NFH presents

summer 2017

nutramedica

integrating nutritional science and clinical application

Nutramedica Gets a Reboot for 2017

Peter Jones, PhD

Nutritional Fundamentals for Health launched its publication *Nutramedica* several years ago as means of supporting our evidence-based platform in communicating the latest developments in natural product discovery to you as health-care professionals and their clients. Since its inception, this publication has featured NFH's Scientific Advisory Panel and Medical Consultancy Group members communicating sound scientific news and views to our readership through their authorship of the content of *Nutramedica*. The articles have been positively received by you, our readership, as accurate, informative, and interesting. However, in the spirit of constant reinvention and improved technology, the format of this publication is to undergo a refresh. The summer 2017 edition of *Nutramedica* will be the last one to be provided in its present written configuration. The intention is to shift from text to a presentation-style format which takes advantage of advances in technology and consumer preference. *Nutramedica* articles will in the future take the form of webinars and YouTube educational posts, provided by the same experts who contributed to this publication in its present configuration. Our Advisory Board members will continue to cover topics of importance to the natural-product industry, but do this in a more engaging and instructive webinar-based format. Many of these webinars and YouTube contributions will be posted on the Nutritional Fundamentals for Health website (www.nfh.ca) for ongoing and future access, as has been the pattern for past versions of *Nutramedica*. It is the belief of the editors of *Nutramedica* that NFH will continue to deliver to you the same high quality of information, but in a more modern and interactive format in keeping with advances in technology. We look forward to hearing your feedback on this fresh face for *Nutramedica* as we release its new configuration in Fall 2017.

An Apple a Day Keeps the Doctor Away

Neil McKinney, ND

Quercetin is the most abundant bioflavonoid in the human diet, particularly in foods such as apples and yellow onions. The average diet provides about 25 mg daily. Quercetin modulates the redox state and oxidative metabolism.[1] Quercetin is significantly higher in plants grown in organic

compost versus chemical fertilizer. The plants use it to extract nitrogen from the soil.

It is a powerful antihistamine.[2] It is very beneficial for inhalant allergies and hay fever, without causing drowsiness.

Quercetin inhibits replication of RNA and DNA viruses, enhances natural killer (NK) cell activity, and is immune-modulating.[3]

Quercetin activates the "fountain of youth" sirtuin protein SIRT1, a NAD-dependent histone deacetylase. This creates an antiaging effect by stimulating biogenesis of new mitochondria.

Quercetin Supports Most Chemotherapy Drugs

Theoretically, antioxidants reduce the prooxidative stress from chemo, resulting in less apoptosis of cancer cells, and thus reduced efficacy. In fact, all the common antioxidants generally improve tumour-cell killing, and patient tolerance too. Only enzymatic, non–food source antioxidants—glutathione and *N*-acetylcysteine—unequivocally interfere with chemo. Many "antioxidants" can also be prooxidants. Melatonin is an "antioxidant" *proven* to improve outcomes and reduce harm from RTx and chemo, when given in prooxidative doses! Research trumps dogma!

Conklin Hypothesis: Chemo prooxidative effect creates toxic aldehydes which prevent cells from cycling. Antioxidants reduce this, allowing more cancer cells to progress through their cell cycle.[4] More cancer cells get to the state where a given chemo drug can kill them. There is less oxidative stress to force apoptosis, but still a net positive effect.

Quercetin is the most common chemo support, which traps more drug in the cancer cell, increasing effectiveness 30%; poisons the P-glycoprotein porter system, aka MDR1—the primary mechanism by which cancer cells become chemoresistant; reduces chemo toxicity—increases liver clearance of drug; interferes with the porter-system ion pump, also called P-glycoprotein, which can pump drugs right out of cancer cells. This is like bailing water out of a sinking boat.[5] Giving quercetin with many chemo drugs helps hold enough chemo inside the cancer cells to overcome multidrug resistance MDR to effect a cure.

Quercetin also restricts drug resistance by inhibition of heat-shock protein HSP-70.[6] Inhibiting heat-shock proteins disrupts formation of complexes of mutant p53 and HSPs, which would allow tumour cells to bypass normal cell cycle checkpoints. No HSPs means no mutant p53 activity. If HSPs are left unchecked, there is a risk of shorter

disease-free survival and increased chemotherapy drug resistance in breast cancer. Quercetin down-regulates expression of mutant p53 protein, arresting human breast cancer cells in G2-M phase of the cell cycle, and human leukemia cells T-cells and human stomach cancer cells in G1-S phase. DNA replication is thus markedly reduced.

Use quercetin with adriamycin, busulphan, camptothecin, capecitabine carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, 5-fluoro-uracil, gemcitabine, irinotecan, melphalen, methotrexate, mitomycin, oxaliplatin, premetrexed, ribavirin, tamoxifen, temozolomide and vinca alkaloids—vincristine and vinblastine.

Do *not* use quercetin with mercaptopurine, taxanes—paclitaxel, docetaxel (taxotere), tarceva aka erlotinib, or velcade aka bortezomib.

Other uses in oncology: Quercetin inhibits cyclooxygenase COX-2 transcription and lipoxygenase, especially the LOX-5/5-HETE eicosanoid pathway. It reduces proinflammatory NFκB nuclear transcription protein. This in turn inhibits invasion and metastasis.

Quercetin induces apoptosis via inhibition of Akt/PKB phosphorylation, an upstream kinase of prosurvival protein kinase cascade. Inhibition of Akt phosphorylation is coupled with a significant decrease of antiapoptotic Bcl-2 and Bcl-XL. Quercetin causes a downregulation of Cu-Zn superoxide dismutase which leads to an increase of reactive oxidative stress (ROS). The decrease of Bcl-2 and Bcl-XL along with this oxidative stress releases mitochondrial cytochrome c into the cytosol and subsequently induces pro-caspase-9 processing.[7] Quercitin is highly synergistic with ellagic acid. The combination markedly increases activation of p53, p21 (cip1/waf1), MAP kinases, JNK1,2, and p38. This results in apoptosis in cancer cells. Quercetin is also quite synergistic with green-tea EGCG and marine omega-3 oils, says a naturopathic oncologist. Other FABNOs suggest there is a synergy with sulforaphane and resveratrol.

Quercetin blocks peroxide inhibition of cell-cell signaling.[8] It suppresses signal transduction pathways such as protein kinase C and casein kinase II, preventing these signals from the cell surface to the nucleus from overriding normal growth controls. Quercetin inhibits lymphocyte tyrosine kinases. Its cytotoxic effect is dose-dependent.

Quercitin blocks epidermal growth factor receptor EGFR active in all carcinomas, and reduces activity in the related HER2 signal pathway.[9]

An aromatase inhibitor, it reduces

estrogen hormone formation in adipose tissue (fat cells). Quercetin binds type II estrogen receptors in breast, colon, ovary, melanoma, leukemia, and meningeal cancer cells, inhibiting growth. ER-2 receptors have only a weak affinity for estrogen, and probably inhibit growth when stimulated by flavonoids. Quercetin inhibits the proliferative effect on breast cancer cells of environmental xenoestrogens such as bisphenol A and diethylstilbesterol (DES).

Quercetin activates aryl hydrocarbon receptor AhR-dependent breast cancer resistance protein BCRP. It can be supported in this action by resveratrol, indole-3-carbinol, and curcumin.

It arrests p21-ras proto-oncogene expression, a mutation found in 50% of colorectal cancers. The p21-ras mutation impairs cellular GTP-ase, allowing continual activation of the signal for DNA replication in colon cancer and many other tumour types.

Quercetin inhibits STAT3 DNA copying factor,[10] critical in pancreatic cancer, lymphomas, and movement of breast cancer into bone.

In my experience, quercetin is most valuable in breast cancer, pelvic cancers, and meningiomas.

Quercetin is also a highly beneficial adjunct to hyperthermia in cancer care.[11]

My learned colleagues prescribe 1,000 mg doses at meals. That is typically two capsules two to three times daily.

Cautions and Contraindications

While quercetin is mutagenic to bacteria, it is not carcinogenic in humans.

Bioflavonoids like quercetin inhibit thyroid peroxidase (which adds the iodine to thyroid hormone), and so will aggravate hypothyroidism in patients with inadequate iodine consumption. Fortunately, iodine deficiency is extremely rare in North America.

Extreme doses are toxic to the kidneys, e.g. if a child eats an entire bottle of pills.

Reactions are extremely rare, but just to illustrate the odd things one must expect in clinical practice, one patient experienced a dull headache, band-like around the head, became very spacy, losing words and thoughts, had a general sick and nauseated feeling, with shaky,

wobbly legs making it hard to stand. This repeated several times until quercetin was stopped.

References

1. Lamson, D.W., and M.S. Brignall. *Alt Med Rev* 2000;5(6):196-208.
2. Marozzi, F.J. Jr., A.B. Kocialski, and M.H. Malone. *Arzneimittelforschung* 1970;20(10):1574–1577.
3. Konrad, M., et al. *Int J Sport Nutr Exerc Metab* 2011;21(4):338–346.
4. Conklin, K.A. *Nutr Cancer* 2000;37(1):1–18.
5. Conklin, K.A. *Integr Cancer Ther* 2004;3(4):294–299.
6. Kim, S.H., et al. *Exp Mol Med* 1998;30(2):87–92.
7. Suolinna, E.M., R.N. Buschbaum, and E. Racker. *Cancer Res* 1975;35(7):1865–1872.
8. Choi, J.A., et al. *Int J Oncol* 2001;19(4):837–844.
9. Jeong, J.H., et al. *J Cell Biochem* 2008;105(2):585–595.
10. Cao, H.H., et al. *Biochem Pharmacol* 2014;87(3):424–434.
11. Shen, J., et al. *Int J Hyperthermia* 2008;24(2):151–159.

Supplements and the Cholesterol-Lowering Dietary Portfolio

David J.A. Jenkins, MD, PhD, DSc

It can be argued that the diet should provide all the food components you need, and that there should be no need for supplements. This food-based preference may be seen as particularly desirable, rather than vitamin and mineral supplements. However, it has also been claimed that North Americans in general do not take "ideal" diets, and therefore supplements—especially multivitamins—may play a role [1]. At the same time, there have been warnings of potential harm from supplements, such as the use of β-carotene in smokers to reduce the risk of lung cancer when the outcome of the CARET trial found an increase in lung cancer.[2] This warning and a lack of endorsement of vitamin and mineral supplements was endorsed by the US Preventive Services Task Force recommendation in 2014.[3] A similar approach has been the stand taken by most agencies concerned with cardiovascular disease (CVD) and cancer, perhaps with the exception of cancer agencies (notably the Canadian Cancer Society) that recommends vitamin D supplementation especially during the winter months (http://www.cancer.ca).

This situation is different from the recommendations of CVD societies in their advice on ways to lower serum cholesterol. Here supplements have been advised. Notably the NCEP ATP III advice for Americans to lower their serum cholesterol levels. ATP III recommended that Americans could be advised to add 2 g plant sterols and 20 g of viscous fibre to their diets to enhance the cholesterol-lowering effect of therapeutic diets. At the same time, the US Food and Drug

Administration began the process of allowing health claims for cholesterol-lowering foods or dietary components that would be expected to reduce the risk of CHD. By the turn of the century, four basic health claims were allowed for individual foods or food components. It is these foods we have used in our dietary portfolio.

Portfolio of Cholesterol-Lowering Components

- Viscous-fibre foods containing appropriate amount of oats and barley β-glucan fibre and also for psyllium (Kelloggs produced a psyllium-containing breakfast cereal)
- Plant sterols and stanols
- Soy-protein foods
- Nuts (almonds, walnuts, hazel nuts, pistachios, etc.)

These foods, interestingly, were the same foods or food components that we had found to produce a drug-like (statin-like) effect on serum cholesterol in healthy volunteers who are taking an "ancestral diet" that we had put together, representing the types of foods our ancestors might have eaten 4–5 million years ago. That diet required people to eat over 5.0 kg of food daily, in some cases nearly 10% of their body weight for the women. Although the obvious virtue of this diet was that you would never get fat, it did become a problem for people to eat all the food they needed to maintain weight and to get the bioactive components that would lower serum cholesterol as dramatically as we had seen on the ancestral (Simian) diet by 35% in two weeks. Therefore, supported also by the FDA health claims, we decided to see if these foods could be taken in a more targeted form, in a diet of reasonable volume for contemporary western eating habits. The Dietary Portfolio was therefore created and focused on nuts 43 g/d, sticky (viscous) fibres from oats barley and psyllium at 18 g/d, soy-protein foods at 43 g/d soy protein, and plant sterols in margarines (or other foods) at 2 g plant sterols per day in a 2,000 kcal diet.

We were able to show that this diet lowered LDL-C by about 30% when all food was provided for a month, and by 13–14% in participants across Canada who were required to do their own shopping and make their own meals. Consequently, their compliance was only 40–45% what had been intended, and their reduction in serum LDL-C, at 13–14%, was half that observed on the metabolic diet (all food provided), at ~ 30%. Nevertheless, the 13–14 % LDL-C reduction is enough to keep many people below the LDL-C level above which they would be prescribed statins.

Nevertheless, a greater LDL-C reduction is still required, and it is here that

supplements may play a role in a clearer way (as judged by LDL-C reduction) than they have using vitamin and mineral supplementation where we have no effect on biomarkers of risk factors.

Margarines are supplemented with plant sterols, as are other foods (even chewing gum) or in powdered form in capsules, that may make it easier to get a therapeutic dose (note 1 g of plant sterol in whole foods was consumed in our ancestral diet). Nuts are themselves sufficiently low-volume to be seen as minisupplements. Viscous fibre can be given as concentrates, as oat or barley bran or purified β-glucan, and psyllium as Metamucil can be taken in as sachet in powder form. Soy protein can also be taken as a powder to be reconstructed as soy milk.

Supplements of food origin may therefore have a role to play to enhance the therapeutic value of a cholesterol-lowering diet. Whatever the approach to the cholesterol lowering, for example when using the Dietary Portfolio, we would also suggest a vegan or plant-based diet as the background diet, with additional vegetable sources of protein also from legumes, peas, beans, and lentils, since both vegetarian diets and legumes have been shown to be associated with low blood cholesterol levels and/or a reduced risk of heart disease.

References

1. Willett, W.C., and P.J. Skerrett. *Eat, Drink, and Be Healthy: The Harvard Medical School Guide to Healthy Eating.* New York: Free Press, 2005, 348 p.
2. Omenn, G.S., et al. *J Natl Cancer Inst* 1996;88(21):1550–1559.
3. Moyer, V.A.; U.S. Preventive Services Task Force. *Ann Intern Med* 2014;160(8):558–564.

nutramedica

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.

Content Director:
Peter Jones, PhD

Editors:
Leah Gillingham, PhD
Peter A.S. Alphonse, PhD

Distribution Manager
Krystle Lussier

NFH
3405 F.-X.-Tessier
Vaudreuil-Dorion (Québec)
J7V 5V5
1 866 510-3123
info@nfh.ca
www.nfh.ca