The Lipid Lowering Activity of NoChol

NoChol is a proprietary blend of natural products including pantethine, berberine, curcumin, chromium polynicotinate and biotin designed to serve as a natural lipid-lowering remedy.

INTRODUCTION:

Cardiovascular disease, including coronary artery disease, atherosclerosis, cerebral vascular disease, cerebral vascular accident (stroke), myocardial infarction, sudden death syndrome, is the number one cause of death in most developed countries all over the world. Elevated circulating cholesterol levels, in particular low-density-lipoprotein cholesterol (LDL-cholesterol) levels have been well established as one of the major risk factors for the development and progression of cardiovascular and cerebral vascular diseases, as have high levels of circulating lipids such as triglycerides. In addition, these subjects often also experience obesity, metabolic disorders (such as syndrome X and diabetes) and hyperlipidemia, which are all major subgroups of the population that are adversely affected by high cholesterol and triglyceride levels.

Although advances have been made in treating cardiovascular disease and metabolic disorders associated with hyperlipidemia, hypercholesterolemia and the like, these conditions still are responsible for significant deterioration of the quality of life and risk of death for many patients. In many cases, medications used to treat these conditions are not well tolerated and have significant side effects. For example, the major drawback to the predominant statin or statin-like compounds is muscle soreness, muscle weakness, muscle tenderness, intense muscle pain (collectively known as statin-induced myopathy), peripheral neuropathy and extreme form of muscle damage called rhabdomylosis. Rhabdomylosis can be both a serious and a life threatening side effect clearly associated with the use of statin drugs where the muscle breakdown causes major organ damage to both the liver and kidney that has resulted in many reported deaths.

PANTETHINE:

Pantethine (bis-pantethine or co-enzyme pantethine) is a dimeric form of pantothenic acid (vitamin B5). It is composed of two molecules of pantothenic acid linked by cysteamine bridging groups. The monomer of this compound is known as pantetheine and is an intermediate in the production of Coenzyme A by the body. Pantethine is considered the more biologically active form of vitamin B5, but it is less stable, decomposing over time if it is not kept refrigerated. Most vitamin B5 supplements are therefore in the form of calcium pantothenate, a salt of pantothenic acid.

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Pantethine may be useful for: (a) prevention and treatment of a pantothenic acid deficiency; (b) replenishment of pantothenic acid to patients suffering from wasting diseases or hyperthyroidism, or to pregnant and parturient women or breast-feeding women who have an increased demand for pantothenic acid that cannot be supplied sufficiently from foods; and (c) prevention and treatment of hyperlipidemia, atonic constipation, and side effects of streptomycin and kanamycin, improvement of acute and chronic eczema, and improvement in platelet counts and hemorrhagic tendency in blood dyscrasias, when these diseases, disorders or symptoms are presumed to be attributable to a deficiency or a metabolic disorder of pantothenic acid.

Pantethine is available as a dietary supplement because of evidence of its health benefits. In multiple clinical trials of patients with elevated cholesterol and triglycerides, total and LDL cholesterol were decreased by 12%, triglycerides decreased by 18%, and HDL cholesterol was increased by 9%. These clinical trials were conducted with daily intakes ranging from 600 to 1200 mg/day. Within this dose range there is no evidence of a dose-effect relationship, i.e. changes in lipid concentrations overlapped across the range of doses. Direct dose-response evidence is not available because no trial tested more than one dose. A few trials tested 300 mg/day with more modest but still statistically significant results. Further carefully controlled trials of 600 and 900 mg/d doses have shown statistically significant lowering of LDL cholesterol in individuals with greatly or moderately elevated levels of blood lipids.

Although pantethine can serve as a precursor for generation of vitamin B5, this is not thought to be the mechanism of action. Vitamin B5 requirements are on the order of 5 mg/day. Two mechanisms of action are proposed for pantethine. In the first, pantethine serves as the precursor for synthesis of coenzyme A. In the second, pantethine is converted to two pantetheine molecules which are in turn metabolized
to form two pantethenic acid and two cysteamine molecules. Cysteamine is theorized to bind to and thus inactivate sulfur-containing amino acids in liver enzymes involved in the production of cholesterol and triglycerides.

BERBERINE:

Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is found in such plants as Berberis [e.g. Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric)], Hydrastis canadensis (goldenseal), Phellodendron amurense (Amur cork tree, huang bai, huang po, po mu) and Coptis chinensis (Chinese goldthread, huang-lian, huang-lien), and Tinospora cordifolia, and to a smaller extent in Argemone mexicana (prickly poppy) and Eschscholzia californica (Californian poppy). Berberine is usually found in the roots, rhizomes, stems, and bark.


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As a traditional medicine or dietary supplement, berberine has shown some activity against fungal infections (for example, infection due to Candida albicans), parasites, and bacterial/viral infections. Berberine is considered antibiotic. When applied in vitro and in combination with methoxyhydnocarpin, an inhibitor of multidrug resistance pumps, berberine inhibits growth of Staphylococcus aureus and Microcystis aeruginosa, a toxic cyanobacterium. Berberine is also considered to have anti-inflammatory properties and modifies production of certain proinflammatory cytokines and E-selectin. It also
increases adiponectin expression which partly explains its versatile health effects. Berberine is a nucleic acid-binding isoquinolone alkaloid with wide potential therapeutic properties.

During the last few decades, many studies have shown berberine has various beneficial effects on the cardiovascular system and anti-inflammatory activities. A Canadian report suggested berberine can effectively reduce intracellular superoxide levels in LPS-stimulated macrophages. Such a restoration of cellular redox by berberine is mediated by its selective inhibition of gp91phox expression and enhancement of SOD activity.

Berberine exerts up-regulating activity on both the low-density-lipoprotein receptor (LDLR) and the insulin receptor (InsR). In addition, berberine has been tested and used in experimental treatment of diabetes mellitus. Further, berberine has been shown to lower elevated blood glucose as effectively as metformin. The mechanisms of action include inhibition of aldose reductase, inducing glycolysis, preventing insulin resistance through increasing insulin receptor expression and acting like incretins. A new study suggested berberine may overcome insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulinresistant cells.

Berberine might exert its insulinotrophic effect in isolated rat islets by upregulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge.

Berberine seems to inhibit human dipeptidyl peptidase-4 (DPP IV), as well as the prodiabetic target human protein tyrosine phosphatase 1B, which explain at least some of its antihyperglycemic activities. Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states. A recent comprehensive metabonomics method, applied to 60 type 2 diabetics, suggested administration of berberine down-regulates the high level of free fatty acids which are known to be toxic to the pancreas and cause insulin resistance. These results suggest berberine might play a role in the treatment of type 2 diabetes. Further, berberine has been shown to boost the effects of metformin and 2,4-thiazolidinedione (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter.

Berberine inhibits Foxo1, which integrates insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during insulin resistance and the metabolic syndrome.

Berberine lowers elevated blood total cholesterol, LDL cholesterol, triglycerides and atherogenic apolipoproteins (apo B) (Apo B), but the mechanism of action is distinct from statins. Berberine reduces LDL cholesterol by upregulating LDLR mRNA expression posttranscriptionally while downregulating the transcription of proprotein convertase subtilisin/kexin type 9 (PCSK9), a natural inhibitor of LDL receptor (LDLR), and increasing in the liver the expression of LDL receptors through extracellular signal-regulated kinase (ERK) signaling pathway, while statins inhibit cholesterol synthesis in the liver by blocking HMG-CoA-reductase. This explains why berberine does not cause side effects typical to statins. Berberine and plant stanols synergistically inhibit cholesterol absorption in hamsters.
Berberine seems to improve the arterial endothelial function in humans. Berberine activates AMP-activated protein kinase (AMPK), specifically extracellular signal-regulated kinases (ERK), which plays a central role in glucose and lipid metabolism, suppresses proinflammatory cytokines, and reduces MMP-9 and EMMPRIN expression, which are all beneficial changes for heart health. Moreover, berberine reduces hepatic fat content in the rats of nonalcoholic fatty liver disease. Berberine also prevents proliferation of hepatic stellate cells (HSCs), which are central for the development of fibrosis during liver injury.

BIOTIN AND CHROMIUM POLYNICOTINATE:

Biotin is a water-soluble vitamin that acts as a prosthetic group of carboxylases. Besides its role as carboxylase prosthetic group, biotin regulates gene expression and has a wide repertoire of effects on systemic processes. The vitamin regulates genes that are critical in the regulation of intermediary metabolism: Biotin has stimulatory effects on genes whose action favors hypoglycemia (insulin, insulin receptor, pancreatic and hepatic glucokinase); on the contrary, biotin decreases the expression of hepatic phosphoenolpyruvate carboxykinase, a key gluconeogenic enzyme that stimulates glucose production by the liver. The findings that biotin regulates the expression of genes that are critical in the regulation of intermediary metabolism are in agreement with several observations that indicate that biotin supply is involved in glucose and lipid homeostasis. Biotin deficiency has been linked to impaired glucose tolerance and decreased utilization of glucose. On the other hand, the diabetic state appears to be ameliorated by pharmacological doses of biotin. Likewise, pharmacological doses of biotin appear to decrease plasma lipid concentrations and modify lipid metabolism. The effects of biotin on carbohydrate metabolism and the lack of toxic effects of the vitamin at pharmacological doses suggest that biotin could be used in the development of new therapeutics in the treatment of hyperglycemia and hyperlipidemia, an area that we are actively investigating.

Several studies have reported a relationship between biotin and blood lipids. The effect of biotin administration on the concentration of plasma lipids, as well as glucose and insulin in type 2 diabetic and nondiabetic subjects was investigated. Eighteen diabetic and 15 nondiabetic subjects aged 30-65 were randomized into two groups and received either 61.4 micromol/day of biotin or placebo for 28 days. Plasma samples obtained at baseline and after treatment were analyzed for total triglyceride, cholesterol, very low density lipoprotein (VLDL), glucose and insulin. We found that the vitamin significantly reduced (P=0.005) plasma triacylglycerol and VLDL concentrations. Biotin produced the following changes (mean of absolute differences between 0 and 28 day treatment+/-S.E.M.): a) triacylglycerol -0.55+/-0.2 in the diabetic group and -0.92+/-0.36 in the nondiabetic group; b) VLDL: -0.11+/-0.04 in the diabetic group and -0.18+/-0.07 in the nondiabetic group. Biotin treatment had no significant effects on cholesterol, glucose and insulin in either the diabetic or nondiabetic subjects. We conclude that pharmacological doses of biotin decrease hypertriglyceridemia. The triglyceride-lowering effect of biotin suggests that biotin could be used in the treatment of hypertriglyceridemia.

A statistically significant inverse association was generally found between plasma total lipid, cholesterol, or phospholipid and biotin status of 300-day-old male inbred BHE (IN-BHE) rats. Plasma, liver, and carcass lipid of both sexes generally had a significant direct association with liver lactate dehydrogenase
activity; an inverse association in males resulted with improved biotin status. Elevated plasma lactate indicative of anaerobic glycolysis was found. It is proposed that an increased reductive environment - a consequence of accumulated NADH - could account for enhanced triglyceride synthesis and that this effect could explain the obesity in the INBHE rats. After the injection of 300 mug of biotin, plasma levels of lactate and pyruvate fell in male rats, indicating a stimulatory effect of biotin upon the oxidative pathways in these animals.

Dyslipidemia, often found in type 2 diabetes mellitus (T2DM) patients, plays an important role in the progression of cardiometabolic syndrome. Two essential nutrients, chromium and biotin, may maintain optimal glycemic control. A randomized, double-blind placebo-controlled trial (N=348; chromium picolinate and biotin combination [CPB]: 226, placebo: 122; T2DM participants with hemoglobin A1c [HbA1c] >or=7%) evaluated the effects of CPB on lipid and lipoprotein levels. Participants were randomly assigned (2:1 ratio) to receive either CPB (600 microg chromium as chromium picolinate and 2 mg biotin) or a matching placebo once daily for 90 days. Statistical analyses were conducted in all eligible participants. Subsequent supplemental analyses were performed in T2DM participants with hypercholesterolemia (HC) and in those using stable doses of statins. In the primary analysis, CPB lowered HbA1c (P<.05) and glucose (P<.02) significantly compared with the placebo group. No significant changes were observed in other lipid levels. In participants with HC and T2DM, significant changes in total cholesterol and low density lipoprotein cholesterol (LDL-C) levels and atherogenic index were observed in the CPB group (P<.05). Significant decreases in LDL-C, total cholesterol, HbA1c, and very low-density cholesterol levels (P<.05) were observed in the CPB group taking statins. CPB treatment was well tolerated with no adverse effects, dissimilar from those associated with placebo. These data suggest that intervention with CPB improves cardiometabolic risk factors.

Chromium functions as a cofactor for insulin. It binds to the insulin receptor and potentiates many, and perhaps all, of its functions (Boyle et al., supra.). These functions include, but are not limited to, the regulation of carbohydrate and lipid metabolism. The introduction of inorganic chromium compounds per se into individuals is not particularly beneficial. Chromium must be converted endogenously into an organic complex or must be consumed as a biologically active molecule. Only about 0.5% of ingested inorganic chromium is assimilated into the body (Recommended Daily Allowances, Ninth Revised Edition, The National Academy of Sciences, page 160, 1980). Only 1-2% of most organic compounds is assimilated into the body. U.S. Patent No. Re. 33,988 discloses that when selected essential metals, including chromium, are administered to mammals as exogenously synthesized coordination complexes of picolinic acid; they are directly available for absorption without competition from other metals. These complexes are safe, inexpensive, biocompatible and easy to produce.

**CURCUMIN:**


**BIOPERIN:**

Bioperin, also known as piperine, is a black pepper extract that is a known inhibitor of glucuronidase in the gastrointestinal tract and in the liver. Bioperin is also a stimulator of thermogenesis. Bioperin has been shown to increase the bioavailability of a large number of drugs, including propranolol. The properties of bioperin are described in U.S. Pat. No. 5,744,161 to Majeed et al. and U.S. Pat. No. 5,972,382 to Majeed et al. both of which are incorporated herein in their entirety by this reference.

**POTENTIAL SIDE EFFECTS:**

All ingredients of the NoChol are food supplements and defined by the FDA as GRAS (Generally Regarded As Safe). Therefore, we do not anticipate any major problems with NoChol. Among potential minor side effects are gastrointestinal discomfort, minor elevation of liver enzymes, lightheadedness and dizziness.