



FDA Regulations for DSHEA; Inflammation, ROS and Cancer; Mitigating Treatment Toxicities with Herbs and Supplements Part 2

By Claudette Baker, Dipl OM (NCCAOM), LAc



Claudette Baker, Dipl OM (NCCAOM), LAc, president emeritus AAAOM (1996-8) and ILaaom (Illinois) (94-97 & 2002-5), has been practicing Oriental medicine with a focus on oncology since 1985. She is the founder/medical director of the Glenview Healing Arts Center.

A pioneer and leader in the AOM profession nationally and locally, Ms. Baker has worked to incorporate Oriental medicine into the Illinois and U.S. health care delivery system, taught Chinese herbal medicine for oncology, is an SIO member, and is currently the chairperson of the State of Illinois Board of Acupuncture.

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In the past several years, a surge has occurred in published scientific research about the important role of acupuncture, herbs, diet, supplements, exercise, and stress reduction for people with cancer. Many presenters at the 2011 SIO conference stressed the importance of eating fresh, whole, organic foods, using supplements and herbs, and exercising during and after treatment. It is exciting to see these principles supported by research and included in cancer protocols by physicians practicing integrative oncology.

Education is one of the most effective strategies to help integrate Oriental medicine with oncology practices for the benefit of our patients. The following research summaries provide information about promising studies and novel therapies currently available for those suffering from cancer. These also provide current data aimed at diminishing resistance from mainstream oncologists towards patients who choose to use herbs and supplements during their cancer treatments.



Robert Newman, PhD

Robert Newman, PhD, a pharmacologist who has spent more than 30 years in academic medical research, gave a comprehensive presentation, "The Status of FDA Regulations of Natural Products." Dr. Newman spent 24 years at the MD Anderson Cancer Center (MDA) and was the director of its Clinical and Drug Development Cancer Center. After retiring from MDA in 2008, he became the chief scientific officer at New Chapter

Herbs. He has authored over 300 peer-reviewed publications in medical journals as well as several books, and he has helped obtain

several Investigational New Drug (IND) applications both for pharmaceutical as well as “botanical” drugs.

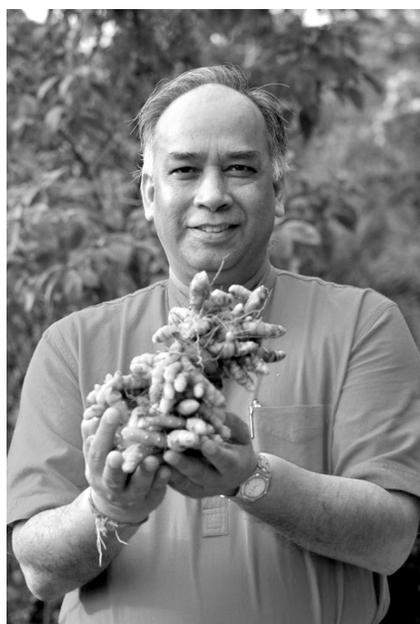
Dr. Newman stressed the importance of understanding and adhering to Food and Drug Administration (FDA) rules by manufacturers and distributors of dietary supplements in the U.S. He shared a number of his challenges and ultimate success in navigating the complicated waters of FDA regulation, reviewing the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, and the passage of Adverse Event Reporting for DSHEA products in 2006 that assists with early detection of a serious adverse event or with adulterated or tampered products.

He discussed the 2007 Good Manufacturing Procedures (GMP) and the FDA’s 2011 Draft Guidance for the Dietary Supplement Industry. He also described the process and rationale behind IND applications, which are required when a botanical drug is studied in the United States for use as a *drug*, (and therefore is *not* a *dietary supplement*) even if such study is intended solely for research purposes. An IND must contain sufficient information to demonstrate that the drug product is safe for testing in humans and that the clinical protocol is properly designed for its intended objectives.

In addressing the misconceptions about the regulation of nutritional supplements Dr. Newman said, “It is the general opinion of many people that dietary supplements are unregulated and that it’s the ‘Wild West’ out there because you never really know what you’re getting when you pick up something off the shelf. While there is some truth to that, by and large I think it isn’t true, having lived in the land of ‘commercial science.’ DSHEA products are actually highly regulated.”

Dr. Newman concluded by saying, “if we ever want to help with the prevention and treatment of cancer with herbs and supplements, we need to continue doing research in humans, both clinically and pre-clinically, especially the ‘gold standard:’ randomized placebo-controlled double-blind clinical studies. There’s so much false information reported on the national news about the ineffectiveness of vitamins and misinformation about the value and

benefit of nutraceuticals and food supplements, but if you dare to look at the actual research, one finds out that this is not true at all.”



Bharat Aggarwal,
PhD in
Costa Rica with
curcumin.
Photo courtesy of
Thomas Newmark,
New Chapter Herbs

Current research on nutraceuticals was presented by Bharat B. Aggarwal, PhD in a fascinating lecture titled “Oxidative Stress and Cancer.” He discussed the consequences of the widespread use of toxic and costly chemotherapeutic agents, saying there is a large database of clinical studies and evidence-based research on herbal medicine for the prevention of and treatment for the side effects of cancer therapies.

Dr. Aggarwal is a professor of cancer medicine, immunology, and biochemistry and also the chief of the Cytokine Research Section at the University of Texas MD Anderson Cancer Center. Currently regarded as one of the top scientists in his field, he has had a long and illustrious research career, having published more than 600 papers in international peer-reviewed journals. Since 1989 he has been investigating the role of inflammatory pathways mediated through TNF, NF- κ B, and STAT3 for the prevention and therapy of cancer. His group has identified over 50 compounds from both dietary sources and traditional medicine that interrupt these cell-signaling pathways. These have been tested in various animal models, some of which are in clinical trials.

Dr. Aggarwal based his talk upon two reviews: “Oxidative Stress, Inflammation, and Cancer: How are They Linked?”¹ and “Upside and Downside of Reactive Oxygen Species for Cancer: The Roles of Reactive Oxygen Species in Tumorigenesis, Prevention, and Therapy.”² He opened by stating: “Even if a drug shrinks tumors, it may do nothing to delay death or to improve patients’ last days. Because so many medicines have toxic side effects as well as high prices, drugs that have no proven benefits may actually be harmful to the patient’s health and economic wellbeing. This is where we stand now and we need to think outside the box. According to manufacturers, pharmaceutical, and biotechnology companies are currently testing 860 new cancer medicines, more than in any other disease category. The cost of this research is why pharmaceutical drugs are so expensive; there has to be a better way to go about it. In that regard, according to the World Health Organization, 80% of the Earth’s inhabitants (6 billion people) rely upon traditional medicine for their primary health care needs, in part due to the high cost of Western pharmaceuticals. If you are looking for something that is safe, effective, and affordable, there is a very long list of natural agents that have this potential.” These are sobering but encouraging words from one of the world’s most accomplished scientists in his field. They give credence to work that traditional Oriental medicine practitioners have been doing for years with cancer patients.

Dr. Aggarwal described the actions and pathways he and his colleagues have discovered about reactive oxygen species (ROS). He explained that scientists used to believe that pro-oxidants were “bad” and anti-oxidants were “good.” Based on the data, they now understand that oxidative stress is both a *cause* and a *treatment* for cancer and that both pro-oxidants and antioxidants need to be in balance for optimal health. If either is off balance, it will become toxic to the body. The following are sources of ROS: chemotherapy, radiation, growth factors, UV light, cytokines, and hypoxia. Extracellular sources of ROS are pollutants, viruses, tobacco, cigarette smoke, chemotherapy, dietary agents, radiation,

and xenobiotics. It is well established that the following enzymes are made endogenously and counteract ROS: superoxide dismutase (SOD), catalase, glutathione, peroxidoredoxin, thioredoxin, reductase and peroxidase. Scientists have found that as much as 80% of ROS is produced by the mitochondria and several other cell organs. Every cellular reaction in the body is a free-radical mediated reaction; however, as one can see, a healthy body produces the antioxidants needed to counteract ROS.

A partial list of diseases that Dr. Aggarwal presented has been linked to ROS. This includes: acute respiratory distress syndrome, Alzheimer's, atherosclerosis, cancer, cardiovascular disease, diabetes, inflammation, inflammatory joint disease, neurological disease, obesity, Parkinson's, pulmonary fibrosis, rheumatoid arthritis, vascular disease, and aging, which is not a disease but involves greater oxidative stress leading to chronic disease. Normal cells are *hypersensitive* to ROS and are more likely to die first, whereas cancer

50% of curcumin's ROS-quenching effect. Dr. Aggarwal reported that as little as 100mg of natural curcumin is enough to down regulate various pro-inflammatory biomarkers.

Interestingly, he and his researchers found that it was the *pro-oxidant* effect of curcumin that induces apoptosis via ROS induction, which is required to induce apoptosis. They also found that using glutathione to quench ROS abolishes the apoptotic effect of the curcumin, thereby proving that it is the pro-oxidant effect of curcumin that is responsible for apoptosis.^{6,7}

Dr. Aggarwal said, "It is now widely accepted that cancer is a preventable disease that requires major changes in life style, as you can see from the following statistics on the causes of cancer: 30% tobacco, 35% diet, 14-20% obesity, 18% infections, 7% environmental pollution/radiation and **only 5% attributed to genes.**⁷ However, MOST of the [research and development] money is going into trying to 'fix' the genes, which is an impossible proposition."

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cells are *hyposensitive* to ROS and are more likely to survive, proliferate, and lead to tumorigenesis. To date, ROS has been linked with inflammation, cell invasion, angiogenesis and metastasis, cell proliferation, cell death, and cell transformation. This research is helping scientists develop new therapies, and to help cancer patients improve their quality and length of life by the use of natural and traditional products.

He reported that the molecule TNF is an anticancer agent and also that TNF is the primary mediator of inflammation. Since inflammation is very closely linked to ROS and hence to cancer, research is being done on the molecules that can down regulate inflammation and thus have a potential against cancer. In their quest to find ways to down regulate TNF—the molecule that is the primary mediator of inflammation in most cancers—he and his associates published a review, "Studying Tumor Necrosis Factor and its Superfamily: Twenty-five Years Later, a Golden Journey."³ He also reminded us there is as much as a 40-50% decrease in the relative risk of colorectal cancer in persons who continuously use aspirin or other NSAIDs, indicating that this is "where the action is" for cancer treatment and prevention.⁴ Another of his reviews discusses ways to stop the inflammation that fuels cancer: "The Relationship Between Inflammation and Cancer is Analogous to that Between Fuel and Fire."⁵

Curcumin, a rhizome that produces turmeric, has been used in India for thousands of years. It is known to be antibacterial, antiviral, antifungal, anticancer, and both antioxidant and pro-oxidant. Curcumin is a much more potent antioxidant than vitamins C and E, as it takes 50 times the amount of those vitamins to equal just

He gave the example that colorectal cancer (CRC) is the second most common cause of cancer deaths in affluent countries. Processed red meat intake is closely linked with the risk of CRC; therefore, dietary modification may reduce this cancer burden by up to 70%. Based on this, Dr. Aggarwal and his colleagues say that "dysregulation and chronic inflammation caused by life style factors mediate chronic diseases, including cancer. A very simple way to fix this is through dietary modifications, and we have identified a number of agents from the diet and from traditional medicines that can control those agents."

In Dr. Aggarwal's opinion, the models now available for cancer prevention are very inadequate. They actually are models of **cancer research** and hence are problematic because they are **not cancer treatments**. He contends we need to rethink the models that are available⁸ and shares one example of a failed model, "It took 22 years of phase one clinical trials that was done on advanced non-small-cell-lung cancer, and at the end of the day, they found out that with the therapy currently available, it gives no more than 2 months increase in life span. This illustrates that there is something fundamentally wrong with this type of model."⁹

Practicing oncologist and SIO Board Member Mary Hardy, MD participated in a panel called "Mitigating Treatment Toxicity and Enhancing Treatment Efficacy." Trained in medical ethics, botanical medicine, and traditional Chinese medicine, she is the medical director for Simms/Mann UCLA Center for Integrative Oncology as well as the associate director of the NIH-funded UCLA Botanical Research Center and co-chair of the Clinical Practice Committee of the Academic Consortium of Integrative Medicine.

Dr. Hardy's presentation focused on dietary supplements used alongside conventional therapies, as this is more controversial during oncology treatment and because of the growing base of evidence that allows the use of smart, targeted therapy. She said "the ultimate goal is to develop multi-disciplinary expertise and therapeutic synergy between conventional and complementary therapies, always looking towards possible future curative therapies that will put patients into durable remissions with much less toxicity. The appropriate goals we look for when using integrative and complementary medicine for cancer patients are to increase general sense of wellbeing, increase energy and decrease pain, decrease side effects, increase the effects of conventional care, decrease emotional pain, anxiety and depression, manage lifestyle issues following treatment, decrease risk of recurrence, and act as safe and effective chemo-preventative agents."

Dr. Hardy provided several current exemplar studies on herbs and nutritional supplements. Starting with a retrospective pooled study reviewing 30 randomized controlled trials featuring 10,000 patients with 11 varieties of cancers, 3 symptoms were examined: physical function, pain, and appetite loss. They found that if these were compromised at the onset of treatment, it had a significantly negative prognosis on the patients' survival and that symptom mitigation improved patients' outcomes and survival.¹⁰

Treatment for most oncologic patients begins at the time of surgery; thus it is important to mitigate surgical complications and toxicities. Dr. Hardy discussed an impressive randomized study on 89 patients who underwent biliary cancer surgery. The only difference between the A and B groups was that Group B received synbiotics for 2 weeks before surgery, mostly *bifidobacterium brevis* and *lactobacillus casei* (one billion each dose). Both groups A and B received standard bowel preps (that strip out the natural bowel flora) and pre and post-operative antibiotics. After surgery, both groups received synbiotics. Group B had a more significant decrease (less than 55%) in infectious complications than Group A and a significant decrease in length of hospital stay (10 days shorter) than Group A. Cumulative length of antibiotic therapy was 4 days shorter in Group B, which represents a significant savings because in-patient antibiotic therapy is extremely expensive. This was a very inexpensive and successful intervention.¹¹

Dr. Hardy said that during cancer treatments nausea is a key function in the impairment of appetite, with up to 70% of cancer patients experiencing this difficult symptom. In one study, a simple intervention of one gram of dried ginger was given to patients. Even though ginger didn't help decrease nausea on day one of chemo, from the second day on, the effect of the ginger was equivalent to conventional nausea treatment. In addition, the group that received metaclopramide without ginger had more significant side effects, and, at the end of the trial, 40% of the patients preferred ginger root to the drug.¹²

Dr. Hardy presented several additional studies relating to natural remedies:

- A randomized, double-blind, placebo-controlled, multi-center trial studied 744 patients who all received 5 HTP receptor antagonist on day one of chemo and either 0.5, 1.0 or 1.5 gm/

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day of ginger for three days before and after day one of chemo. There was significant benefit for the 0.5gm and 1gm dose but less benefit for the 2gm dose, which suggests that there may be a threshold above which additional ginger does not provide benefit and might cause some minor discomfort. However, the severity of nausea and the ginger dose needed to control nausea on the first day were well described in this large clinical trial.¹³

- A meta-analysis on melatonin supplementation showed there was a significant reduction in the most worrisome side effects of chemo: fatigue, alopecia, neutropenia, nausea/vomiting and thrombocytopenia. Most of the studies used 20mg of melatonin, which was generally well tolerated. There was significant improvement in one-year mortality in partial and complete response as well as stable disease.¹⁴ One of the studies within this meta-analysis showed there were significant increases in complete remission, partial remission, and stable disease among the group that took 20mg of melatonin seven days before and throughout chemotherapy.¹⁵
- Neuropathy is one of the most bothersome side effects of chemotherapy. Not only does serious neuropathy limit the amount of treatments that patients can take and thereby compromise the success of chemotherapy, but it is a symptom that often persists (sometimes permanently) after completion of chemotherapy. One study on neuropathy was a very simple and safe intervention of 360 IU of vitamin E (synthetic alpha tocopherol, not natural mixed tocopherols) in patients receiving platinum-based chemotherapy. The study measured nerve conduction and amplitude in addition to checking reflexes and parasthesia and doing a complete neurotoxicity score. The vitamin E group showed benefit while the group not treated with vitamin E developed the toxicity that was expected. This is an especially important intervention for patients who need to receive higher doses of cisplatin (more than 300 mg/m²) because 90% of them will develop severe neurotoxicity. The incidence of neurotoxicity was 5.9% in the vitamin E group vs. 41.7% in the untreated group, a highly significant statistical result.¹⁶

Along with several other researchers, Dr. Hardy addressed recent media reports on negative results from a particular vitamin E study on head and neck cancer. The author of the trial reported significant harm done to patients who used vitamin E while undergoing combined chemo and radiation because it increased the rate of cancer recurrence. However, when reading the study a significant flaw in the analysis was noted in that the study concluded that both current smokers and non-smokers were affected, although virtually all of



Jennifer Stone, LAc.
Photo by Buffalo Child

“As part of this presentation, Jennifer Stone, LAc, from the Indiana University School of Medicine, encouraged physicians to collaborate with acupuncturists to foster ‘better research, better ideas, and better results.’ She stressed that this is advantageous to physicians because acupuncturists’ clinical experience can help design the treatment plan and research design options.”

the patients had a smoking history. When the analysis was redone eliminating the current smokers from the data set, it became clear that all of the risk accrued to the current smokers and that there was also a modest benefit and protection for the subgroup that took vitamin E, showing that it is important to look at the subgroup analysis when reviewing this type of study.¹⁷

Aromatase inhibitors cause pain and are commonly used for post-breast cancer treatment. Two studies showed that patients who begin vitamin D supplementation to raise their levels to at least 40, and preferably above 50, prior to starting the drug had their pain-related symptoms almost completely mitigated. This allows patients to receive this therapy without having the pain that interferes with their life while they are on the drug.^{18, 19}

A treatment for radiation side effects was completed in the largest clinical Phase III randomized trial of 254 breast cancer patients with Grade 2 dermatitis using a homeopathic ointment of *Calendula officinalis* versus Trolamine, a strong moisturizing agent. This study showed that the patients using *Calendula* during radiation therapy were less likely to interrupt treatment (1vs15), and the *Calendula* group also had less pain (1.54 vs 2.10 p=.03). *Calendula* is easy to apply, not expensive, and it is commercially available.²⁰

Dr. Hardy concluded by saying, “Patients do benefit when we combine integrative and complementary therapies when we work collaboratively. We need to use high-quality products where the

manufacturers are known to have high standards. Research efforts should allow us to make deeper and more appropriate observations about how to use and time these products during and after cancer treatment.”

Charlotte Gyllenhaal, PhD, research manager of the Block Center for Integrative Cancer Treatment, research assistant professor in the Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois, and a coordinator for this year’s scientific program spoke about treatment toxicities and use of supplements. She stressed that practitioners need to be aware of possible drug/supplement interactions when using them to address toxicities of conventional treatment. Some interactions are: St John’s Wort alters metabolism of many drugs by stimulating breakdown of cytochrome P450 enzymes, the use of herbs with anticoagulant or antiplatelet properties alongside anticoagulant drugs or during chemotherapy may interact when platelets are suppressed, and the use of stimulant or sedative herbs may interact the week before having surgery with general anesthesia.

Dr. Gyllenhaal spoke about the important role research plays in finding natural supplements to support patients receiving chemotherapies for the variety of typical side effects that they experience. Fatigue commonly occurs during and after conventional treatments. In patients not undergoing current treatment, American ginseng was found to improve vitality in a large dose-finding pilot

study; the effective dose selected was 2.0 g daily.²¹ She also said that improvement of chemotherapy efficacy is an important potential role for supplements. Curcumin is being tested in conjunction with the chemotherapeutic agent gemcitabine for improving chemotherapy efficacy.²² She concluded by citing a trial finding that fish oil given to patients receiving chemotherapy for lung cancer improved response rate (tumor shrinkage); it also reduced loss of body weight and muscle commonly seen in this situation.²³

As part of this presentation, Jennifer Stone, LAc, from the Indiana University School of Medicine, encouraged physicians to collaborate with acupuncturists to foster “better research, better ideas, and better results.” She stressed that this is advantageous to physicians because acupuncturists’ clinical experience can help design the treatment plan and research design options. By the same token, licensed acupuncturists can benefit from increased opportunities to publish in MEDLINE-indexed journals; they will gain university-affiliated access to research resources for animal and human subjects as well as data from pilot studies and therefore help secure funding.

Regarding overall benefit of collaboration, Ms. Stone said, “We end up with better results because we have a more informed team.”²⁴

It is hoped that the information discussed here will encourage all healthcare providers to take diet and nutrition very seriously. These studies show the importance of patient education and emphasize the vital role that a wholesome diet complete with healing spices, herbs, and supplements plays in the prevention and treatment of chronic disease, including cancer.

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