

Caucasian Blueberry Leaf Extract

(Caucasian Bilberry Leaf)

The Phytomedicine for Diabetes
The Glucose "Paradox" of Diabetes
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Glucose is the major source of energy for many mammalian cells, much of which is provided through the bloodstream. That is why the level of blood glucose is regulated very strictly. The liver and kidneys are the major organs responsible for maintaining a balance between dietary glucose, its storage, production and release into the body.

Two metabolic processes in our body, glycogenolysis and glyconeogenesis maintain blood glucose within a narrow range. The enzyme glucose-6-phosphatase is involved in both processes and plays a dominant role in the regulation of glucose balance in our body.

Diabetes mellitus is a complex chronic disease which affects millions of people. It is characterized by a progressive breakdown in normal insulin-related usage of glucose, the body's basic source of blood sugar energy.

The body's use of insulin and glucose are a paradoxical "double-edged sword". On the one hand, we cannot live without them. The body requires balanced insulin output from the pancreas and liver to transport glucose effectively to all the other organs and tissues to maintain healthy metabolic function. On the other hand, any insulin imbalance or loss of insulin sensitivity can cause a chronic overabundance of glucose and result in diabetes.

When diabetes develops in children or young adults it is caused by a fundamental breakdown in the body's ability to produce enough insulin for normal function. This is called *juvenile insulin-dependent* diabetes. When diabetes develops later in life it is usually when organs and tissues lose their ability to respond effectively to insulin, which is called *adult-onset non-insulin-dependent* diabetes. In adult-onset diabetics, glucose is over-produced by the liver and under-utilized by other organs and tissues.

Either form of diabetes is a disease with serious, deleterious health consequences. If left untreated, diabetes can cause retinal degeneration and blindness, lead to kidney and nerve damage, contribute to atherosclerosis, poor circulation and in extreme cases even result in amputations and death.

Three Strategies for Diabetic Treatment

The primary objective in the treatment of diabetes is to lower abnormally high levels of blood sugar and to stabilize it at normal levels. Three therapeutic strategies are generally used to achieve this:

1. Reduce glucose *absorption* from the diet
2. Reduce glucose *synthesis* in the liver
3. Accelerate glucose *metabolism*

Ideally, the most effective strategy would be to achieve *all three* at the same time.

The Triple Solution of Caffeoylquinic and Caffeic Acids

Recent research has identified two unique natural compounds that appear to do just that. The two compounds are: **caffeoylquinic acid and caffeic acids**. New studies suggest that taken together these two unique compounds may:

1. help reduce dietary glucose absorption in the intestines,
2. help reduce glucose synthesis in the liver, and

3. speed up the metabolism of glucose - simultaneously.

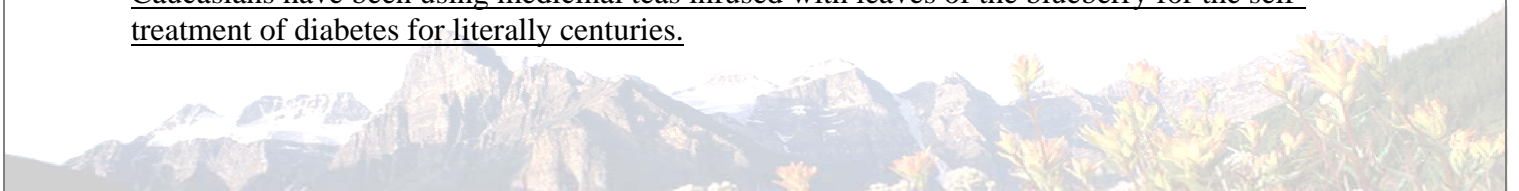
To fully appreciate the importance of this new development a brief explanation of glucose biochemistry is essential to understand the context and full value of this discovery:

- The enzyme glucose-6-phosphatase (G6P) plays a major role in the homeostatic regulation of blood glucose, which is responsible for the formation of glucose in our body. Chlorogenic acid was recently discovered to *specifically inhibit the activity of this key enzyme*.
- Inhibition of G6P activity in the liver results in a reduction of hepatic glucose production and may be useful for the reduction of the abnormally high rates of hepatic glucose output often found in non-insulin-dependent diabetes (Arion et al. 1997; Hemmerle et al. 1997).
- Chemically, chlorogenic acid is an ester formed between caffeic and quinic acids. It is interesting to note that *both* chlorogenic and caffeic are involved in the glucose reduction in our body. Research of Dr. Welsch and his colleges at Rutgers University reveals that the glucose transport across brush border membrane vesicles isolated from the small intestine were reduced to 80% in the presence of chlorogenic acid and 30-40% in the presence of caffeic acid, while treatment with gallic acid had no effect (*Welsch et al.* 1989). These results suggest that both chlorogenic and caffeic acids are involved in the regulation of glucose level including the unique ability to inhibit dietary glucose absorption in the intestines. Recent research of Cheng and Liu (2000) also indicates that the presence of caffeic acid accelerated the metabolism of glucose, which can reduce the total glucose concentration circulated in blood plasma. Results of Hsu et al. (2000) studies provide further evidence that caffeic is involved in the reduction of plasma glucose in diabetic rats.
- Pharmaceutical companies also actively interested in this important area of research have already synthesized several *synthetic analogs* of chlorogenic acid. These compounds are potent inhibitors of the glucose-6-phosphatase activity in human liver microsomes (Arion et al. 1997). Simon et al. (2000) recently provided evidence that chlorogenic acid derivatives reduce blood glucose in overnight-fasted rats, which also confirms the blood glucose lowering properties of chlorogenic acid. Herling et al. (1998) provided further strong arguments that chlorogenic acid based compounds produced a concentration-dependent inhibition of glucose synthesis in isolated rat liver tissue.

Therefore, it is strongly suggested from all of the above that the effectiveness of chlorogenic and caffeic acids in glucose reduction and diabetes relief will *depend on whether these compounds are taken simultaneously and in sufficient amounts*.

Link to Caucasian Blueberry (Bilberry) Leaf

Surprisingly enough, chlorogenic and caffeic have recently been discovered in the Caucasian herbal folk remedy most renowned for the treatments of diabetes: *blueberry leaf*. In fact, Caucasians have been using medicinal teas infused with leaves of the blueberry for the self-treatment of diabetes for literally centuries.



Caucasian Blueberry (*Vaccinium Arctostaphylos* L) is an elegant bush, inhabiting the elevations of 3,000-5,000 feet high in the Caucasus Mountains of the northern region in the Republic of Georgia. Caucasian Blueberry has a legendary reputation as an aid to diabetics. Decoctions and infusions of the leaves are used in folk medicine as hypo-glycemic agents and is usual major component of "anti-diabetes teas".

Even more impressive, in Russia, *a standardized blueberry leaf extract, known as "Diabetic Chai Cherniki"* effectively used for the treatment of diabetes, gastric colitis and high cholesterol, and has been repeatedly shown to contain *pharmaceutically significant levels of both chlorogenic and caffeic acids* (Mshavanadze et al 1971).

Phytochemistry of Caucasian Blueberry Leaf

The phytochemical composition of Caucasian Blueberry leaf has been studied at the Georgian Institute of Plant Biochemistry for decades (Durmishidze et al. 1981). The investigation of phytochemical composition indicates blueberry leaf contains large amounts of caffeoylquinic 3,5-dicaffeoylquinic, neochlorogenic, 4-caffeoylquinic, 3coumaroylquinic and caffeic acid (Mzhavanadze et al. 1972). The concentration of these two major phenolic compounds in the extract can reach as high as 15-20% dry weight.

In addition to chlorogenic and caffeic acids, the following compounds have been identified in blueberry leaf:

Coumaric Acid
Salidroside
Tyrosol
Ericolin

Rutin
Arbutin
Anthocyanosides
Quercetin

The content of chlorogenic and caffeic acids in blueberry leaf is dependent on vegetation period. The maximum level of chlorogenic and caffeic acids observed in young spring leaf extract were 15-20%, while their concentrations are dramatically reduces to 3% in mature leaves (Mshavanadze, 1971; Durmishidze et al. 1981). Traditionally, the Caucasian Blueberry leaf is harvested in early spring to assure the maximum yield and the highest concentration of chlorogenic and caffeic acids, which guarantees its efficacy. In fact, blueberry leaf extract has been *standardized to a minimum of 18% chlorogenic and caffeic acids*.

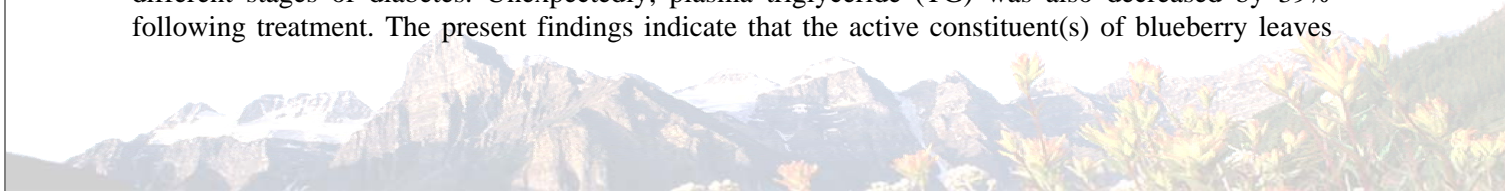
Chlorogenic Acid

To better understand and appreciate fully the health-promoting properties of blueberry leaf extract it is important to describe the pharmacological properties of its major constituent, chlorogenic acid.

Researchers have reported that chlorogenic acid possess pharmacologically relevant health promoting properties, particularly in lowering plasma glucose and in treatment of diabetes. Among more than a dozen positive physiological actions of chlorogenic acid, the plasma glucose lowering properties are the most impressive.

Diabetes: Animal Studies

Cirnarella et al. (1996) studied the therapeutic action of the blueberry leaf extract on streptozotocin-diabetic rats for 4 days. Plasma glucose levels were consistently found to drop by about 26% at two different stages of diabetes. Unexpectedly, plasma triglyceride (TG) was also decreased by 39% following treatment. The present findings indicate that the active constituent(s) of blueberry leaves



may prove potentially useful for treatment of dyslipidaemiae associated with impaired TG-rich lipoprotein clearance.

Therefore, the reduction in blood sugar by 26% recently reported by Cirnarella et al. (1996) is a rather expected result. The present findings indicate that active constituents of blueberry leaf extract may prove potentially useful for treatment of high blood sugar and plasma triglyceride level (Cirnarella et al. 1996).

Human Clinical Studies: Healthy Volunteers

Russian scientist Dr. M. Abidoff evaluated the glucose lowering properties of blueberry leaf extract in a double blind placebo controlled study at The Moscow Center for Modern Medicine, Russian Ministry for National Defense Industries (Abidoff 1999, Abidoff-Farma). According to this research the CA and HCA make up as much as $18\pm 2\%$ of blueberry leaf extract.

Seventy-five healthy volunteers ages 37 years through 66 years were invited to participate in a double-blind placebo-controlled five-week trial. Sixty days before beginning the drug phase of this trial, volunteers underwent a period of diet counseling and surveillance. Their dietary intakes were standardized to contain 55-60% total calories from carbohydrates. At 3-week intervals throughout the study, volunteers were evaluated for fasting plasma glucose values. Standard food record analysis and a symptom questionnaire were also included at the laboratory intervention times.

After the initial dietary run-in phase, subjects were randomly assigned to receive 150mg of standardized blueberry leaf extract or a placebo to be taken three times a day in 200ml of water before meals.

Results of this study revealed that there were significant changes in blood glucose values for both groups of volunteers. The after meal blood glucose level increased from 102mg/dL ± 8 mg/dL (baseline) to 142mg/dL ± 7 mg/dL in the placebo group. Those volunteers taking the blueberry leaf extract experienced plasma glucose level increases from approximately 109mg/dL ± 9 mg/dL to 121mg/dL ± 6 mg/dL. The results of this clinical trial indicate that the blueberry leaf extract possess physiologically significant glucose lowering property.

According to Prof. Abidoff MD (1999) the glucose-lowering effect of blueberry leaf extract is due to the unique properties of chlorogenic acid that inhibit the activity of G6P, a key enzyme in glycogenolysis and gluconeogenesis, although the direct inhibition of intestinal amylase, a key enzyme in dietary carbohydrates absorption, by the blueberry leaf extract cannot be ruled out. In addition, results of Welsh et al. (1987) indicated that chlorogenic acid could inhibit the intestinal absorption of glucose.

Human Clinical Study: Diabetes Patients

In a second clinical trial the effect of blueberry leaf extract on plasma glucose level was studied in patients with Type II Diabetics (Abidoff 1999).

Twenty-nine patients with type II diabetes, average age of 50 years, were selected to participate in a double-blind, placebo-controlled, 60-days trial. Sixty days before beginning the drug phase of clinical study patients underwent a period of diet counseling and surveillance. Their dietary intakes were standardized to contain 40-45% total calories from carbohydrates. Patients in the study were asked to maintain their medications throughout the dietary and drug phase of the trial. On admission and at two-week intervals throughout the study, patients were evaluated for fasting glucose, triglycerides serum values. Food record analysis, body mass index, and a symptom questionnaire were also

included at the laboratory intervention times. After the initial dietary run-in phase, subjects were randomly assigned to receive 200mg of standardized blueberry leaf extract powder in capsule form or a placebo, to be taken three times a day in 200ml of water before meals. During the initial period of diet counseling there was no significant change in fasting blood glucose values for either of the groups. However, beginning with week 6 and continuing to the end of the trial, those individuals taking the blueberry leaf extract showed a significant reduction in mean plasma glucose levels, from approximately 169 mg/dL to 136 mg/dL ($p < 0.01$). Furthermore, by the end of the clinical study, those taking the blueberry leaf extract showed a reduction of triglyceride and LDL values from 179 ± 95 mg/dL to 130 ± 53 mg/L ($p < 0.005$) and 141 ± 47 mg/dL to 115 ± 34 mg/dL ($p < 0.01$) respectively. All patients tolerated well blueberry leaf extract even at 400mg, three times a day (1200mg/day).

Results of the clinical trial are confirmed, well know and previously described phenomenon that blueberry leaf extract possess antidiabetic properties. The use of blueberry leaf extract may provide a first line approach to the reduction of blood glucose in type II diabetic patients before other prescriptive avenues are employed. Improvement in total cholesterol and LDL level observed in various studies is possibly due to the protective role of caffeic and chlorogenic acids in LDL oxidation that was recently described in scientific literature.

Blueberry Leaf Extract: *Science Re-Discovers Another Ancient Truth of Folk Medicine*

The long history of blueberry leaf extract use in folk medicine and its growing popularity by the informed public is no longer a scientific mystery. Blueberry leaf extract is a safe, natural, potent source of critical chlorogenic and caffeic acids has a long and venerable history and an even more promising future in the long-term care of diabetics everywhere.

Once again, as has been the case with many other leading health supplements for the last two decades, science finally, reluctantly proves the efficacy of what it once not only ignored but openly denigrated! Yet, what is profoundly fascinating is how often and how accurately the lore and legends of folk medicine so often proves to clinically accurate!

When we delve deeper into the fast-growing, impressive body of new research, we find in many cases the active compound(s) identified and responsible for an herb or food's traditional health benefits have been somehow empirically understood and used for the appropriate purpose in some form by many of our ancestors well into the past. Often such use has occurred for thousands of years, in a variety of different cultures, spread over many continents. Although the folklore may have been local, taken as a whole the use of these natural medicines were regional, if not actually global.

Ironically, modern researchers appear to be learning once again about the complex relationships between our bodies and these traditional food and medicinal plants in a somewhat backward fashion.

If researchers took a more humble and open-minded approach to the potential wisdom of traditional medicines like blueberry leaf extract, they might accelerate their understanding and serve the mass acceptance and use of these very real "cultural treasures".

Genuine scientific enthusiasm for this task would help set better standards for product formulation, consumer education, and public regulation, which in turn could help alleviate and even prevent the suffering of millions of people around the world from major chronic diseases such as diabetes in the future.



References:

Abraham SK, Sarma L, Kesavan PC (1993) Protective effects of chlorogenic acid, curcumin and beta- carotene against gamma-radiation-induced in vivo chromosomal damage. *Mutat Res*; 303 (3): 109-12

Arion WJ, Canfield WK, Ramos FC, Schindler PW. (1997)
Chlorogenic acid and hydroxynitrobenzaldehyde: new inhibitor of hepatic glucose 6-phosphatase. *Arch Biochem Biophys* 15; 339(2): 315-22

Arion WJ, Canfield WK, Ramos FC, Su ML, Burger HJ, Hemmerle H, Schubert G, Below P, Herling AW Chlorogenic acid analogue S 3483: a potent competitive inhibitor of the hepatic and renal glucose-6-phosphatase systems. *Arch Biochem Biophys* 1998 15; 351 (2): 279-85

Azuma K, Ippoushi K, Nakayama M, Ito H, Higashio H, Terao J (2000) Absorption of Chlorogenic Acid and Caffeic Acid in Rats after Oral Administration *J Agric Food Chem* 20; 48 (11): 5496-5500

Bailey GS, Scanlan RA, Selivonchick DP, Williams DE (1991)
Food toxicology. In "Encyclopedia of Human Biology," ed. R. Dulbecco, Vol. 3, pp. 671-681. Academic Press, New York.

Burke TR Jr, Fesen MR, Mazumder A, Wang J, Carothers AM, Grunberger D, Driscoll J, Kohn K, Pommier Y (1995)
Hydroxylated aromatic inhibitors of HIV-1 integrase. *J Med Chem*, 38 (21): 4171-8

Butland BK, Fehily AM, Elwood PC Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. *Thorax* 2000; 55(2): 102-108

Chang WS, Wen PC, Chiang HC (1995) Structure-activity relationship of caffeic acid analogues on xanthine oxidase inhibition. *Anticancer Res*, 15(3): 703-7 10

Chang WS, Chang YH, Lu FJ, Chiang HC (1994) Inhibitory effects of phenolics on xanthine oxidase. *Anticancer Res*, 14(2A): 501-6

Cheng JT, Liu IM (2000) Stimulatory effect of caffeic acid on alpha1A-adrenoceptors to increase glucose uptake into cultured C2C12 cells. *Naunyn Schmiedebergs Arch Pharmacol* 362 (2): 1227

Cho JY, Moon JH, Seong KY, Park KH (1998) Antimicrobial activity of 4-hydroxybenzoic acid and trans 4-hydroxycinnamic acid isolated and identified from rice hull. *Biosci. Biotechnol Biochem* 1998; 62 (11): 2273-6

Cignarella A, Nastasi M, Cavalli E, Puglisi L (1996) Novel lipid-lowering properties of *Vaccinium myrtillus* L. leaves, a traditional antidiabetic treatment, in several models of rat dyslipidaemia: a comparison with ciprofibrate. *Thromb Res* 1; 84(5):311-22

Cornicelli JA, Trivedi BK (1999) 15-lipoxygenase and its inhibition: A novel therapeutic target for vascular disease. *Current Pharmaceutical Design*, 5: 11-12

Costantino L, Albasini A, Rastelli G, Benvenuti S (1992)

Activity of polyphenolic crude extracts as scavengers of superoxide radicals and inhibitors of xanthine oxidase. *Planta Med*; 58(4): 342-4

Dhar K, Rosazza JP (2000) Purification and characterization of streptomyces griseus catechol O-methyltransferase. *Appl Environ Microbiol*; 66(11):4877-82

Dombrowicz E, Zadernowski R, Swiatek L (1991) Phenolic acids in leaves of *Arctostaphylos uva ursi* L., *Vaccinium vitis idaea* L. and *Vaccinium myrtillus* L *Pharmazie*; 46(9): 680-681

Fe inmark SJ, Cornicelli JA (1997) Is there a role for 15lipoxygenase in atherogenesis? *Biochem Pharmacol* 1; 54 (9): 953-9

Fernández MA, García MD, Sáenz MT (1996) Antibacterial activity of the phenolic acids fractions of *Scrophularia frutescens* and *Scrophularia sambucifolia*. *J Ethnopharmacol*, 53(1): 11-4

Folkers K, Langsjoen P, Willis R, Richardson P, Xia LJ, Ye CQ, Tamagawa H (1990) Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci U S A*; 87(22): 8931-4

Fraisse D, Carnat A, Lamaison JL (1996) Polyphenolic composition of the leaf of bilberry *Ann Pharm Fr*, 54(6): 280-3

Hecht SS, Hoffman D (1988) Tobacco-specific nitrosamines, An important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 9: 875-884.

Hemmele H, Burger HJ, Below P, Schubert G (1997)

Chlorogenic acid and synthetic chlorogenic acid derivatives: novel inhibitors of hepatic glucose-6-phosphate translocase. *J Med Chem* 17; 40(2): 137-145

Hotchkiss JH (1989) Relative exposure to nitrite, nitrate, and Nnitroso compounds from endogenous and exogenous sources. In "Food Toxicology, A Perspective on the Relative Risks," ed. S.L. Taylor and R.A. Scanlan, pp. 57-100. Marcel Dekker, Inc., New York.

Hsu FL, Chen YC, Cheng JT (2000) Caffeic acid as active principle from the fruit of *Xanthium strumarium* to lower plasma glucose in diabetic rats. *Planta Med*; 66(3): 228-30

Huang MT, Smart RC, Wong CQ, Conney AH (1988) Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-tetradecanoylphorbol-13-acetate. *Cancer Res* 1; 48(21): 5941-6

Human JA, Ubbink JB, Jerling JJ, Delport R, Vermaak WJ, Vors ter HH, Legendijk J, Potgieter HC (1997) The effect of Simvastatin on the plasma antioxidant concentrations in patients with hypercholesterolaemia. *Clin Chim Acta* 4; 263(1): 67-77

Iwahashi H, Negoro Y, Ikeda A, Morishita H, Kido R (1986)

Inhibition by chlorogenic acid of haematin-catalysed retinoic acid 5,6-epoxidation. *Biochem J* 1; 239(3): 641-6

Kasai H, Fukada S, Yamaizumi Z, Sugie S, Mori H (2000)

Action of chlorogenic acid in vegetables and fruits as an inhibitor of 8-hydroxydeoxyguanosine formation in vitro and in a rat carcinogenesis model. *Food Chem Toxicol* 2000 1; 38 (5): 467-471

Kerry N, Rice-Ewans C (1999) Inhibition of peroxynitrite-mediated oxidation of Dopamine by flavonoid and phenolic antioxidants and their structural relationships. *Journal of Neuroscience*, 73, N1 pp. 247-253

Kim YK, Hwang MY, Woo JS, Jung JS, Lee SH (2000) Effect of arachidonic acid metabolic inhibitors on hypoxia/reoxygenation-induced renal cell injury. *Ren Fail* 2000; 22(2): 143-57

Kim SR, Kim YC (2000) Neuroprotective phenylpropanoid esters of rhamnose isolated from roots of *Scrophularia buergeriana*. *Phytochemistry*; 54(5): 503-9

King A, Young G (1999) Characteristics and occurrence of phenolic phytochemicals. *J Am Diet Assoc*; 99(2): 213-8

Kitts DD, Wijewickreme AN (1994) Effect of dietary caffeic and chlorogenic acids on in vivo xenobiotic enzyme systems. *Plant Foods Hum Nutr.* 45(3): 287-98

Kono Y, Shibata H, Kodama Y, Sawa Y (1995) The suppression of the N-nitrosating reaction by chlorogenic acid. *Biochem J* 15; 312, 947-953

Kono Y, Shibata H, Kodama Y, Ueda A, Sawa Y (1995)
Chlorogenic acid as a natural scavenger for hypochlorous acid. *Biochem Biophys Res Commun*, 217(3): 972-8

Kono Y, Kobayashi K, Tagawa S, Adachi K, Ueda A, Sawa Y, Shibata H (1997) Antioxidant activity of polyphenolics in diets. Rate constants of reactions of chlorogenic acid and caffeic acid with reactive species of oxygen and nitrogen. *Biochim Biophys Acta*, 1335 (3): 335-42

Kooy NW, Lewis SJ, Royall JA, Ye YZ, Kelly DR, Beckman JS (1997) Extensive tyrosine nitration in human myocardial inflammation: evidence for the presence of peroxynitrite. *Crit Care Med* 25(5):812-9

Koshihara Y, Neichi T, Murota S, Lao A, Fujimoto Y, Tatsuno T (1984) Caffeic acid is a selective inhibitor for leukotriene biosynthesis *Biochim Biophys Acta* 17; 792(1): 92-7

Millet J, et al. (1984) Improvement of blood filtrability with a purified extract of *black currant* anthocyanosides in cynomolgus monkeys on a fat diet. *J Pharmacol*, 15: 439-45

Morton LW, Croft KD, Puddey IB, Byrne L (2000) Phenolic acids protect low-density lipoproteins from peroxynitrite-mediated modification in vitro. *Redox Rep*; 5(2-3): 124-5

Laranjinha J, Vieira O, Madeira V, Almeida L (1995) Two related phenolic antioxidants with opposite effects on vitamin E content in low density lipoproteins oxidized by ferrylmyoglobin: consumption vs regeneration. *Arch Biochem Biophys*, 323(2): 373-81

Laranjinha JA, Almeida LM, Madeira VM (1994) Reactivity of dietary phenolic acids with peroxy radicals: antioxidant activity upon low-density lipoprotein peroxidation. *Biochem Pharmacol*, 48 (3): 487

Lo HH, Chung JG (1999) The effects of plant phenolics, caffeic acid, chlorogenic acid and ferulic acid on arylamine Nacetyltransferase activities in human gastrointestinal microflora. *Anticancer Res*; 19(1A): 133-9

Mortensen SA, Leth A, Agner E, Rohde M (1997) Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. *Mol Aspects Med*; 18 Suppl: S137-44

Mori H, Tanaka T, Shima H, Kuniyasu T, Takahashi M (1986) Inhibitory effect of chlorogenic acid on methylazoxymethanol acetate-induced carcinogenesis in large intestine and liver of hamsters. *Cancer Lett*; 30 (1): 49-54

Nardini M, D'Aquino M, Tomassi G, Gentili V, Di Felice M, Scaccini C (1995) Inhibition of human low-density lipoprotein oxidation by caffeic acid and other hydroxycinnamic acid derivatives. *Free Radic Biol Med*, 19(5): 541-52

Nardini M, Natella F, Gentili V, Di Felice M, Scaccini C (1997) Effect of caffeic acid dietary supplementation on the antioxidant defense system in rat: an in vivo study. *Arch Biochem Biophys* 1; 342(1): 157-160

NAS (1981) The health effects of nitrate, nitrite and N-nitroso compounds. Natl. Acad. of Sciences, Natl. Acad. Press Washington, D.C.

NAS. (1982) Diet, nutrition and cancer. Natl. Acad. of Sciences, Natl. Acad. Press, Washington, D.C.

Nicklaus M, Neamati N, Hong H, Mazumder A, Sunder S, Chen J, Milne G, Pommier Y (1997) HIV-1 integrase pharmacophore: discovery of inhibitors through three-dimensional database searching. *J Med Chem*, 40(6): 920-9

Paganga G, Miller N, Rice-Evans CA (1999) The polyphenolic content of fruit and vegetables and their antioxidant activities. What does a serving constitute? *Free Radic Res*; 30(2): 153-62

Robinson WE, Cordeiro M, Abdel-Malek S, Jia Q, Chow S, Reinecke M, Mitchell WM (1996) Dicafeoylquinic acid inhibitors of human immunodeficiency virus integrase: inhibition of the core catalytic domain of human immunodeficiency virus integrase. *Mol Pharmacol*, 50(4): 846-55

Shimizu M, Yoshimi N, Yamada Y, Matsunaga K, Kawabata K, Hara A, Moriwaki H, Mori H (1999) Suppressive effects of chlorogenic acid on N-methyl-N-nitrosourea-induced glandular stomach carcinogenesis in male F344 rats. *J Toxicol Sci*; 24(5): 433-9

Sigal E, Laughton CW, Mulkins MA (1994) Oxidation, lipoxygenase, and atherogenesis. *Ann N Y Acad Sci* Apr 18; 714: 211-24

Tanaka T, Nishikawa A, Shima H, Sugie S (1990) Inhibitory effects of chlorogenic acid, reserpine, polyprenic acid (E-5166), or coffee on hepatocarcinogenesis in rats and hamsters. *Japan. Basic Life Sci*; 52: 429-34

Thieme H, Winkler HJ (1966) On the occurrence of salidroside in the leaves of the red whortleberry (*Vaccinium vitis-idaea* L.). *Pharmazie* 21(3): 182

Thieme H, Walewska E, Winkler HJ (1969) Isolation of salidroside from leaves of Rhododendron. *Pharmazie* 24 (12): 783

Tsuchiya T, Suzuki O, Igarashi K (1996) Protective effects of chlorogenic acid on paraquat-induced oxidative stress in rats. *Bioscience Biotechnol Biochem*; 60 (5): 765-8

Uz T, Pesold C, Longone P, Manev H (1998) Aging-associated up-regulation of neuronal 5-lipoxygenase expression: putative role in neuronal vulnerability. *Journal ASEB*; 12(6): 439-449

Vieira O, et al. (1998) Effect of dietary phenolic compounds on apoptosis of human cultured endothelial cells induced by oxidized LDL. *J Pharmacology*; 123 (3): 565-573

Yamada J, Tomita Y (1996) Antimutagenic activity of caffeic acid and related compounds. *Biosci Biotechnol Biochem*, 60(2):328-9