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REPORT

Antioxidants

By Terri Mitchell

It's hard to imagine a health world without antioxidants. They stand alongside aspirin and Band-Aids as mainstays of the American landscape. Hundreds line the shelves of Wal-Mart and Rite Aid, avidly sought by the masses. Yet 25 years ago, antioxidants didn't exist for most people.

It was a strange turn of events that made antioxidants mainstream. In a brew that threw together a physicist, an oil chemist, an adventurer, and a Hollywood talk show host, what emerged was the idea that average people could use science to advance their health, and the antioxidant boom was born.

Oh, and Playboy. In 1968, MIT wunderkind Durk Pearson read an article from the magazine about Dr. Denham Harman's theory on free radicals and aging. Intrigued, Pearson and Sandy Shaw dug into the UCLA library and pulled out Harman's scientific publications. Harman, a chemist working in the then-obscure field of oxygen chemistry for the research arm of Shell Oil, had come up with the notion that the by-products of oxygen reactions ("free radicals") cause aging. (Anything that aged rubber probably wouldn't do much for internal organs, Harman rightfully reasoned.) Armed with degrees in physics and chemistry, Pearson and Shaw immediately took to Harman's scientifically based concept, and began looking into it further. That was fine, and it might have been the end of it except for the well-timed entrance of a genuine Indiana Jones-type adventurer named Jack Wheeler.

Wheeler was a regular guest on the then-popular Merv Griffin talk show, and when he went to California for filming, he hung out with Durk and Sandy. They had become immersed in the idea of testing Harman's theory, and every time Wheeler showed up, they regaled him with their latest ideas about aging and free radicals. Durk's knack for whacking complicated science down to size got Wheeler to thinking there might be a wider audience for the finer points of free radical chemistry (hey, the stuff was interesting the way Durk explained it). So Wheeler approached Merv about Durk going on the show. Incredibly (it seems now), Merv consented, and the rest is history. Durk's second visit provoked over 100,000 letters—the single most popular appearance ever recorded for a talk show. As Wheeler tells it, Merv's entire office was covered in letters asking Durk and Sandy questions about health and aging.

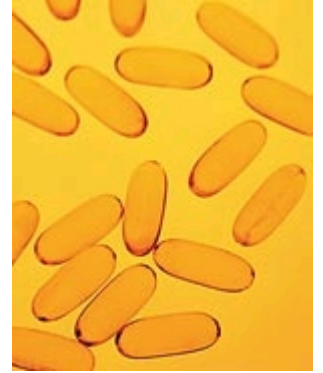
Clearly, the idea that average people could use science for their own benefit was immensely popular. Until then, science on free radicals wasn't even known to most chemists, let alone medical doctors. TV viewers of the time had two health care options: they could go to a doctor who would give them a drug, or consult a nutritionist who would make them eat wheat germ and desiccated liver. Here was something different. Here was a guy in lederhosen talking about a whole new world of antioxidants: vitamins and drugs, amino acids and hormones—things that a person could get ahold of and actually try. This was beyond prednisone and liver tablets. Now people could actually do something about their widening girth, chronic allergies, and cross-linked skin. And aging of all things! Durk said you could actually do something about aging! The fact that the man looked like an escapee from a commune was of no importance. Free radicals—boo! Antioxidants—yea! Americans had new weapons against the things that plagued them.

That was then and this is now. Things are a little more complicated than they seemed to be back in the Merv era. The connection between oxidative damage and the degenerative diseases of aging, as well as aging itself, remains strong. Yet the world of antioxidants has gotten substantially more complex.

THE VITAMIN E SHIELD

Vitamin E is one of America's most popular antioxidant supplements. According to a recent USDA study, that's a good thing, because only 2.4% of American women and 8% of men get enough of the vitamin from food.¹

Vitamin E is fat-soluble and reduces the level of free radicals associated with lipids, such as those that affect cholesterol and those that affect the brain. For this reason, vitamin E has been intensively studied for its ability to prevent cardiovascular and Alzheimer's diseases.



Taking relatively high doses of vitamin E (2000 IU/day) may protect against Alzheimer's disease, especially if begun early in life and combined with relatively high doses of vitamin C (1000 mg.)²⁻⁴ There are two good reasons for people worried about Alzheimer's to take vitamin E: Alzheimer's patients have significantly reduced levels of antioxidants in their brains and blood, which can be raised with supplements such as vitamin E; and biochemical studies show that the high level of oxidative stress found in Alzheimer's patients is ameliorated with antioxidants, including vitamin E.⁵⁻⁹ Vitamin E is one of the best-known antioxidants, but by no means the only one.

FREE RADICALS AND INFLAMMATION

One of the most important medical discoveries of the past decade is the connection between inflammation and diseases like cancer and Alzheimer's. The finding that people who take anti-inflammatory drugs have a lower risk of cancer was, at first, very surprising. How could something that lowers pain and reduces swelling possibly inhibit cancer? Researchers soon discovered inflammatory factors that enhance the ability of cancer cells to multiply and spread. Now we know that things that block inflammation—including aspirin—also impede cancer.



Things have been ratcheted up in the antioxidant world with new research showing that some antioxidants have powerful anti-inflammatory action. Although inflammation involves free radicals, it's somewhat more complicated, involving the activation and inactivation of genes as well. Some antioxidants also block inflammation in addition to having radical-scavenging effects.

For example, when the antioxidant curcumin is given as a dietary supplement to animals with a mouse model of Alzheimer's disease, it blocks the oxidation of certain proteins. This is the antioxidant effect, which in turn lowers the activation of inflammation signals. The net result is that abnormal Alzheimer's proteins are lowered by about 40%.¹⁰ This may slow disease progression. If this experiment held up in humans, and abnormal proteins could be retarded by 40%, it might translate into years of life that would otherwise be lost to a disease for which there is presently no cure.¹⁰



Combinations of antioxidants can have greater effects than single agents on certain types of inflammation. A recent study focuses on an inflammation marker known as C-reactive protein (CRP), which is elevated in people who may appear healthy but could have a sudden heart attack and die. This study is important because it used baboons, whose biochemistry is more human-like than that of rodents.¹¹ It shows that elevated CRP can be dramatically reversed with a combination of two antioxidants. Vitamin E (DL-alpha-tocopheryl acetate) at a human dose of approximately 200 IU/day reduces CRP by 50%. Adding coenzyme Q10 further reduces CRP by about 20% more, for a 70% reduction overall.¹¹ Two other studies of primates demonstrated beneficial effects of vitamin E, for both the prevention and treatment of cardiovascular disease.^{12,13}

Curcumin and vitamin E are only two of the many antioxidants that inhibit inflammation. Information on others can be found in past and future issues of this magazine. The important thing is to be aware that some antioxidants go a step further and reduce inflammation, which may block serious diseases including cancer.

DOES DIET INCREASE FREE RADICALS?

When free radicals first hit the radar screen, the emphasis was on taking antioxidants to counteract them. While this is still a good idea, the complementary approach is to generate as few free radicals as possible in the first place. Diet, it has been discovered, can undermine this goal.

Iron and copper are required elements of human nutrition. However, an overabundance of either or both promotes free radicals that destroy healthy tissue. Iron has been the focus of several recent studies that are extremely important.

One of them shows that the risk of type II diabetes increases with greater amounts of iron in the diet. In a 12-year study of more than 30,000 men, "heme" iron from red meat doubled the risk of type II diabetes.¹⁴ Dietary heme from red meat is also a potent promoter of colon cancer.¹⁵ And an analysis of two large American studies shows that excess iron increases the risk of a fatal heart attack more than fivefold and raises the risk of all-cause mortality over threefold.¹⁶ Iron from plant sources is known as "nonheme" iron and doesn't appear to carry the same risks. One reason may be that it's not absorbed as well. Plants contain natural metal inhibitors.



The principal source of iron in the American diet is fortified cereals such as Kellogg's Product 19, which contains 18 mg in a one-cup serving. The iron in fortified cereal, however, is non-heme iron, and its absorption is impeded by the phytate in the cereal. By comparison, three ounces of beef contain 3 mg of heme iron that

is readily absorbed.¹⁷ The US Food and Nutrition Board has set an upper limit on iron intake of 45 mg/day. Postmenopausal women and men are advised to avoid highly fortified foods and iron supplements.¹⁸

Copper is another metal that promotes damaging free radicals. Copper combined with homocysteine (a natural byproduct of methionine metabolism) creates a lethal brew that can harm the brain and heart.^{19,20} Copper promotes the spread of cancer, and a copper chelator known as tetrathiomolybdate has been successfully used to combat some types of cancer, including squamous cell.^{21,22}

Copper accumulates in the brains of Alzheimer's patients.²³ The phytochemical curcumin again appears on the scene. It has been proposed that curcumin be used as a treatment to chelate copper and prevent it from triggering free radical damage.²⁴ Curcumin naturally chelates both iron and copper.²⁴ Resveratrol, from wine and grapes, is also a copper chelator that keeps the metal from oxidizing LDL (low-density lipoprotein),²⁵ which can be found in the brain as well as the heart and blood vessels.

Although resveratrol doesn't chelate iron, it's one of the strongest antioxidants ever discovered for protecting against iron-induced free radicals.²⁶ Quercetin, a natural cousin of resveratrol in grapevine and other plants, neutralizes both iron and copper better than 10 other phytochemicals.²⁷ "Remarkable protection against lipid peroxidation" is how researchers in Italy described quercetin after studying its ability to chelate iron in LDL.²⁸ This is important, because current research indicates that it's not cholesterol per se that's bad, it's oxidized cholesterol—that is, oxidized LDL.

The number-one source of copper in the American diet is beef. According to the USDA database, beef contains whopping amounts of copper. Three ounces of American beef contain nearly 4 mg of copper. By comparison, one cup of chickpeas contains 0.58 mg.²⁹

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ANTIOXIDANTS REDUCE MORTALITY

Researchers in Belgium theorized that people have a certain balance of antioxidants and free radicals in their bodies, and if the balance were tipped toward free radicals, they would be more likely to die. So they came up with a scoreboard for oxidative balance in a group of smokers.³⁰ Using diet as the basis, the smokers were divided into groups with low, medium, and high oxidative stress (which generates free radicals). Those with the highest iron intake and/or the lowest antioxidant vitamin intake had the worst score. At follow-up 10 years later, those with the worst score (based on high iron intake plus low beta-carotene and vitamin C intake) had a 44% higher risk of all-cause mortality and a 62% higher risk of cancer mortality than those with a good level of antioxidants.³⁰

The study is confirmed by others showing that blood levels of antioxidants are “strongly predictive of mortality.”³¹ Lycopene and other carotenoids can slash the risk of mortality in half in nonsmokers.³² Antioxidant supplements and vitamin E can likewise reduce the risk of breast cancer recurrence,³³ and lycopene can do the same in relation to oral cancers.³⁴ Adequate levels of vitamin E, vitamin A, and lycopene are associated with a reduced risk of microangiopathy-related cerebral damage,³⁵ and vitamins C and E taken as supplements at levels much higher than the US RDA can help protect against ovarian cancer.³⁶ These findings are from just a few of the hundreds of published studies.

DIFFERENT RADICALS, DIFFERENT ANTIOXIDANTS

Of the several different types of free radicals, some are related to fat and others to water. Antioxidants that are great at scavenging one type of radical may have no effect on another. This was illustrated by researchers at the USDA’s Fruit Laboratory who studied different berries.³⁷

The researchers found, for example, that juice from the “Hull Thornless” blackberry could inhibit four different types of radicals (hydroxyl, superoxide, singlet oxygen, and hydrogen peroxide) a lot better than vitamins E and C and all other berries tested. They discovered that beta-carotene is good at stopping singlet oxygen, but has no effect against hydrogen peroxide. Alpha tocopherol inhibited singlet oxygen radicals by 22.5%, better than strawberries at 15.41%.³⁷

Not only does the type of berry make a difference, but whether it’s organic also counts. Researchers at the University of California at Davis found that organic frozen corn contains 50% more vitamin C than regular frozen corn, and that levels of phenolics were likewise higher in organic frozen strawberries.³⁸

THE BODY’S OWN ANTIOXIDANTS

It’s not possible to avoid free radicals. Humans are bombarded with radical-generating radiation and toxins every day. On top of that, the body makes its own radicals. Energy production creates them and so does the immune system, where radical promoters such as hydrogen peroxide are synthesized inside cells and used to destroy invaders such as bacteria.

The body, however, has a remedy for its radicals: it creates its own antioxidants. Some of them are in the form of enzymes, which rely on metals such as selenium and zinc; these include glutathione peroxidase, superoxide dismutase, and catalase. Others are sulfur-related, and include lipoic acid, N-acetylcysteine, and glutathione.

Cysteine, one of the sulfur-related antioxidants, is a critical component of glutathione, a major antioxidant for the liver, kidney, blood cells, and lungs, which are said to have an since they are exposed to both external and internal radicals.³⁹ Prolonged or very intense oxidative stress can deplete glutathione and leave cells vulnerable to free radical damage. A quick route to glutathione depletion is drug and alcohol abuse.



Lipoic acid is another sulfur-related antioxidant synthesized in the body. It is unique because it can scavenge both water- and fat-type radicals, unlike most other antioxidants that go after one or the other. In a study of humans taking 600 mg of lipoic acid a day, three major areas of oxidative stress—LDL peroxidation, protein carbonyls, and isoprostanes—were reduced, a clear demonstration of lipoic acid's multi-system activity.⁴⁰ Lipoic acid is well known for its beneficial effects against diabetes, and has been used extensively in Germany and other countries to help manage diabetic neuropathy, protect the eyes, and more.⁴¹⁻⁴³ Not only does lipoic acid help reverse the effects of diabetes, but Korean researchers recently demonstrated that the supplement can also help prevent diabetes from developing in the first place, at least in overweight rats.⁴⁴

Glutathione levels decrease with age.⁴⁵ Part of the problem occurs at the genetic level, where the genes that help manufacture it slow down.⁴⁶ Supplemental lipoic acid not only can help reverse this loss and protect the heart and brain, but also can actually jump-start an aging gene into working again.⁴⁵⁻⁴⁷

Supplemental lipoic acid and L-carnitine are a powerful antidote to age-related antioxidant and energy loss. The two work synergistically in the body's power plants known as mitochondria.⁴⁸

ANTIOXIDANTS AND CHEMOTHERAPY

A study from the MD Anderson Cancer Center found that 62% of the patients at its clinics were taking herbs and/or vitamins,⁴⁹ yet oncologists know little or nothing about how these supplements might affect conventional cancer treatment.

Chemotherapeutic drugs and radiation generate free radicals that damage both cancerous and healthy cells. It was previously thought that causing free radical damage to cancer cells was the principal way these treatments work. However, new research indicates that that's not necessarily true. Some chemotherapies actually work better when free radicals are reduced.⁵⁰ There is no definitive answer at the present time as to whether or not antioxidants should be taken during chemotherapy; it may depend on the type of cancer and type of drug being used.

Very few studies of antioxidants and chemotherapy have been done to date. Some confirm that antioxidants are beneficial during cancer treatment, while others indicate that some antioxidants may interfere with treatment. Still others show that certain antioxidants may enhance the cancer-killing effects of chemotherapeutic drugs.

As an example of the type of research that's emerging, researchers at Columbia University report that children with acute lymphoblastic leukemia whose intakes of vitamin E, carotenoids, beta-carotene, and vitamin A are below the recommended daily allowance have more side effects from chemotherapy.⁵¹ In another study of women undergoing treatment for breast cancer, vitamin E or multivitamins helped maintain white blood cell counts (neutrophils), while folate had a negative impact on white cells.⁵²



British researchers analyzed levels of selenium in people diagnosed with B-cell non-Hodgkin's lymphoma.⁵³ They found that if patients had high levels of selenium upon entering treatment, they had a better response, could tolerate higher doses, and were more likely to have long-term survival.

Italian researchers gave 300 mg of vitamin E a day to people undergoing chemotherapy with the drug cisplatin. When the vitamin was given prior to the drug and for three months after, toxicity to the brain was reduced from 85% to 30%. It's not known whether a higher dose or different form of vitamin E might have slashed toxicity even further.⁵⁴

Melatonin is well documented as a powerful antioxidant, particularly against radicals caused by radiation.⁵⁵ In a study of people with metastatic non-small cell lung cancer, 20 mg of melatonin taken each night increased their ability to tolerate chemotherapy and achieve a better result. Three of 49 people were still alive at five years in the melatonin group, whereas none of the people in the group not receiving melatonin was still alive at two years.⁵⁶

These and other studies are showing the effects of antioxidants in humans treated for cancer. Many animal studies already show beneficial effects for certain antioxidants used in conjunction with certain chemotherapies. But caution is warranted because some antioxidants can interfere with the ability of some chemotherapies to kill cancer cells.⁵⁷

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CONCLUSION

In the relatively short time that antioxidants have been on the radar screen, much progress has been made in understanding just how important they are for health and longevity. The critical roles they play in counteracting the toxic effects of environment and normal cellular processes are undisputed. Block a critical antioxidant in a laboratory fly, and it will live less than a quarter of its life span. Add more of the same antioxidant, and it will live much longer than it's supposed to.⁵⁸ People with greater amounts of antioxidants in their blood are more likely to survive cancer and critical illness.⁵⁹⁻⁶¹

Strange coincidences and blind luck put free radical research on the map—a field that may have been destined to a dusty corner until the day in 1954 when Dr. Denham Harman had the epiphany that the same chemical reactions that age windshield wipers might age human beings. This epiphany was made possible by his training in both fields—petroleum chemistry and medicine, that is. Free radical research might still be languishing in obscure journals had not Durk Pearson and Sandy Shaw realized the potential of Harman's "free radical theory of aging" to be useful to humans in everyday life. Such is science.

References

1. Maras JE, Bermudez OI, Qiao N, Bakun PJ, Boody-Alter EL, Tucker KL. Intake of alpha-tocopherol is limited among U.S. adults. *J Am Diet Assoc.* 2004 Apr;104:567-75.
2. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA.* 2002 Jun 26;287(24):3223-9
3. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol.* 2004 Jan;61(1):82-8.
4. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med.* 1997 Apr 24;336(17):1216-22.
5. Pratico D, Zhukareva V, Yao Y, et al. 12/15-lipoxygenase is increased in Alzheimer's disease: possible involvement in brain oxidative stress. *Am J Pathol.* 2004 May;164(5):1655-62.
6. Kontush A, Mann U, Arlt S, et al. Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease. *Free Radic Biol Med.* 2001 Aug 1;31(3):345-54.
7. Rinaldi P, Polidori MC, Metastasio A, et al. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. *Neurobiol Aging.* 2003 Nov;24(7):915-9.
8. Mhatre M, Floyd RA, Hensley K. Oxidative stress and neuroinflammation in Alzheimer's disease and amyotrophic lateral sclerosis: common links and potential therapeutic targets. *J Alzheimers Dis.* 2004 Apr;6(2):147-57.
9. Tamagno E, Aragno M, Parola M, et al. NT2 neurons, a classical model for Alzheimer's disease, are highly susceptible to oxidative stress. *Neuroreport.* 2000 Jun 26;11(9):1865-9.
10. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci.* 2001 Nov 1;21(21):8370-7.
11. Wang XL, Rainwater DL, Mahaney MC, Stocker R. Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. *Am J Clin Nutr.* 2004 Sep;80(3):649-55.
12. Verlangieri AJ, Bush MJ. Effects of d-alpha-tocopherol supplementation on experimentally induced primate atherosclerosis. *J Am Coll Nutr.* 1992 Apr;11(2):131-8.

13. Sharma N, Desigan B, Ghosh S, Sanyal SN, Ganguly NK, Majumdar S. Effect of antioxidant vitamin E as a protective factor in experimental atherosclerosis in rhesus monkeys. *Ann Nutr Metab.* 1999;43(3):181-90.
14. Jiang R, Ma J, Ascerio A, Stampfer MJ, Willett WC, Hu FB. Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am J Clin Nutr.* 2004 Jan;79(1):70-5.
15. Pierre F, Tache S, Petit CR, Van der Meer R, Corpet DE. Meat and cancer: haemoglobin and haemin in a low-calcium diet promote colorectal carcinogenesis at the aberrant crypt stage in rats. *Carcinogenesis.* 2003 Oct;24(10):1683-90.
16. Wells BJ, Mainous AG 3rd, King DE, Gill JM, Carek PJ, Geesey ME. The combined effect of transferrin saturation and low density lipoprotein on mortality. *Fam Med.* 2004 May;36(5):324-9.
17. Available at: <http://ods.od.nih.gov/factsheets/iron.asp#h4>. Accessed May 12, 2005.
18. Schümann K, Borch-Iohnsen B, Hentze M, Marx JJ. Tolerable upper intakes for dietary iron set by the US Food and Nutrition Board. *Am J Clin Nutr.* 2002 Sept;76(3):499-500.
19. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's type neurodegenerative pathways. *J Neurochem.* 2001 Mar;76(5):1509-20.
20. Starkebaum G, Harlan JM. Endothelial cell injury due to copper-catalyzed hydrogen peroxide generation from homocysteine. *J Clin Invest.* 1986 Apr;77(4):1370-6.
21. Brewer GJ, Merajver SD. Cancer therapy with tetrathiomolybdate: antiangiogenesis by lowering body copper—a review. *Integr Cancer Ther.* 2002 Dec;1(4):327-37.
22. Cox C, Merajver SD, Yoo S, et al. Inhibition of the growth of squamous cell carcinoma by tetrathiomolybdate-induced copper suppression in a murine model. *Arch Otolaryngol Head Neck Surg.* 2003 Jul;129(7):781-5.
23. Atwood CS, Perry G, Zeng H, et al. Copper mediates dityrosine cross-linking of Alzheimer's amyloid-beta. *Biochemistry.* 2004 Jan 20;43(2):560-8.
24. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. *J Alzheimers Dis.* 2004 Aug;6(4):367-77.
25. Belguendouz L, Fremont L, Linard A. Resveratrol inhibits metal ion-dependent and independent peroxidation of porcine low-density lipoproteins. *Biochem Pharmacol.* 1997 May 9;53(9):1347-55.
26. Tadolini B, Juliano C, Piu L, Franconi F, Cabrini L. Resveratrol inhibition of lipid peroxidation. *Free Radic Res.* 2000 Jul;33(1):105-14.
27. Mira L, Fernandez MT, Santos M, Rocha R, Florencio MH, Jennings KR. Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity. *Free Radic Res.* 2002 Nov;36(11):1199-208.
28. Ferrali M, Signorini C, Caciotti B, et al. Protection against oxidative damage of erythrocyte membrane by the flavonoid quercetin and its relation to iron chelating activity. *FEBS Lett.* 1997 Oct 20;416(2):123-9.
29. Available at: <http://www.nal.usda.gov/fnic/foodcomp/Data/SR14/wtrank/sr14w312.pdf>. Accessed May 16, 2005.
30. Van Hoydonck PG, Temme EH, Schouten EG. A dietary oxidative balance score of vitamin E, beta-carotene and iron intakes and mortality risk in male smoking Belgians. *J Nutr.* 2002 Apr;132(4):756-61.
31. Fletcher AE, Breeze E, Shetty PS. Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr.* 2003 Nov;78(5):999-1010.
32. Ito Y, Suzuki K, Suzuki S, Sasaki R, Otani M, Aoki K. Serum antioxidants and subsequent mortality rates of all causes or cancer among rural Japanese inhabitants. *Int J Vitam Nutr Res.* 2002 Jul;72(4):237-50.

33. Fleischauer AT, Simonsen N, Arab L. Antioxidant supplements and risk of breast cancer recurrence and breast cancer-related mortality among postmenopausal women. *Nutr Cancer*. 2003;46(1):15-22.
34. Mayne ST, Cartmel B, Lin H, Zheng T, Goodwin WJ Jr. Low plasma lycopene concentration is associated with increased mortality in a cohort of patients with prior oral, pharynx or larynx cancers. *J Am Coll Nutr*. 2004 Feb;23(1):34-42.
35. Schmidt R, Fazekas F, Hayn M, et al. Risk factors for microangiopathy-related cerebral damage in the Austrian stroke prevention study. *J Neurol Sci*. 1997 Nov 6;152(1):15-21.
36. Fleischauer AT, Olson SH, Mignone L, Simonsen N, Caputo TA, Harlap S. Dietary antioxidants, supplements and risk of epithelial ovarian cancer. *Nutr Cancer*. 2001;40(2):92-8.
37. Wang SY, Jiao H. Scavenging capacity of berry crops on superoxide radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen. *J Agric Food Chem*. 2000 Nov;48(11):5677-84.
38. Asami DK, Hong Y-J, Barrett DM, Mitchell AE. Comparison of the total phenolic and ascorbic acid content of freeze-dried and air-dried marionberry, strawberry, and corn grown using conventional, organic, and sustainable agricultural practices. *J Agric Food Chem*. 2003 Feb 26;51(5):1237-41.
39. Comhair SA, Erzurum SC. The regulation and role of extracellular glutathione peroxidase. *Antioxid Redox Signal*. 2005 Jan-Feb;7(1-2):72-9.
40. Marangon K, Devaraj S, Tirosh O, Packer L, Jialal I. Comparison of the effect of alpha-lipoic acid and alpha-tocopherol supplementation on measures of oxidative stress. *Free Radic Biol Med*. 1999 Nov;27(9-10):1114-21.
41. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabet Med*. 2004 Feb;21(2):114-21.
42. Kowluru RA, Odenbach S. Effect of long-term administration of alpha-lipoic acid on retinal capillary cell death and the development of retinopathy in diabetic rats. *Diabetes*. 2004 Dec;53(12):3233-8.
43. Hahm JR, Kim BJ, Kim KW. Clinical experience with thioctacid (thioctic acid) in the treatment of distal symmetric polyneuropathy in Korean diabetic patients. *J Diabetes Complications*. 2004 Mar-Apr;18(2):79-85.
44. Song KH, Lee WJ, Koh JM, et al. Alpha-lipoic acid prevents diabetes mellitus in diabetes-prone obese rats. *Biochem Biophys Res Commun*. 2005 Jan 7;326(1):197-202.
45. Suh JH, Wang H, Liu RM, Liu J, Hagen TM. (R)-alpha-lipoic acid reverses the age-related loss in GSH redox status in post-mitotic tissues: evidence for increased cysteine requirement for GSH synthesis. *Arch Biochem Biophys*. 2004 Mar 1;423(1):126-35.
46. Suh JH, Shenvi SV, Dixon BM, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. *Natl Acad Sci USA*. 2004 Mar 9;101(10):3381-6.
47. Smith AR, Shenvi SV, Widlansky M, Suh JH, Hagen TM. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. *Curr Med Chem*. 2004 May;11(9):1135-46.
48. Kumaran S, Savitha S, Anusuya DM, Panneerselvam C. L-carnitine and DL-alpha-lipoic acid reverse the age-related deficit in glutathione redox state in skeletal muscle and heart tissues. *Mech Ageing Dev*. 2004 Jul;125(7):507-12.
49. Richardson MA. Research of complimentary/alternative medicine therapies in oncology: promising but challenging. *J Clin Oncol*. 1999 Nov;17(11 Suppl):38-43.
50. Conklin KA. Cancer chemotherapy and antioxidants. *J Nutr*. 2004 Nov;134(11): 3201S-4S.
51. Kennedy DD, Tucker KL, Ladas ED, Rheingold SR, Blumberg J, Kelly KM. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr*. 2004 Jun;79(6):1029-36.
52. Branda RF, Naud SJ, Brooks EM, Chen Z, Muss H. Effect of vitamin B12, folate, and dietary supplements on breast

carcinoma chemotherapy-induced mucositis and neutropenia. *Cancer*. 2004 Sep 1;101(5):1058-64.

53. Last KW, Cornelius V, Delves T, et al. Presentation serum selenium predicts for overall survival, dose delivery, and first treatment response in aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2003 Jun 15;21(12):2335-41.
54. Pace A, Savarese A, Picardo M, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol*. 2003 Mar 1;21(5):927-31.
55. Vijayalaxmi, Reiter RJ, Tan DX, Herman TS, Thomas CR Jr. Melatonin as a radioprotective agent: a review. *Int J Radiat Oncol Biol Phys*. 2004 Jul 1;59(3):639-53.
56. Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. *J Pineal Res*. 2003 Aug;35(1):12-5.
57. Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern Med Rev*. 1999 Oct;4(5):304-29.
58. Kirby K, Hu J, Hilliker AJ, Phillips JP. RNA interference-mediated silencing of Sod2 in *Drosophila* leads to early adult-onset mortality and elevated endogenous oxidative stress. *Proc Natl Acad Sci USA*. 2002 Dec 10;99(25):16162-7.
59. Jaakkola K, Lahteenmaki P, Laakso J, Harju E, Tykka H, Mahlberg K. Treatment with antioxidant and other nutrients in combination with chemotherapy and irradiation in patients with small-cell lung cancer. *Anticancer Res*. 1992 May-Jun;12(3):599-606.
60. Lovat R, Preiser JC. Antioxidant therapy in intensive care. *Curr Opin Crit Care*. 2003 Aug;9(4):266-70.
61. Roth E, Manhart N, Wessner B. Assessing the antioxidative status in critically ill patients. *Curr Opin Clin Nutr Metab Care*. 2004 Mar;7(2):161-8.

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