NFH presents

fall 2012

nutramedica

integrating nutritional science and clinical application

Natural Health Products: Looking Back from the Future?

Peter Jones, PhD

Although we presently enjoy a healthy natural health product industry in Canada, we need to consider whether consumption of these seemingly novel ingredients truly represents a step forward or is merely a way of regaining ground lost from stepping backwards in the past. Our typical pattern of food intake has changed substantially over the past centuries. Particularly, the "whitening" or refinement of Western diets has seen the removal of many of the same ingredients that we now actively add as natural health products. For many of these ingredients, including omega-3 fats, fibers, probiotics, lutein, lycopene and plant sterols, consumption levels were substantially higher in our ancestral period. Indeed, it can be argued that the genetic make-up of our body systems is tailored to higher intakes of what we now call functional ingredients. A case in point is that scientists argue that key sites of human development over the ages have existed at the junction of ocean and land; areas where omega-3 fat intakes would be expected to be much higher from seafood than what we typically consume in present day diets. This speculation is supported by the vital role of omega-3 fats in human metabolism; for instance, omega-3 fats are the major type of fatty acids found in phospholipids of cells found in the retina.

What do we learn from identifying parallels between current use of natural health products and our ancestral food intake patterns? Two lessons emerge. First, efforts should be made to avoid promotion of food refinement and processing in Western societies. Although these activities increase desirability, taste and stability of foods, they often deplete such foods of important functional ingredients. The second lesson concerns defining these functional ingredients, which we now recognize as important for healthy maintenance, as necessary and indeed required in our daily lives, usually through the consumption of supplements. At present, several of these important dietary agents are not recognized by appropriate agencies as vital to health. The convergence of knowledge concerning the prevalence of these ingredients in our ancestral diets, together with our improved current scientific understanding, empower us to see consumption of these natural health product ingredients becoming more prevalent in our daily lives.

What Not To Do: Vitamin A and beta-*Carotene*

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Despite evidence from large, well-controlled, long-term human intervention trials highlighting significant and relevant harm from supplemental vitamin A and *beta*-carotene, the two constituents remain mainstays in formulas offered by the natural health products industry, most notably among multivitamin preparations.

We hope this brief review serves as a reminder to integrated health care practitioners to diligently screen all products prescribed for vitamin A and/or *beta*-carotene content, and strictly avoid their use. There is presently quite clear evidence of harm regarding risk of all cause mortality, cancer incidence, and perinatal morbidity.[1–5]

A Global Perspective

Vitamin A deficiency is estimated to affect approximately 30% of preschool age children in the developing world.[6, 7] A recent meta-analysis published in the *British Medical Journal* including 43 trials found that vitamin A supplementation among impoverished children under the age of five significantly reduced the risk of mortality by 24% in 17 trials (rate ratio 0.76, 95% CI 0.69-0.83), and reduced the prevalence of vision problems including night blindness by 68% (RR 0.32, 0.21-0.50).[6]

Nonetheless, although this is undoubtedly a crucial therapy regionally, the generalizability of this practice to well-nourished North American populations remains minimal. Among Western populations, vitamin A deficiency is virtually non-existent, with the possible exceptions of select cases among very limited and specific subgroups such as patients who have undergone bariatric surgery or who are severely anorexic.[8, 9] In an excellent review of vitamin A's safety, the case is presented that hypervitaminosis A is a growing problem in Western populations, in part due to an increasing number of products and foods containing preformed vitamin A: multivitamins, cod liver oil, and the fortification of common foods such as milk, butter, margarine, breakfast cereals, and some snack foods.[5]

The Evidence

A Cochrane meta-analytic review combined data from 67 randomized trials assessing antioxidant supplementation, including 232,550 participants. Among trials assessing vitamin A or *beta*-carotene, supplementation was associated with a significant increase in all cause mortality (RR 1.16, 95% CI 1.10 to 1.24) and (RR 1.07, 95% CI 1.02 to 1.11) respectively.[1]

Baseline Status: the Africa Experience

Supplementation among individuals on the brink of scurvy with vitamin C would be expected to deliver an important magnitude of benefit to an array of outcome measures,

while the same intervention administered to a population of citrus farmers is far less likely to yield benefit, given the expectation that citrus farmers enjoy a relatively high dietary intake of the vitamin.

HIV-positive, pregnant women in Tanzania, Africa, were recruited and assigned to one of four groups; multivitamin, vitamin A (5000 IU) and *beta*-carotene (30 mg); multivitamin free of vitamin A and *beta*-carotene; and placebo. Outcomes were presented in a series of papers, following the women throughout their pregnancy, as well as following the resulting offspring until age 18 months.[3, 10–12]

The multivitamin free of vitamin A and *beta*-carotene achieved highly significant benefit to a wide array of clinically important outcome measures, including but not limited to reduced risk of progression to stage IV AIDS/ reduced risk of death from AIDS-related causes, improved weight gain during pregnancy, reduced risk of over a dozen AIDS-related complications, improved $CD4^+$ counts and reduced viral load, reduced risk of hypertension during pregnancy, and greater scores on several developmental scales in the resulting offspring. The multi with vitamin A and *beta*-carotene demonstrated no impact to most of these measures, marginally improving a small, select number of the outcomes; most notably, the multi with vitamin A and *beta*-carotene achieved no impact to the outcome of progression to stage IV AIDS or risk of mortality. Vitamin A and *beta*-carotene alone achieved no significant impact to any outcome measure.[3, 10–12]

If vitamin A and *beta*-carotene are incapable of materially benefiting this obviously malnourished population, what benefit can possibly be hoped for when supplementing relatively well-nourished, free-living North American populations?

Biomarker Hypothesis

Why have trials assessing dietary *beta*-carotene intake, or better yet, studies assessing plasma levels of *beta*-carotene, reproducibly demonstrated highly reduced risk of chronic degenerative disease among populations with greater plasma levels of the nutrient? Hindsight has indeed proven 20/20. In such studies, participants are not using vitamin supplements. The *beta*-carotene is in fact serving as a biomarker of exposure to fruit and vegetables, as opposed to providing a link between the nutritional properties of *beta*-carotene in isolation. Modern trials of this nature conclude that their findings reinforce recommendations to eat more fruit and vegetables.[13] Modern intervention trials that include diet modification as part of the intervention measure plasma *beta*-carotene as a means of tracking compliance: if subjects truly increase their fruit and vegetable consumption, their plasma *beta*-carotene will be significantly elevated relative to the "control" group.[14, 15]

Conclusion

An eloquent and well-developed body of research has emerged that clearly delineates the detrimental effects associated with use of supplemental vitamin A and

beta-carotene. Concrete harm has been reproducibly documented with respect to a number of important clinical outcomes, including all-cause mortality, cancer incidence, and perinatal morbidity. Given the range of safe and effective interventions available, we recommend against the routine use of vitamin A and *beta*-carotene in North American naturopathic medical practice.

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Grapeseed Extract: Antioxidant Extraordinaire

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Proanthocyanidins are found in many plants, including pine bark, goji, hawthorne and edible berries, cocoa, almonds, pomegranate and grapes. Grapeseed extract (GSE) is the most potent and clinically useful single antioxidant, providing abundant and stable oligomeric proanthocyanodins (OPCs). GSE recycles and reactivate glutathione, *alpha*-lipoic acid, and vitamins E and C, allowing the antioxidant network to repeatedly capture and dissipate the oxidative stress.[1]

GSE has potent effects on the vascular endothelial nitric-oxide system. Intracellular formation of reactive oxygen species (ROS) in endothelium leads to the Src kinase/phosphoinositide 3-kinase/ Akt-dependent phosphorylation of eNOS. Antioxidant, anti-ROS effects of GSE cause a relaxation of blood vessels, improving circulation for healing and repair.[2]

GSE penetrates the blood-brain barrier freely, fosters repair of this critical structure, and of cerebral vessels damaged by reperfusion injury. It is invaluable for treating stroke or traumatic brain injury. GSE inhibits proteases: collagenase, elastase, hyaluronidase and *beta*-glucoronidase. This reduces arterial and venous inflammation and permeability, i.e. leakage in diabetic retinopathy, venous thrombosis, hemosiderosis and lymphedema.[3]

GSE lowers oxidation of bad LDL cholesterol, phopholipase-2, and xanthine oxidase; chelates free iron; blocks platelet aggregation; and inhibits foam cells. GSE is a uniquely potent protectant against atherosclerotic plaque.[4]

GSE enhances wound healing and stabilizes connective tissue, particularly in epidermis, capillary walls, and GI mucosa.

Its effects on skin disorders such as psoriasis, sun damage, or eczema is significant, taking out redness of inflammation, as well as healing and preventing lipid peroxidation.[5] The anti-inflammatory effects stem from inhibition of COX-1, COX-2, LOX and the inflammatory regulator NF-κB. It also reduces inflammation via chelation of free iron.

GSE will relax the airways and block lung inflammation, providing a remarkable benefit in asthma.[6] GSE squelches histamine/allergy responses. It can reduce or eliminate the need for steroid inhalers in many cases, which has profound implications for long-term health in asthmatics.

The contributions of GSE to the control of many cancers stem from a multitude of mechanisms. GSE regulates cell cycle/apoptosis genes *p53, Bcl-2, JNK* and *c-myc*.[7] Do not give *N*-acetylcysteine with GSE if using it to induce apoptosis in cancer cells.

GSE also suppresses cancer by reducing ROS activation of AP-1 protein; reducing TNF-α induction of VEGF angiogenesis; inhibiting EGF, MAPK, cyclin kinase. P21, and Cip-1. It up-regulates insulin-like growth factor-binding protein 3 (IGFBP3) by several-fold. It is a significant suppressor of aromatase expression, blocking conversion of androgens to estrogen.[8] Procyanidin B dimers suppress estrogen biosynthesis, reducing circulating estrogen by about 80%, on par with some aromatase inhibitor drugs. Some have implied GSE can increase cancer metastasis because it is a "circulation enhancer"; this sketchy concept is dead wrong—GSE actually inhibits metastasis through its inhibition of proteases and its strengthening of glycosaminoglycans in the intracellular matrix.[9]

GSE is very chemoprotective and repairs DNA, and so is a reasonable cancer preventative strategy.[10]

The daily dose should be 400 to 500 mg. In acute inflammation, give up to 1,600 mg daily for one week. GSE is synergistic with omega-3 oils for inflammation.

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One Patient's Food May Be Another Patient's Poison: The T_h-Cell Stimulating Effects of Nutrients

Leah Gillingham, PhD

While many foods and nutraceuticals have a wealth of clinical attributes, some specific nutrients can be therapeutically beneficial or detrimental depending on a patients' T_h1/T_h2 dominance. Indeed, one person's food may be another person's poison.

Why is T_h-Balance Clinically Relevant?

T_h1 and T_h2 are balanced in a healthy immune system. This balance is transiently shifted when needed to support cell-mediated immunity (T_h1 cell pathway) or humoral immunity (T_h2 cell pathway). A healthy immune system quickly rebalances once the specific immune challenge is mitigated. However, if a cytokine imbalance persists, a specific overactive T_h-cell pathway is maintained and immunopathological diseases like atopy, hypersensitivity reactions, and chronic inflammation can occur.[1, 2] Therefore, restoring T_h1/T_h2 balance via specific supplements can help prevent and treat many autoimmune conditions and associated diseases.

T_h1 Dominant Disorders

Persistent T_h1-mediated response will produce organ-specific autoimmune diseases and inflammation associated with pathologies like Crohn's disease, IBD, type 1 diabetes, thyroid disease, *H. pylori* gastritis, cellular autoimmunity, chronic recurrent inflammation, rheumatoid arthritis, and multiple sclerosis.[1, 2] The goal in prevention and treatment of T_h1 rigidity-associated diseases is up-regulating the production of T_h2-stimulating cytokines (IL-4, IL-13, IL-5, IL-10) as well as T_h3 and T_{reg} cytokines (IL-10 and TGF-β), ultimately inhibiting the development of T_h1 cellular dominance.[1]

T_h2 Dominant Disorders

Persistent, uncontrolled T_h2 activation is associated with systemic autoimmune diseases including the atopic triad (allergies, eczema, and asthma), chronic fatigue and immunodeficiency syndrome, eosinophilic rhinosinusitis, ulcerative colitis, viral infections, and possibly certain cancers. Up-regulating the production of T_h1 stimulating cytokines (IL-12, IL-18, INF-γ, TNF-α) and T_h3 and T_{reg} cytokines (IL-10 and TGF-β) is targeted in prevention and treatment of T_h2 rigidity-associated diseases.[1]

T_h1- or T_h2-Skewing Supplements in Clinical Practice

Certain nutrients, as well as specific probiotic strains, can stimulate the secretion of specific cytokines, facilitating the development of native T-cells towards a particular immunomodulating T_h1 or T_h2 pathway. So, what supplements are most ideal for your patients' health?

T_h1-Stimulating Supplements:
Astragalus,[4] ashwagandha,[5] licorice,[6] *beta*-sitosterols,[7] grapeseed extract,[8] panax ginseng,[9] chlorella,[10] green tea,[11] and specific *Lactobacillus* strains.[1, 3]

T_h2-Stimulating Supplements:
Curcumin,[12] quercetin,[13] resveratrol,[14] genistein, and specific *Bifidobacterium* probiotic strains.[1, 3]

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is proudly produced and distributed by *Nutritional Fundamentals for Health (NFH),* a Canadian-based nutraceutical organization focused on bridging the gap between clinical, evidence-based medicine and the nutraceuticals available to those industry professionals.

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