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. 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. 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.

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### Human Studies

- Decreased toxicity (CYC+DOC+5FU)\(^{23}\)  
- Reduced toxicity, possible increased therapeutic effect (CYS+CIS)\(^{30,31}\)

### Animal Studies

- Increased therapeutic effect (CYC)\(^5\)
- Increased therapeutic effect (CYC)\(^{5,18}\)
- Increased therapeutic effect (CYC)\(^{19}\)
- Increased therapeutic effect (CYC)\(^{20}\)
- Decreased toxicity, no change in therapeutic effect (CYC)\(^{24}\)
- Decreased toxicity, no change in therapeutic effect (CYC)\(^{25,26,27}\)
- Increased therapeutic effect (BUS)\(^{32}\)

### In vitro Studies

- Decreased toxicity, no change in cytotoxic effect (MEL)\(^{21}\)
- Increased cytotoxic effect (BUS)\(^{32}\)

### Comments

- *Both studies used combined therapy
- *with selenium, zinc, and copper

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

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

*note: "decreased toxicity" refers to effect on healthy tissue.*
### Table 2: Antibiotic-type Agents: doxorubicin (adriamycin) (DOX), bleomycin (BLE), epirubicin (EPI), daunorubicin (DAU)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Human Studies</th>
<th>Animal Studies</th>
<th>In vitro studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Decreased toxicity; increased survival (DOX+BLE+5FU+MT)³⁵</td>
<td></td>
<td></td>
<td>Increased cell differentiation;³³ cells less or more sensitive to DOX</td>
</tr>
<tr>
<td>Beta carotene</td>
<td></td>
<td>Increased therapeutic effect (DOX)¹⁸</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Increased therapeutic effect; decreased toxicity (DOX)¹⁹³⁶</td>
<td>Increased cytotoxic effect in human breast CA cells (DOX)³⁷</td>
<td>Another in vitro study using ascorbic acid 2-phosphate found no change in drug-sensitive cells and decreased effect in resistant lines (DOX)³⁸</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Decreased toxicity and possible increased therapeutic effect (DOX)³⁷</td>
<td>Increased cytotoxic effect (DOX)⁴⁰⁴²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>Decreased toxicity (DOX)⁴³⁴⁴; increased therapeutic effect* (DOX)⁴⁵</td>
<td>No reduction of cytotoxic effect (DOX)⁵⁰</td>
<td>* in drug-resistant tumors</td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Decreased toxicity (DOX)⁴⁷⁴⁹</td>
<td>Decreased toxicity; no change in therapeutic effect (DOX)⁵⁰</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Decreased toxicity (EPI)⁵¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>No decrease of therapeutic effect; no reduction of toxicity (DOX)⁵²⁵³</td>
<td>Decrease* or no change in therapeutic effect; decreased toxicity (DOX)⁵⁴⁵⁵</td>
<td>*First of three in vivo studies showing reduced therapeutic effect of chemotherapy with an antioxidant</td>
<td></td>
</tr>
<tr>
<td>Glutathione (GSH)</td>
<td>Effective results with GSH plus EPI+ClS+5FU</td>
<td>Increased resistance to drug* (DOX)⁵⁶</td>
<td>*In cell lines with the highest concentrations of glutathione</td>
<td></td>
</tr>
<tr>
<td>Green tea</td>
<td>Increased therapeutic effect* (DOX)⁵⁸⁵⁹</td>
<td></td>
<td>*In drug-resistant tumors</td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td></td>
<td>Increased cytotoxic effect* (DOX, DAU)⁶⁰⁶²</td>
<td>* drug-resistant cell lines</td>
<td></td>
</tr>
</tbody>
</table>

Note: *decreased toxicity* refers to effect on healthy tissue.
### Table 3: Antimetabolites: 5-fluorouracil (5-FU), methotrexate (MT)

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

Note: "decreased toxicity" refers to effect on healthy tissue.
**Table 4:** Platinum Compounds: cisplatin (CIS)

<table>
<thead>
<tr>
<th>Nutrient</th>
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<th>Animal Studies</th>
<th>In vitro Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Increased therapeutic effect (CIS)&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
<td>Increased cytotoxic effect (CIS)&lt;sup&gt;34&lt;/sup&gt; no change in therapeutic effect (CIS+ETO)&lt;sup&gt;64&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td></td>
<td>Increased cytotoxic effect (CIS)&lt;sup&gt;37&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>Increased therapeutic effect (CIS)&lt;sup&gt;71&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy (Beta carotene, A*, C, E)</td>
<td></td>
<td></td>
<td>Increased cytotoxic effect (CIS+ETO)&lt;sup&gt;64&lt;/sup&gt; *13-cis-retinoic acid</td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>Decreased toxicity (CIS)&lt;sup&gt;75&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Increased survival, decreased toxicity (CIS+ETO)&lt;sup&gt;67,68*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>*Not significant at high chemotherapy doses</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Possible decrease in toxicity (CIS)&lt;sup&gt;76,77&lt;/sup&gt;</td>
<td></td>
<td>Decreased cytotoxic effect (CIS)&lt;sup&gt;78&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Glutathione</td>
<td>Slight increase or no change in therapeutic effect, decreased toxicity (CIS+Cyc)&lt;sup&gt;30,31&lt;/sup&gt;, (CIS)&lt;sup&gt;79,80,81&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genistein</td>
<td></td>
<td></td>
<td>Increased cytotoxic effect (CIS)&lt;sup&gt;62&lt;/sup&gt; *Against a drug-resistant cell line.</td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td></td>
<td></td>
<td>Increased therapeutic effect (CIS)&lt;sup&gt;32,83&lt;/sup&gt;</td>
<td>Increased cytotoxic effect (CIS)&lt;sup&gt;32,83&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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 5: Radiotherapy

<table>
<thead>
<tr>
<th>Nutrient</th>
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<th>Animal Studies</th>
<th>In vitro Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Increased therapeutic effect, decreased toxicity⁴</td>
<td>Increased therapeutic effect, decreased toxicity⁵</td>
<td>Increased therapeutic effect, decreased toxicity³</td>
<td></td>
</tr>
<tr>
<td>Beta carotene</td>
<td>Decreased toxicity, no change in therapeutic effect⁶</td>
<td>Increased therapeutic effect, decreased toxicity⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Increased therapeutic effect, decreased toxicity⁷</td>
<td>Increased therapeutic effect, decreased toxicity⁸,⁹,¹⁰</td>
<td>Increased therapeutic effect, no change in therapeutic effect¹¹</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>Increased therapeutic effect¹²</td>
<td>*Doses below 500 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>Decreased toxicity¹³</td>
<td></td>
<td></td>
<td>*Influence on therapeutic effect unknown</td>
</tr>
<tr>
<td>Coenzyme Q10*</td>
<td></td>
<td>No change in therapeutic effect¹⁴</td>
<td></td>
<td>Doses below 10 mg/kg</td>
</tr>
<tr>
<td>Melatonin</td>
<td>increased therapeutic effect, decreased toxicity¹⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>No change in therapeutic effect or toxicity¹⁶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutathione</td>
<td>Decreased toxicity, no change in therapeutic effect¹⁷</td>
<td></td>
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<td></td>
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</tbody>
</table>

Note: "decreased toxicity" refers to effect on healthy tissue.
Table 6: Hormonal Therapies: tamoxifen (TAM)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Human Studies</th>
<th>Animal Studies</th>
<th>In vitro Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Increased therapeutic effect (TAM)</td>
<td>No change in therapeutic effect (TAM)</td>
<td>*In one study vitamin A enhanced response to TAM in cases where tumor had progressed with TAM alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*90,91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td>Increased cytotoxic effect (TAM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>Increase or no change in cytotoxic effect (TAM)</td>
<td>*Tocotrienols had greater effect than tocopherol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed: Vitamins C and E, beta carotene, and 13-cis-retinoic acid</td>
<td></td>
<td>Increased cytotoxic effect (CIS+TAM+ decarbazine+ interferon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Increased therapeutic effect (TAM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangeretin</td>
<td></td>
<td>Decreased therapeutic effect (TAM)</td>
<td>*Third of three in vivo studies showing reduced therapeutic effect with an antioxidant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>2</em></td>
<td></td>
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</tbody>
</table>

References

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

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

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