeretin and tamoxifen is a good example of the risk in placing too much emphasis on *in vitro* evidence. Tangeretin was found *in vitro* to act synergistically with tamoxifen; but *in vivo* tangeretin completely reversed the inhibitory action of the drug on experimental mammary tumors.² The authors wish to emphasize that combinations not studied *in vivo* risk potential adverse reactions and should be monitored closely or avoided altogether. Similarly, it must be assumed that any antioxidant found to reduce *in vivo* toxicity of cancer therapy on healthy tissue has the potential to decrease effectiveness of the chemotherapy unless this was specifically studied. The studies reporting reduced toxicity to healthy tissue of a therapeutic agent with unknown effects on treatment outcomes are only reported if the reduction was noted in human studies. The following tables summarize the effect of various antioxidants when combined with specific chemotherapeutic agents or radiation.

Davis W. Lamson, MS, ND
Private practice, Tahoma Clinic- Kent, WA. Coordinator of Oncology, Bastyr University- Kenmore, WA. Correspondence Address: 9803 17th Ave. NE, Seattle, WA. 98115.

Matthew S. Brignall, ND
1999 graduate, Bastyr University. Currently doing a research fellowship at Tahoma Clinic in Kent, WA.
e-mail: mattandmolly@w-link.net

Table 1: Alkylating Agents: cyclophosphamide (CYC), ifosfamide (IFO), busulphan (BUS), melphan (MEL)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A		Increased therapeutic effect (CYC) ⁵		
Beta carotene		Increased therapeutic effect (CYC) ^{5,18}		
Vitamin C		Increased therapeutic effect (CYC) ¹⁹		
Vitamin E		Increased therapeutic effect (CYC) ²⁰		
Selenium			Decreased toxicity,* no change in cytotoxic effect (MEL) ²¹	*with selenium, zinc, and copper
Coenzyme Q10	Decreased toxicity (CYC+DOC+5FU) ^{*23}	Increased therapeutic effect (CYC+Coriolus versicolor or OK-432) ^{*22}		*Both studies used combined therapy
Melatonin		Reduced toxicity, no change in therapeutic effect (CYC) ²⁴		
N-acetylcysteine	Decreased toxicity (IFO) ^{28,29}	Decreased toxicity, no change in therapeutic effect (CYC) ^{25,26,27}		
Glutathione (GSH)	Reduced toxicity, possible increased therapeutic effect (CYS+CIS) ^{30,31}			
Quercetin		Increased therapeutic effect (BUS) ³²	Increased cytotoxic effect (BUS) ³²	

note: "decreased toxicity" refers to effect on healthy tissue.

Table 2: Antibiotic-type Agents: doxorubicin (adriamycin) (DOX), bleomycin (BLE), epirubicin (EPI), daunorubicin (DAU)

Nutrient	Human Studies	Animal Studies	In vitro studies	Comments
Vitamin A	Decreased toxicity; increased survival (DOX+BLE+5FU+MT) ³⁵		Increased cell differentiation; ³³ cells less ³³ or more sensitive ³⁴ to DOX	
Beta carotene		Increased therapeutic effect (DOX) ¹⁸		
Vitamin C		Increased therapeutic effect; decreased toxicity (DOX) ^{19,36}	Increased cytotoxic effect in human breast CA cells (DOX) ³⁷	Another <i>in vitro</i> study using ascorbic acid 2-phosphate found no change in drug-sensitive cells and decreased effect in resistant lines (DOX) ³⁸
Vitamin E		Decreased toxicity and possible increased therapeutic effect (DOX) ³⁷	Increased cytotoxic effect (DOX) ⁴⁰⁻⁴²	
Selenium		Decreased toxicity (DOX); ^{43,44} increased therapeutic effect* (DOX) ⁴⁵	No reduction of cytotoxic effect (DOX) ⁵⁰	* in drug-resistant tumors
Coenzyme Q10	Decreased toxicity (DOX) ⁴⁷⁻⁴⁹	Decreased toxicity; no change in therapeutic effect (DOX) ⁵⁰		
Melatonin	Decreased toxicity (EPI) ⁵¹			
N-acetylcysteine	No decrease of therapeutic effect; no reduction of toxicity (DOX) ^{52,53}	Decrease* or no change in therapeutic effect; decreased toxicity (DOX) ^{54,55}		*First of three <i>in vivo</i> studies showing reduced therapeutic effect of chemotherapy with an antioxidant
Glutathione (GSH)	Effective results with GSH plus EPI+CIS+5FU		Increased resistance to drug* (DOX) ⁵⁶	*In cell lines with the highest concentrations of glutathione
Green tea		Increased therapeutic effect* (DOX) ^{58,59}		*In drug-resistant tumors
Quercetin			Increased cytotoxic effect* (DOX, DAU) ⁶⁰⁻⁶²	* drug-resistant cell lines

note: "decreased toxicity" refers to effect on healthy tissue.

Table 3: Antimetabolites: 5-fluorouracil (5-FU), methotrexate (MT)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Decreased toxicity; increased survival (DOX+BLE+5FU+MT) ³⁵	Decreased toxicity; no change in therapeutic effect (MT) ⁸⁴		
Beta carotene		Decreased therapeutic effect in fibrosarcoma; no change in squamous cell carcinoma (5FU) ^{18*}		*Second of three cited <i>in vivo</i> studies showing reduced therapeutic effect of chemotherapy with an antioxidant
Vitamin C		Increased therapeutic effect (5FU) ¹⁹		
Vitamin E		Increased therapeutic effect (MT) ⁴⁰	Increased cytotoxic effect (MT) ⁴²	
Selenium		Increased therapeutic effect (MT) ⁸⁵		
Coenzyme Q10	Decreased toxicity (CYC+DOX+5FU) ²³			
Melatonin			5FU decreased cytostatic effect of melatonin; effect of combined tx greater than effect of 5FU alone ⁸⁶	
Glutathione	Effective results with GSH plus EPI+CIS+5FU ⁵⁷	Decreased toxicity; no reduction in therapeutic effect (5FU) ^{87,88}		

note: "decreased toxicity" refers to effect on healthy tissue.

Table 4: Platinum Compounds: cisplatin (CIS)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect (CIS) ³⁴		Increased cytotoxic effect (CIS); ³⁴ no change in therapeutic effect (CIS+ETO) ⁶⁴	
Vitamin C			Increased cytotoxic effect (CIS) ³⁷	
Vitamin E		Increased therapeutic effect (CIS) ⁷¹		
Combination Therapy (Beta carotene, A*, C, E)			Increased cytotoxic effect (CIS+TAM+ decarbazine+ interferon) ⁷⁰	*13-cis-retinoic acid
Selenium	Decreased toxicity (CIS) ⁷⁵	Increase or no change in therapeutic effect, decreased toxicity (CIS) ^{72,73,74}		
Melatonin	Increased survival, decreased toxicity (CIS+ETO) ^{67,68*}			*Not significant at high chemotherapy doses
N-acetylcysteine	Possible decrease in toxicity (CIS) ^{76,77}		Decreased cytotoxic effect (CIS) ⁷⁸	
Glutathione	Slight increase or no change in therapeutic effect, decreased toxicity (CIS+CYC); ^{30,31} (CIS); ^{79,80,81}			
Genistein			Increased cytotoxic effect (CIS) ^{*82}	*Against a drug-resistant cell line.
Quercetin		Increased therapeutic effect (CIS) ^{32,83}	Increased cytotoxic effect (CIS) ^{32,83}	

note: "decreased toxicity" refers to effect on healthy tissue.

Table 5: Radiotherapy

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect, decreased toxicity ⁴	Increased therapeutic effect, decreased toxicity ⁵	Increased therapeutic effect, decreased toxicity ³	
Beta carotene	Decreased toxicity, no change in therapeutic effect ⁶	Increased therapeutic effect, decreased toxicity ⁵		
Vitamin C	Increased therapeutic effect, decreased toxicity ⁷	Increased therapeutic effect; ^{8,9,10} decreased toxicity, no change in therapeutic effect ¹¹		
Vitamin E		Increased therapeutic effect ^{*12}		*Doses below 500 mg/kg
Selenium	Decreased toxicity ^{*13}			*Influence on therapeutic effect unknown
Coenzyme Q10*		No change in therapeutic effect ¹⁴		Doses below 10 mg/kg
Melatonin	increased therapeutic effect, decreased toxicity ¹⁵			
N-acetylcysteine	No change in therapeutic effect or toxicity ¹⁶			
Glutathione	Decreased toxicity, no change in therapeutic effect ¹⁷			

note: "decreased toxicity" refers to effect on healthy tissue.

Conclusion

There are only three presently known examples in which an agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy *in vivo*. The vast majority of both *in vivo* and *in vitro* studies have shown enhanced effectiveness of

standard cancer therapies or a neutral effect on drug action.

The authors wish to thank Richard Russell and the Smiling Dog Foundation for financial support of this project and Bastyr University for its administration.

Table 6: Hormonal Therapies: tamoxifen (TAM)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect* (TAM) ^{90,91}	No change in therapeutic effect (TAM) ⁸⁹		*In one study vitamin A enhanced response to TAM in cases where tumor had progressed with TAM alone
Vitamin C			Increased cytotoxic effect (TAM) ⁷⁰	
Vitamin E			Increase or no change in cytotoxic effect (TAM) ^{*92}	*Tocotrienols had greater effect than tocopherol
Mixed: Vitamins C and E, beta carotene, and 13-cis-retinoic acid			Increased cytotoxic effect (CIS+TAM+ decarbazine+ interferon) ⁷⁰	
Melatonin	Increased therapeutic effect (TAM) ⁹³			
Tangeretin		Decreased therapeutic effect (TAM) ^{2*}		*Third of three <i>in vivo</i> studies showing reduced therapeutic effect with an antioxidant

References

1. Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern Med Rev* 1999;4:303-328.
2. Bracke ME, Depypere HT, Boterberg T, et al. Influence of tangeretin on tamoxifen's therapeutic benefit in mammary cancer. *JNCI* 1999;91:354-359.
3. Duchesne GM, Hutchinson LK. Reversible changes in radiation response induced by all-trans retinoic acid. *Int J Radiat Oncol Biol Phys* 1995;33:875-880.
4. Park TK, Lee JP, Kim SN, et al. Interferon-alpha 2a, 13-cis-retinoic acid and radiotherapy for locally advanced carcinoma of the cervix: a pilot study. *Eur J Gynaecol Oncol* 1998;19:35-38.
5. Seifter E, Rettura G, Padawer J. Vitamin A and beta-carotene as adjunctive therapy to tumour excision, radiation therapy and chemotherapy. In: Prasad K, ed. *Vitamins Nutrition and Cancer*. New York: Karger Press; 1984:2-19.
6. Mills EED. The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. *Br J Cancer* 1988;57:416-417.

Table 7: Plant Alkaloids: etoposide (ETO), vincristine (VIN), paclitaxel (TAX)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	No change in therapeutic effect, (ETO+CIS) ⁶⁴		Increased cytotoxic effect (ETO) ⁶³ ; Increased cytotoxic effect (VIN) ⁶⁵	
Beta-carotene		Increased therapeutic effect (ETO) ¹⁸		
Vitamin C		Increased therapeutic effect (VIN) ¹⁹	Increased cytotoxic effect (TAX); ³⁷ Increased cytotoxic effect (VIN)* ⁶⁶	* In drug-resistant cell lines
Vitamin E			Increased cytotoxic effect (VIN) ⁴²	
Melatonin	Increased survival, decreased toxicity (ETO+CIS) ^{67, 68*}			*Results not significant at high chemotherapy doses (ETO+carboplatin)

note: "decreased toxicity" refers to effect on healthy tissue.

- | | |
|---|--|
| <ol style="list-style-type: none"> 7. Hanck AB. Vitamin C and cancer. <i>Prog Clin Biol Res</i> 1988;259:307-320. 8. Taper HS, Keyeux A, Roberfroid M. Potentiation of radiotherapy by nontoxic pretreatment with combined vitamins C and K3 in mice bearing solid transplantable tumor. <i>Anticancer Res</i> 1996;16:499-504. 9. Okunieff P, Suit HD. Toxicity, radiation sensitivity modification, and combined drug effects of ascorbic acid with misonidazole in vivo on FSall murine fibrosarcomas. <i>JNCI</i> 1987;79:377-381. 10. Tewfik FA, Tewfik HH, Riley EF. The influence of ascorbic acid on the growth of solid tumors in mice and on tumor control by X-irradiation. <i>Int J Vitam Nutr Res Suppl</i> 1982;23:257-263. 11. Okunieff P. Interactions between ascorbic acid and the radiation of bone marrow, skin, and tumor. <i>Am J Clin Nutr</i> 1991;54:1281S-1283S. | <ol style="list-style-type: none"> 12. Kagreud A, Peterson HI. Tocopherol in irradiation of experimental neoplasms. <i>Acta Radiol Oncol</i> 1981;20:97-100. 13. Hehr T, Hoffmann W, Bamberg M. Role of sodium selenite as an adjuvant in radiotherapy of rectal carcinoma. <i>Med Klin</i> 1997;92:48-49. [Article in German] 14. Lund EL, Quistorff B, Spang-Thomsen M, Kristjansen PEG. Effect of radiation therapy on small-cell lung cancer is reduced by ubiquinone intake. <i>Folia Microbiol</i> 1998;43:505-506. 15. Lissoni P, Meregalli S, Nosetto L, et al. Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. <i>Oncology</i> 1996;53:43-46. |
|---|--|

16. Maasilta P, Holsti LR, Blomqvist P, et al. N-acetylcysteine in combination with radiotherapy in the treatment of non-small cell lung cancer: a feasibility study. *Radiother Oncol* 1992;25:192-195.
17. DeMaria D, Falchi AM, Venturino P. Adjuvant radiotherapy of the pelvis with or without reduced glutathione: a randomized trial in patients operated on for endometrial cancer. *Tumori* 1992;78:374-376.
18. Teicher BA, Schwartz JL, Holden SA, et al. In vivo modulation of several anticancer agents by beta-carotene. *Cancer Chemother Pharmacol* 1994;34:235-241.
19. Taper HS, de Gerlache J, Lans M, et al. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. *Int J Cancer* 1987;40:575-579.
20. Vinitha R, Thangaraju M, Sachdanandam P. Effect of administering cyclophosphamide and vitamin E on the levels of tumor-marker enzymes in rats with experimentally induced fibrosarcoma. *Jpn J Med Sci Biol* 1995;48:145-156.
21. Tobey RA, Tesmer JG. Differential response of cultured human normal and tumor cells to trace element-induced resistance to the alkylating agent melphalan. *Cancer Res* 1985;45:2567-2571.
22. Kokawa T, Shiota K, Oda K, et al. Coenzyme Q10 in cancer chemotherapy—experimental studies on augmentation of the effects of masked compounds, especially in the combined chemotherapy with immunopotentiators. *Gan To Kagaku Ryoho* 1983;10:768-774. [Article in Japanese]
23. Takimoto M, Sakurai T, Kodama K, et al. Protective effect of CoQ 10 administration on cardiac toxicity in FAC therapy. *Gan To Kagaku Ryoho* 1982;9:116-121. [Article in Japanese]
24. Musatov SA, Rosenfeld SV, Togo EF, et al. The influence of melatonin on mutagenicity and antitumor action of cytostatic drugs in mice. *Vopr Onkol* 1997;43:623-627. [Article in Russian]
25. Levy L, Vredevoe DL. The effect of N-acetylcysteine on cyclophosphamide immunoregulation and antitumor activity. *Semin Oncol* 1983;10:7-16.
26. Harrison EF, Fuquay ME, Hunter HL. Effect of N-acetylcysteine on the antitumor activity of cyclophosphamide against Walker-256 carcinosarcoma in rats. *Semin Oncol* 1983;10:25-28.
27. Palermo MS, Olabuenaga SE, Giordano M, Isturiz MA. Immunomodulation exerted by cyclophosphamide is not interfered with by N-acetylcysteine. *Int J Immunopharmac* 1986;8:651-655.
28. Slavik M, Saiers JH. Phase I clinical study of acetylcysteine's preventing ifosfamide-induced hematuria. *Semin Oncol* 1983;10:62-65.
29. Holoye PY, Duelle J, Hansen RM, et al. Prophylaxis of ifosfamide toxicity with oral acetylcysteine. *Semin Oncol* 1983;10:66-71.
30. Di Re F, Bohm S, Oriana S, et al. High-dose cisplatin and cyclophosphamide with glutathione in the treatment of advanced ovarian cancer. *Ann Oncol* 1993;4:55-61.
31. Locatelli MC, D'Antonia A, Lablanca R, et al. A phase II study of combination chemotherapy in advanced ovarian carcinoma with cisplatin and cyclophosphamide plus reduced glutathione as potential protective agent against cisplatin toxicity. *Tumori* 1993;79:37-39.
32. Scambia G, Ranelletti FO, Panici PB, et al. Inhibitory effect of quercetin on primary ovarian and endometrial cancers and synergistic activity with cis-diamminedichloroplatinum(II). *Gynecol Oncol* 1992;45:13-19.
33. Doyle LA, Giangiulo D, Hussain A. Differentiation of human variant small cell lung cancer cell lines to a classic morphology by retinoic acid. *Cancer Res* 1989;49:6745-6751.
34. Adwankar M, Banerji A, Ghosh S. Differential response of retinoic acid pretreated human synovial sarcoma cell line to anticancer drugs. *Tumori* 1991;77:391-394.
35. Thatcher N, Blackledge G, Crowther D. Advanced recurrent squamous cell carcinoma of the head and neck. *Cancer* 1980;46:1324-1328.
36. Shimpo K, Nagatsu T, Yamada K, et al. Ascorbic acid and adriamycin toxicity. *Am J Clin Nutr* 1991;54:1298S-1301S.
37. Kurbacher CM, Wagner U, Kolster B, et al. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. *Cancer Lett* 1996;103:183-189.

38. Wells WW, Rocque PA, Xu DP. Ascorbic acid and cell survival of adriamycin resistant and sensitive MCF-7 breast tumor cells. *Free Rad Biol Med* 1995;18:699-708.
39. Myers CE, McGuire WP, Liss RH, et al. Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumor response. *Science* 1977;197:165-167.
40. Chinery R, Brockman JA, Peeler MO, et al. Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21 via C/EBP-beta. *Nat Med* 1997;3:1233-1241.
41. Perez Ripoll EA, Rama BN, Webber MM. Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro. *J Urol* 1986;136:529-531.
42. Prasad KN, Edwards-Prasad J, Ramanujam S, Sakamoto A. Vitamin E increases the growth inhibitory and differentiating effects of tumor therapeutic agents on neuroblastoma and glioma cells in culture. *Proc Soc Exp Biol Med* 1980;164:158-163.
43. Boucher F, Coudray C, Tirard V, et al. Oral selenium supplementation in rats reduces cardiac toxicity of adriamycin during ischemia and reperfusion. *Nutrition* 1995;11:708-711.
44. Coudray C, Hida H, Boucher F, et al. Modulation by selenium supplementation of lipid peroxidation induced by chronic administration of adriamycin in rats. *Nutrition* 1995;11:512-516.
45. Shallom J, Juvekar A, Chitnis M. Selenium (Se) cytotoxicity in drug sensitive and drug resistant murine tumour. *Cancer Biother* 1995;10:243-248.
46. Dimitrov NV, Hay MB, Siew S. Abrogation of adriamycin-induced cardiotoxicity by selenium in rabbits. *Am J Pathol* 1987;126:376-383.
47. Cortes EP, Gupta M, Chou C, et al. Adriamycin cardiotoxicity: early detection by systolic time interval and possible prevention by coenzyme Q10. *Cancer Treat Rep* 1978;62:887-891.
48. Iarussi D, Auricchio U, Agretto A, et al. Protective effect of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Molec Aspects Med* 1994;15:207-212.
49. Okuma K, Furuta I, Ota K. Protective effect of coenzyme Q10 in cardiotoxicity induced by adriamycin. *Gan To Kagaku Ryoho* 1984;11:502-508. [Article in Japanese]
50. Shaeffer J, El-Mahdi AM, Nichols RK. Coenzyme Q10 and adriamycin toxicity in mice. *Res Commun Chem Pathol Pharmacol* 1980;29:309-315.
51. Lissoni P, Tancini G, Paolorossi F, et al. Chemoneuroendocrine therapy of metastatic breast cancer with persistent thrombocytopenia with weekly low-dose epirubicin plus melatonin: a phase II study. *J Pineal Res* 1999;26:169-173.
52. Myers C, Bonow R, Palmeri S, et al. A randomized controlled trial assessing the prevention of doxorubicin cardiomyopathy by N-acetylcysteine. *Semin Oncol* 1983;10:53-55.
53. Unverferth DV, Jagadeesh JM, Unverferth BJ, et al. Attempt to prevent doxorubicin induced acute human myocardial morphologic damage with acetylcysteine. *JNCI* 1983;71:917-920.
54. Olson RD, Stroo WE, Boerth RC. Influence of N-acetylcysteine on the antitumor activity of doxorubicin. *Semin Oncol* 1983;10:29-34.
55. Schmitt-Graff A, Scheulen ME. Prevention of adriamycin cardiotoxicity by niacin, isocitrate, or N-acetylcysteine in mice. *Path Res Pract* 1986;181:168-174.
56. Zhang K, Yang EB, Wong KP, Mack P. GSH, GSH-related enzymes and GS-X pump in relation to sensitivity of human tumor cell lines to chlorambucil and adriamycin. *Int J Oncol* 1999;14:861-867.
57. Cascinu S, Labianca R, Graziano F, et al. Intensive weekly chemotherapy for locally advanced gastric cancer using 5-fluorouracil, cisplatin, epidoxorubicin, 6S-leucovorin, glutathione and filgrastim: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Br J Cancer* 1998;78:390-393.
58. Sadzuka Y, Sugiyama T, Hirota S. Modulation of cancer chemotherapy by green tea. *Clin Cancer Res* 1998;4:153-156.
59. Sugiyama T, Sadzuka Y. Enhancing effects of green tea components on the antitumor activity of adriamycin against M5076 ovarian sarcoma. *Cancer Lett* 1998;133:19-26.

60. Scambia G, Ranelletti FO, Panici PB, et al. Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF-7 human breast cancer cell line: P-glycoprotein as a possible target. *Cancer Chemother Pharmacol* 1994;34:459-464.
61. Critchfield JW, Welsh CJ, Phang JM, Yeh GC. Modulation of adriamycin accumulation and efflux by flavonoids in HCT-15 colon cells. *Biochem Pharm* 1994;48:1437-1445.
62. Versantvoort CHM, Schuurhuis GJ, Pinedo HM, et al. Genistein modulates the decreased drug accumulation in non-P-glycoprotein mediated multidrug resistant tumour cells. *Br J Cancer* 1993;68:939-946.
63. Doyle LA, Giangiulo D, Hussain A. Differentiation of human variant small cell lung cancer cell lines to a classic morphology by retinoic acid. *Cancer Res* 1989;49:6745-6751.
64. Kalemkerian GP, Jiroutek M, Ettinger DS, et al. A phase II study of all-trans-retinoic acid plus cisplatin and etoposide in patients with extensive stage small cell lung carcinoma. *Cancer* 1998;83:1102-1108.
65. Adwankar M, Banerji A, Ghosh S. Differential response of retinoic acid pretreated human synovial sarcoma cell line to anticancer drugs. *Tumori* 1991;77:391-394.
66. Chiang CD, Song EJ, Yang VC, Chao CCK. Ascorbic acid increases drug accumulation and reverses vincristine resistance of human non-small-cell lung-cancer cells. *Biochem J* 1994;301:759-764.
67. Lissoni P, Paolorossi F, Ardizzoia A. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state. *J Pineal Res* 1997;23:15-19.
68. Ghielmini M, Pagani O, de Jong J. Double-blind randomized study on the myeloprotective effect of melatonin in combination with carboplatin and etoposide in advanced lung cancer. *Br J Cancer* 1999;80:1058-1061.
69. Weisman RA, Christen R, Los G, et al. Phase I trial of retinoic acid and cis-platinum for advanced squamous cell cancer of the head and neck based on experimental evidence of drug synergism. *Otolaryngol Head Neck Surg* 1998;118:597-602.
70. Prasad KN, Hernandez C, Edwards-Prasad J, et al. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. *Nutr Cancer* 1994;22:233-245.
71. Sue K, Nakagawara A, Okuzono SI, et al. Combined effects of vitamin E (alpha-tocopherol) and cisplatin on the growth of murine neuroblastoma in vivo. *Eur J Cancer Clin Oncol* 1988;24:1751-1758.
72. Naganuma A, Satoh M, Imura N. Effect of selenite on renal toxicity and antitumor activity of cis-diamminedichloroplatinum in mice inoculated with Ehrlich ascites tumor cell. *J Pharmacobiodyn* 1984;7:217-220.
73. Berry JP, Pauwella C, Thouzeau S, et al. Effect of selenium in combination with cis-diamminedichloroplatinum(II) in the treatment of murine fibrosarcoma. *Cancer Res* 1984;44:2864-2868.
74. Ohkawa K, Tsukada Y, Dohzono H, et al. The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumor activity. *Br J Cancer* 1988;58:38-41.
75. Hu YJ, Chen Y, Zhang YQ, et al. The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. *Biol Trace Elem Res* 1997;56:331-341.
76. Roller A, Weller M. Antioxidants specifically inhibit cisplatin cytotoxicity of human malignant glioma cells. *Anticancer Res* 1998;18:4493-4497.
77. Miyajima A, Nakashima J, Tachibana M, et al. N-acetylcysteine modifies cis-dichlorodiammineplatinum induced effects in bladder cancer cells. *Jpn J Cancer Res* 1999;90:565-570.
78. Sheikh-Hamad D, Timmins K, Jalali Z. Cisplatin-induced renal toxicity: possible reversal by N-acetylcysteine treatment. *J Am Soc Nephrol* 1997;8:1640-1644.
79. Smyth JF, Bowman A, Parren T, et al. Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial. *Ann Oncol* 1997;8:569-573.
80. Bogliun G, Marzorati L, Marzola M, et al. Neurotoxicity of cisplatin +/- reduced glutathione in the first-line treatment of advanced ovarian cancer. *Int J Gynaecol Cancer* 1996;6:415-419.

81. Cascinu S, Cordella L, Del Ferro E, et al. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995;13:26-32.
82. Marverti G, Andrews PA. Stimulation of cis-diamminedichloroplatinum(II) accumulation by modulation of passive permeability with genistein: an altered response in accumulation-defective resistant cells. *Clin Cancer Res* 1996;2:991-999.
83. Hofmann J, Fiebig HH, Winterhalter BR, et al. Enhancement of the antiproliferative activity of cis-diamminedichloroplatinum(II) by quercetin. *Int J Cancer* 1990;45:536-539.
84. Nagai Y, Horie T, Awazu S. Vitamin A, a useful biochemical modulator capable of preventing intestinal damage during methotrexate treatment. *Pharmacol Toxicol* 1993;73:69-74.
85. Milner JA, Hsu CY. Inhibitory effects of selenium on the growth of L1210 leukemic cells. *Cancer Res* 1981;41:1652-1656.
86. Furuya Y, Yamamoto K, Kohno N, et al. 5-Fluorouracil attenuates an oncostatic effect of melatonin on estrogen-sensitive human breast cancer cells (MCF7). *Cancer Lett* 1994;81:95-98.
87. Danysz A, Wierzba K, Wutkiewicz M, et al. Influence of some sulfhydryl compounds on the antineoplastic effectiveness of 5-fluorouracil and 6-mercaptopurine. *Arch Immunol Ther Exp* 1984;32:345-349.
88. Danysz A, Wierzba K, Pniewska A, et al. The effect of sulfhydryl compounds on 5-fluorouracil toxicity and distribution. *Arch Immunol Ther Exp* 1983;31:373-379.
89. Conley BA, Ramsland TS, Sentz DL, et al. Antitumor activity, distribution, and metabolism of 13-cis-retinoic acid as a single agent or in combination with tamoxifen in established human MCF-7 xenografts in mice. *Cancer Chemother Pharmacol* 1999;43:183-197.
90. Recchia F, Rea S, De Filippis S, et al. Beta-interferon, retinoids and tamoxifen combination in advanced breast cancer. *Clin Ter* 1998;149:203-208.
91. Budd GT, Adamson PC, Gupta M, et al. Phase I/II trial of all-trans retinoic acid and tamoxifen in patients with advanced breast cancer. *Clin Cancer Res* 1998;4:635-642.
92. Guthrie N, Gapor A, Chambers AF, et al. Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. *J Nutr* 1997;127:544S-548S.
93. Lissoni P, Barni S, Meregalli S, et al. Modulation of cancer endocrine therapy by melatonin: a phase II study on tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone. *Br J Cancer* 1995;71:854-856.