SPECIAL NEWSLETTER SUPPLEMENT TO ANNOUNCE GROUNDBREAKING WORK!!

A MAJOR BREAKTHROUGH IN THE NUTRITIONAL MANAGEMENT OF SYNDROME X: CITRUS BERGAMOT

Editors Note:
I have been self-challenged for many years to find nutritional solutions to the complex pathophysiology that underlies the Metabolic Syndrome X. My initial excitement about the use of gel fibers in the management of regulation of blood glucose and blood lipids remains following my studies published in the Lancet more than 30 years ago (1, 636-9, 1979). My excitement is now reactivated by the discovery of the multifunctional effects of extracts of Citrus bergamot which has demonstrable effects on helping to normalize blood lipids assisting with weight control and exhibiting clear effects on glucose homeostasis. These problems of body function are the hallmark of Metabolic Syndrome X which is underpinned by the presence of insulin resistance. The information provided in this newsletter has emanated from collaborative work from Annie Eng at HP Ingredients who are the bulk suppliers of special forms of Citrus bergamot that are derived exclusively from citrus orchids in calabria in the south of Italy. I trust that the readers of this newsletter will share my excitement on these new discoveries.

Key Nutraceutical Approaches to Syndrome X
Following the publication of my studies on the physiological basis of blunting post-prandial blood glucose levels with soluble fiber in 1979 (Holt S et al, Lancet, 1, 636-9, 1979), I was captured by an odyssey to find natural ways of reversing Metabolic Syndrome X and treating type II diabetes mellitus. The work by my colleagues and I in the 1970’s started to explain the physiological
basis of what was termed “the glycemic index” in the 1980’s. During my days as a lecturer in therapeutics (Edinburgh University, Scotland), the language of Metabolic Syndrome, Syndrome X, insulin resistance and the glycemic index were not in medical parlance. However, my colleagues and I discussed these matters constantly. After all, abnormalities of blood glucose do not cause direct death in many circumstances, but they underlie the common causes of death that are encountered in Syndrome X and type II diabetes (notably, cardiovascular disease and renal disease).

My colleagues and I believe that glucose absorption shared much in common with drug absorption, where the limiting factor in reaching peak blood concentrations of almost any orally administered substance was dependent upon the rate of which most of these substances were delivered to their site of maximal absorption in the small bowel. Of course, there are compounds with highly complex facilitate absorption processes and some small molecular weight substances (e.g. alcohol) may be absorbed in the stomach bed. However, reaching peak blood concentrations of absorbed material is highly dependant upon the rate of stomach emptying (Holt S et al, Lancet, 1, 636-9, 1979).

A logical outcome of my work was to use viscous soluble fiber to blunt blood glucose levels following meals or specifically glucose intake. I did not find it easy to get individuals to eat significant quantities of gel fiber to control post-prandial blood glucose, but this simple action of gel fiber seemed to be readily applicable in the management of diabetes mellitus. Despite the hurdle of getting individuals to eat soluble fiber loads, I persisted in this therapeutic maneuver and it is still used today in various forms. In fact, I have applied this approach to the management of Syndrome X for two decades (www.naturalclinician.com).

Of course, it is the power of Mother Nature that confers the dual power of soluble fibers to smooth out blood glucose following meals and correct abnormal blood lipids (cholesterol). Stopping swings in blood glucose is beneficial in the presence of any abnormalities of glucose homeostasis. This maneuver not only deals with hyperglycemia, it can correct hypoglycemia in some circumstances.

I indulge in this history of personal reasoning because the real task was for me to find nutritional or natural substances that would start to connect the dots among the constellation of problems that are present in a condition that we now call Metabolic Syndrome X (overweight status, hypertension, dyslipidemia and insulin resistance). I believe that science is coming closure to showing the multifunctional nature of certain natural substances with the discovery of the versatile benefits of Citrus bergamot (with greater understanding of the benefits of niacin).

**Citrus Bergamot: A Miracle of Nature**

The most important milestone in my odyssey to correct Syndrome X is
the recognition of the multifunctional effects of Citrus Bergamia Risso (Bergamot). This citrus plant grows preferentially in Calabria, Italy and it has been the focus of much research that has defined its potent and beneficial properties on the correction of dyslipidemia, improvements in blood glucose control and adjunctive weight loss effects! I emphasize the common occurrence of Syndrome X and its ability to increase death rates from all causes (Trevisan et al, American Journal of Epidemiology, 148, 958-966, 1998, Ford ES et al, JAMA, 297, 3, 356-359, 2002, Holt S, Combat Syndrome X, Y, and Z., Little Falls, NJ, 2002, www.hiom.org).

Clinical trials have been completed in 274 patients with significant dyslipidemia and the variable presence of excessive body weight or evidence of impaired glucose tolerance (Mollace V, Romeo F, University of Rome, Italy, In Press 2010). In 82 patients, polyphenolic extracts of Citrus bergamot (500 or 1000mg/day) were administered for 30 days and in the remaining 192 patients a specific standardized preparation of Bergamot juice was used for the same period. Table 1 shows a striking statistically significant reduction in LDL, triglycerides, total cholesterol and blood glucose, with a concomitant increase in HDL levels. In collective trial experiences, Bergamot lowers LDL levels in a range of 20-59% (c.f. statins 18 to 55%) and raises HDL in a range of 7-83% (c.f. statins 5-15%).

<table>
<thead>
<tr>
<th></th>
<th>TOTAL CHOLESTEROL</th>
<th>HDL CHOLESTEROL</th>
<th>LDL CHOLESTEROL</th>
<th>TRYGLYCERIDES</th>
<th>BLOOD GLUCOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BERGAMOT JUICE 100 ML/DAY</td>
<td>-35.72%</td>
<td>+56.05%</td>
<td>-41.95%</td>
<td>-38.31%</td>
<td>-22%</td>
</tr>
<tr>
<td>BERGAMOT EXTRACT 500 MG, 1 OR 2 CAPS PER DAY</td>
<td>-31.44%</td>
<td>+42.82%</td>
<td>-38.84%</td>
<td>-41.54%</td>
<td>~21.93%</td>
</tr>
</tbody>
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Table 1: Striking corrections of dyslipidemia and glucose regulation with bergamot(4)

The results of treatment with specific forms of Citrus bergamot under the conditions of several studies are superior to the use of statin drugs.
because of consistent increases in HDL and improvement in glucose homeostasis without any of the onerous adverse effects of statin drugs (e.g. muscle pain, weakness, rhabdomyolysis, potential hepatotoxicity and altered cognition). Statin drugs have a minor anti-inflammatory effect, but bergamot preparations contain powerful antioxidant polyphenols with anti-inflammatory properties that are ideal to help control chronic inflammation, consequential upon oxidative stress. In a separate group of 20 patients, weight control was observed to occur with bergamot use, resulting in an average weight loss of 2Kg/month. Recent studies indicate that bergamot reduces induced intimal vascular damage and lecitine-like oxyLDL receptor-1 expression (Mollace V et al, J of Cardiovasc Pharm and Ther, 13, 2, 120-129, 2008).In summary, specific extracts of bergamot provide outstanding and safe actions on the reversal of dysglycemia and dyslipidemia with secondary benefits of weight loss. While Citrus bergamot extracts have multi-functional effects for the adjunctive nutraceutical management of Metabolic Syndrome X, they represent a major breakthrough in the nutritional support of cardiovascular health. No other nutraceutical or nutrient or drug has been shown to have the versatile therapeutic effects that have been experienced with Citrus bergamot extracts. If further research confirms the findings to date, Citrus bergamot will revolutionize natural approaches to cardiovascular health with a role as a viable, value-added alternative to statin drugs.

### Actions of Citrus Bergamot

The beneficial actions of Citrus bergamot are listed in Table X. below:

- Cardiovascular Health
- Reduction in Total Cholesterol
- Reduction in LDL
- Reduction in Blood Triglycerides
- Increases in HDL
- Reduction in Blood Sugar Levels (Diabetes and Pre-Diabetes)
- Adjunct to the promotion of healthy weight loss

### Table X. Actions of Citrus bergamot

Citrus bergamot works by clocking a key enzyme in the production of cholesterol. It inhibits the HMG-CoA (3-hydroxy-3-methyglutaryl COA) reductase, an enzyme linked to the liver’s cholesterol production, thus inhibiting the liver’s ability to produce LDL. These results in reduced cholesterol levels in liver cells, which then meet their cholesterol requirements by taking up cholesterol circulating in blood, via a protein on the liver cell
surface called LDL receptor. LDL receptors break down the circulating cholesterol, which results in reduced levels of LDL cholesterol in the bloodstream, and a reduction in risk for high-cholesterol related diseases.

HMG-CoA reductase is active when blood glucose is high. Thus, by lowering blood sugar levels, Citrus bergamot also indirectly affect the activity of HMG-CoA reductase. Recently published research shows Citrus Bergamot has statin like principles, carrying the 3-hydroxy-3-methylglutaric acid (HMG moiety. Four flavonoids, have been identified that are able to interfere with the natural synthesis of cholesterol in human body, by inhibiting the activity of the first enzyme in the cholesterol synthesis pathway: HMG-CoA reductase (3-hydroxy-3-methyl glutarilcoenzyme A reductase). These flavonoids is linked to 3-metil-3-hydroxy glutarile portion, which is exactly the substrate of HMG-CoA reductase, suggesting that these compounds mimic endogenous HMG-CoA substrate and interfere with the synthesis of mevalonate, a critical compound at the top of the cholesterol synthesis pathway.

By interfering with mevalonate synthesis, the polyphenolic flavanoids block the cholesterol production in the human body similar to statins. The presence of these flavones in the bergamot juice or powdered extracts explains popular knowledge and recent clinical data on blood cholesterol reducing potential of citrus bergamot (Table Y.)

- Two of the active compounds in Bergamot have 3-hydroxy-3-methylglutaric acid (HMG) bound to neohesperidin (Brutieridin) and naringin (Melitidin).
- Brutieridin and Melitidin have shown in research to inhibits HMG reductase, which leads to the catalyze of mevalonate biosynthesis (key intermediate in cholesterol metabolism)
- Consumption of Bergamot in 30 days reduces MVA Concentration (end product of HMGCoA reductase)
- Bergamot reduce oxidative stress, neutralize free radicals in vascular walls, enhance vasodilatation, and restore endothelial function
- Consumption of bergamot enhances fecal sterol excretion, binding bile acids and increase the turnover rate of blood and liver cholesterol
- Bergamot significantly reduces Triglycerides level via reduction in hepatic Triglycerides accumulation
- The active compound Neoeriocitrin & rutin has been proven to inhibit LDL Oxidation

Table Y: A Summary of Scientific Findings with Citrus bergamot
Conclusion

Scientific data collected to this point in time show highly favorable multifunction actions of Citrus bergamot, with basic science studies supported by clinical observations. To have a gift of nature that can lower LDL, raise HDL, form an adjunct to weight control and improve glucose homeostasis is a major breakthrough. Inquiries about Citrus bergamot can be directed to www.hpingredients.com Natural Clinician and HP Lifesciences intend to launch a professional form of Citrus bergamot in cooperative marketing agreements.