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Coenzyme Q_{10} for Diabetes

By Dónal P. O'Mathúna, PhD

DIABETES REMAINS A SERIOUS HEALTH PROBLEM THROUGHOUT THE world. In the United States, its prevalence has increased by more than 50% over the last 10 years, and it is predicted to increase by another 165% over the next 50 years.[1] Although diabetes occurs more commonly in older people, the increased incidence is expected to be most dramatic among working-age people, leading to huge social and economic implications. Currently, more than 17 million Americans have this condition, with the vast majority having Type 2 diabetes, for which obesity is a major determinant.

Treatment of diabetes and its complications costs the United States $132 billion annually. Cardiovascular disease is the principal complication, and the leading cause of death.[2] In addition, diabetes is the leading cause of kidney failure, adult blindness, and amputations.[1] While increasing physical activity and reducing calorie consumption remain important interventions in preventing and treating the condition, many people are looking to dietary supplements for additional help. Coenzyme Q_{10} (CoQ_{10}) is one of the supplements commonly recommended for those with diabetes.

Mitochondrial Diabetes

A number of problems can underlie the development of Type 2 diabetes. Much research has focused on problems with insulin sensitivity in peripheral tissue, but there also can be dysfunction in the pancreatic beta-cells.[3] One form of beta-cell dysfunction can be traced to mitochondrial problems, which have been cited as rationale for the potential beneficial effects of CoQ_{10}. This connection originally was proposed based on observations that Type 2 diabetes appeared to be transmitted maternally.[4]

Although almost all genetic material is transmitted to offspring from both parents, all people receive a small amount of DNA exclusively from their mother's mitochondria (mtDNA). Controlled studies have not supported the original hypothesis that all Type 2 diabetes is maternally transmitted, but at least some cases have been shown to be caused by mutations in mtDNA.[4] Mitochondria are known to play a role in regulating insulin secretion in beta-cells. Also, while mitochondrial myopathies have been associated

primarily with neurodegenerative diseases, diabetes often can be a complicating factor. A specific mtDNA mutation labeled 3243 leads to Type 2 diabetes and deafness.[5] While its incidence among all diabetic patients is well under 1%, 1.5% of the Japanese general population carries the defect.[4]

Mechanism of Action

Mitochondria replenish the chemical energy of cells by generating a molecule called adenosine triphosphate (ATP). CoQ_{10} plays a vital role in a number of complexes involved in this process.[6] The biochemical background for CoQ_{10} was reported in this newsletter recently.[7] Administration of CoQ_{10} has thus been proposed to compensate for the effects of mtDNA mutations, which lead to fewer mitochondria and less mtDNA in those that are made. This has been shown to negatively affect glucose-stimulated insulin release.[3] In addition, CoQ_{10} is a more powerful antioxidant than vitamin E and may be beneficial in diabetes as a means of reducing cardiovascular damage caused by free radicals and superoxide.[2]

Clinical Studies

The earliest clinical trial was conducted after several patients with Type 1 diabetes reported reducing their dose of insulin after initiating CoQ_{10} therapy. In a double-blind study, 34 subjects were randomly assigned to receive placebo or 100 mg CoQ_{10} daily.[8,9] Subjects adjusted their insulin doses based on home monitoring of glucose levels. After 12 weeks, there were no significant differences between the groups in total insulin dose, overall glycemic control, cholesterol levels, or general well-being.

Another trial was conducted with subjects with the 3243 mutation in mtDNA.[5] In addition to diabetes and a family history of Type 2 diabetes, symptoms included impaired hearing, mitochondrial encephalomyopathy, lactic acidosis, and recurrent headaches. This open study observed 11 subjects who received between 30 and 210 mg CoQ_{10} daily for 3-5 months. Subjects reported reductions in fatigue, heart palpitations, and leg paresthesia, all suggesting improvements in mitochondrial metabolism. However, no improvements were reported in glycemic parameters.

An open trial involved 76 subjects with the 3243 mtDNA mutation who presented with a family history of Type 2 diabetes, deafness, and various degrees of glucose intolerance.[10] Fifty subjects received 150 mg CoQ_{10} daily for three years and 26 matched controls received no intervention. For the first three months, no significant differences existed between the two groups. After three years, the condition of the control group had progressively worsened while those receiving CoQ_{10} showed significantly less deterioration in insulin secretion ($P < 0.02$), deafness ($P < 0.02$), and exercise tolerance ($P < 0.001$). No significant differences were found for the incidence of diabetic retinopathy, nephropathy, neuropathy, or any other chronic diabetic symptom.

A randomized, double-blind, placebo-controlled trial enrolled 23 subjects with Type 2 diabetes.[11] The active arm of the trial received 100 mg CoQ_{10} bid for six months. Serum CoQ_{10} levels rose more than threefold, but no significant differences were found in glycemic control, blood pressure, or lipid levels.

An additional study focused on the cardiovascular complications of Type 2 diabetes.[12] Forty subjects with diabetes and dyslipidemia were randomly assigned to receive placebo or CoQ_{10} (100 mg bid) for 12 weeks. Peripheral circulation was assessed using brachial artery ultrasonography. Resting blood flow and endothelial function were significantly improved in those receiving CoQ_{10} ($P = 0.005$). No significant changes were found in serum glucose or lipid levels, antioxidant capacity, or blood pressure.

A study by the same research group randomly divided 74 Type 2 diabetes patients with dyslipidemia into four groups.[13] Subjects received either fenofibrate (200

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mg daily), CoQ_{10} (100 mg bid), fenofibrate plus CoQ_{10} (200 mg/200 mg daily), or placebo for 12 weeks. Fenofibrate is the most potent member of a class of drugs used to treat cardiovascular disease in high-risk patients, including diabetics. Those receiving CoQ_{10} alone had significantly reduced blood pressure, both systolic ($P = 0.021$) and diastolic ($P = 0.048$), and improved glycemic control as measured by reduced glycated hemoglobin (HbA_{1c}) levels ($P = 0.032$). Fenofibrate alone significantly improved all serum lipid levels, but no significant lipid level changes were found with CoQ_{10} or either of the two other groups.

The same researchers randomly divided 80 Type 2 diabetes patients with dyslipidemia into the same four groups as above.[2] Fenofibrate alone significantly increased HDL-cholesterol levels and lowered all other serum lipid levels ($P < 0.001$); glucose levels were unchanged. CoQ_{10} alone did not significantly change glucose, insulin, or any lipid levels. However, it did lower blood pressure and HbA_{1c} levels ($P < 0.05$). In forearm vasodilatation tests, only the combined therapy led to normalized blood flow. Significant results were found with three of the four different agonists used in the vasodilation tests ($P = 0.001, 0.016, 0.006$).

Adverse Effects

No adverse effects were reported in the clinical trials discussed above. Other studies have reported mild adverse effects, primarily GI disturbances. The authors of one study recommended prudent monitoring of renal function of patients taking high CoQ_{10} doses after two of 15 subjects had abnormal urinalyses.[14]

Drug Interactions

CoQ_{10} is chemically similar to vitamin K and may have pro-coagulant activity, with four cases of decreased effectiveness of warfarin reported and thought to be related to CoQ_{10}.[15] The HMG CoA reductase inhibitors (statins) inhibit cholesterol and CoQ_{10} synthesis, leading to lower CoQ_{10} levels. Whether this is clinically significant is unknown. CoQ_{10} may have additive effects with other hypoglycemic or anti-hypertensive agents requiring caution and close monitoring.[15]

Formulation

CoQ_{10} supplements are formulated as oil-based capsules, powder-filled capsules, tablets, wafers, and softgel capsules containing microemulsions.[16] The highly lipophilic nature of CoQ_{10} makes its absorption poor, highly variable, and strongly dependent on the contents of the stomach. It is best taken with food, especially fat-rich foods. Solubilized formulations have been found to have better bioavailability than powders.[7]

Conclusion

A relatively small number of trials have examined the effectiveness of CoQ_{10} supplementation in diabetes. The one trial with Type 1 diabetes found no benefit, and all other trials involved Type 2 diabetes. Cases of diabetes due to mtDNA mutations appear to respond well to CoQ_{10}, although controlled trials are needed in this area. Results of controlled clinical trials with general forms of Type 2 diabetes have been somewhat variable. However, one research group has published three reports indicating improvements in glycemic control and cardiovascular parameters. The most significant improvements were found when CoQ_{10} was combined with fenofibrate.

Recommendation

Given the lack of adverse effects, CoQ_{10} can be recommended for patients with Type 2 diabetes even though a large number of studies have not been conducted in this area. There is evidence from other groups of patients that CoQ_{10} can be beneficial for vascular function and blood pressure.[17] Given the importance of reducing cardiovascular complications in diabetes, this benefit alone warrants further study. Patients whose diabetes is already stabilized should have their glucose levels monitored if they begin using CoQ_{10}. Practitioners should offer help in evaluating the quality of available brands, especially since these supplements can be costly. Patients should be actively monitored for potential adverse effects or drug interactions. ❖

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Horse Chestnut Seed Extract vs. Pycnogenol® for Chronic Venous Insufficiency

By Francis Brinker, ND

CHRONIC VENOUS INSUFFICIENCY (CVI) IS A PROBLEM OF the lower extremities for both youth and adults, affecting 20%-25% of women and 10%-15% of men. Though it can be more cosmetic than symptomatic, it often increases in severity until complications such as dermatitis, ulceration, or phlebitis result. Progressive etiology begins with weakness of the connective tissue and smooth muscle in the vessel wall, leading to damage to the endothelium and valves, which ultimately results in disturbed microcirculation and stasis. Hospitalization and surgery may be warranted when mechanical compressive therapy is inadequate. Therefore, botanical approaches with evidence of efficacy and safety deserve to be seriously considered as alternative or complementary therapies and potential preventive measures.

In 1984 the German Commission E approved the oral use of horse chestnut seed extract (HCSE) from *Aesculus hippocastanum*, supplying 100 mg/d of escin (a saponin mixture also spelled as "aescin"), for pathological conditions of veins. This approval was renewed in 1994 for CVI characterized by leg pains with associated itching, swelling, and/or a sense of heaviness, as well as nocturnal cramps in the calves.[1] HCSEs are 5-8:1 (w/w) strength dry native extracts made from dried seeds, normally standardized to a 16%-20% triterpene saponin escin fraction, while containing flavonoids and other relatively minor constituents. The seeds contain at least 3% escin.[2] HCSE is recommended clinically in conjunction with other prescribed non-invasive treatments including supportive elastic stockings, leg compresses, or cold water applications.[1]

In addition to HCSE, another botanical extract is gaining attention for positive effects observed in clinical trials for CVI. The French maritime pine bark extract from *Pinus pinaster* ssp. atlantica, in the form of the commercial product Pycnogenol®, has been studied for this vascular disorder. This extract consists largely of oligomeric procyanidins and their monomeric catechin and epicatechin units, along with minor constituents such as taxifolin, phenolic acids, and their glucosides and glucose esters, respectively. The comparative usefulness of HCSE and Pycnogenol has become relevant as they may both provide suitable options for treating CVI, varicosities, and associated symptoms.[2]

Pharmacology of HCSE and its Saponins

Within the last decade, pre-clinical studies have documented several mechanisms that appear to be major contributors to HCSE's beneficial effects. Ex vivo research demonstrated its independent contractile properties on isolated veins, increase in the contractile response to norepinephrine, and resultant increase in venous pressure. In a dose-dependent fashion it was found to decrease experimental edema and capillary hyperpermeability induced by inflammatory agents such as histamine and serotonin when given orally to rats. HCSE also inhibits free radical damage in vitro and in vivo in mice and rats.[3]

The escin components of the saponin fraction of the seeds given orally to rats likewise inhibited experimental edema and reduced vascular permeability induced by histamine and serotonin.[4] The mechanisms involved in these effects include calcium ion channel sensitization to reduce vascular permeability and enhanced generation of prostaglandin F2α in the veins to increase venous tone. Additional inhibition of proteoglycan degradation in the capillary endothelium and extravascular matrix also may be involved.[5] By inhibiting the enzyme hyaluronidase, escin may facilitate venous strengthening provided by perivascular connective tissue.[6]

Prior HCSE Reviews and Meta-Analyses

An excellent review of CVI treatment with HCSE by Szapary and Cirigliano published in this newsletter[7] discussed a 1998 systematic review of 13 randomized controlled trials (RCTs) meeting suitable methodological criteria.[8] The relative value of these isolated studies was limited by their small sizes (20-240 participants) and short durations (2-12 weeks). However, since HCSE compared favorably to other therapies (including one compression study and three studies with 500-2,000 mg/d oxerutin) and was found superior to placebo (eight studies) in 1,083 total participants, it has demonstrable clinical applicability.

A subsequent meta-analysis considered, in addition to 13 RCTs of at least 20 days with HCSE (1,051 patients), three observational studies with compiled results from 10,725 patients with CVI.[9] The quality of each study, assessed in a range from 0 (poor) to 6 (excellent), found the average was 5 for the RCTs and 3 for the observational studies. Compared to placebo in the RCTs, those patients taking HCSE had reductions in leg volume and ankle circumference. In two of the observational studies 84% more patients had improved edema, 91% had reduced pain, and 85% had improved leg fatigue and heaviness. The third study supported these findings but its results could not be pooled because of differences in reporting data. No severe adverse events were reported.

Pharmacology of Pycnogenol and its Procyanidin Polyphenols

The anti-inflammatory activity demonstrated in mice by Pycnogenol and its fractions correlated with free radical scavenging effects demonstrated in vitro.[10] One potential mechanism of the anti-inflammatory effect of this polyphenolic-rich extract was shown in down-regulation of pro-inflammatory interleukin-1β gene expression and production in vitro.[11] Pycnogenol's protective effect as an antioxidant was demonstrated by increasing oxygen radical absorbance capacity in a six-week study of 25 healthy subjects taking 150 mg/d.[12] When 60 patients with coronary artery disease were studied in a randomized, four-week, controlled, double-blind trial using 150 mg Pycnogenol three times daily, peripheral microcirculation improved as did myocardial ischemia.[13] This may be due in part to increased nitric oxide production by vascular endothelium.[10]

Capillary fragility was reduced in rats with oral Pycnogenol comparable or superior to the effect of flavonoids given at higher doses.[10] Oligomeric procyanidins as found in Pycnogenol have been shown to bind to elastin fibers and diminish their degradation in vitro and in vivo by the elastase enzymes that are released as part of inflammatory processes.[14] Elastin fibers help maintain connective tissue integrity that is involved in vascular support. Procyanidins further protect connective tissue by their potent antihyaluronidase activity as demonstrated in vitro, while the Pycnogenol component taxifolin likewise has a mild antihyaluronidase effect.[15]

Review and Recent Clinical Studies with Pycnogenol for CVI

A 1999 review examined 15 clinical trials in which 595 of 784 patients were treated with Pycnogenol.[10] This review included seven open studies (404 patients), five placebo-controlled, double-blind trials (149 patients), and three double-blind studies with placebo or reference drugs (231 patients). Overall, these clinical studies demonstrated clinical efficacy of Pycnogenol in patients with veno-capillary diseases, suggesting that oxidative processes have a role in venous diseases. A reduction in subcutaneous edema was associated with alleviation of the sensation of heavy legs. Reduced capillary permeability was observed, but not modification of venous blood flow.

One placebo-controlled trial with 40 patients found significant ($P < 0.01$) reduction on hydrostatic edema from sitting for one and two hours with 360 mg Pycnogenol daily for six days. In an unpublished controlled double-blind study with 40 patients, 300 mg daily for 60 days resulted in significant symptomatic improvement for Pycnogenol but not placebo, including reduced leg swelling (63%) and pain (67%). Another unpublished placebo-controlled study with 300 mg Pycnogenol daily involving 50 CVI and varicose vein patients found heaviness and edema steadily improved from baseline to 30 days (by 37%) and then from 30 to 60 days (by 36%) for a total reduction of 55%. In an active-medication controlled trial, Pycnogenol had no side effects and equivalent efficacy based on signs and symptoms when 240 mg for one week and 180 mg for five weeks were compared to 600 mg oxerutin for six weeks.[10]

A subsequent randomized, placebo-controlled, double-blind trial with 40 CVI patients studied 100 mg Pycnogenol three times daily for two months.[16] Compared to placebo, significant reductions in subcutaneous edema ($P < 0.01$), heaviness ($P < 0.01$), and pain in the legs ($P < 0.05$) occurred after 30 and 60 days. After two months, 60% had complete disappearance of edema and pain. This was accompanied by a reduction of leg heaviness in almost all patients with its complete absence in about 33%. Placebo patients experienced no benefits; no effect on venous blood flow was observed in either group.

A more recent published study with 40 CVI patients treated 20 in an open phase and 20 in a double-blind phase with 100 mg Pycnogenol three times daily for two months.[17] In the open phase there was significant reduction of heaviness and swelling after 30 days ($P < 0.05$) and 60 days ($P < 0.01$) compared to baseline. The double-blind phase found significant reductions for swelling after 30 days ($P < 0.05$), and in both parameters after 60 days ($P < 0.05$), compared to placebo. Venous pressure was significantly reduced after 60 days ($P < 0.001$) for those using Pycnogenol but not for placebo.

Comparative Study of HCSE and Pycnogenol

In 2002 Koch published the results of an open trial using the two botanical extracts with 20 CVI patients each over a four-week period.[18] There were no significant differences between the two groups in their conditions or previous treatments. The relative doses were three 40 mg tablets of Pycnogenol three times daily (360 mg) or one capsule with 300 mg HCSE standardized to 50 mg escin twice daily (600 mg HCSE = 100 mg escin/d). Baseline parameters (leg circumference and symptoms scores) were re-measured at two-week intervals. Symptoms subjectively evaluated included pain, cramps, nighttime swelling, heaviness, and skin reddening. HCSE moderately, but not significantly, decreased leg circumference and reduced symptoms scores compared to baseline values. On the other hand, Pycnogenol significantly reduced leg circumference ($P < 0.01$) and subjective scores for pain, cramps, nighttime swelling, heaviness ($P < 0.01$), and reddening ($P < 0.05$) after two and four weeks. Both therapies were well tolerated. Unlike HCSE, Pycnogenol also significantly decreased cholesterol and LDL values by the end of the trial ($P < 0.001$).

Bioavailability and Relative Doses

Knowledge of the pharmacokinetics of escin in HCSE is based on studies using radioimmunoassays of β-escin, the major active component in the saponin mixture. Two HCSE tablet products standardized to 50 mg escin were compared in a randomized, open, crossover study with 18 healthy subjects through two 24-hour dosing cycles.[5] The two products proved bioequivalent, with maximum β-escin serum concentrations from 16-18 ng/mL and the average concentration about 10 ng/mL. The second dosing cycle produced lower maximum (10-11 ng/mL) and average (7 ng/mL) levels. Effective adult HCSE doses in clinical studies provide the equivalent of 50-150 mg escin daily, with a typical dose of 300 mg extract (50 mg escin) every 12 hours.[2,19]

HCSE has been empirically used externally for symptoms associated with varicose veins, including leg swelling, pain, and heaviness and/or calf pain. The gel is standardized to 2% escin and usually applied to the affected area twice daily.[2] Escin was shown to be absorbed after cutaneous application and to significantly reduce experimentally induced exudation by 19.9% ($P < 0.005$).[20]

Bioavailability of Pycnogenol is assumed on the basis of its clinical efficacy. None of its known components are excreted unchanged, but metabolites appear in the urine after oral ingestion. Taxifolin and ferulic acid are excreted as esters of glucuronic acid or sulphuric acid after four hours. The procyanidin metabolites are active valerolactones that are excreted as sulphates or glucuronides after 12-14 hours.[21] Effective daily doses of Pycnogenol for CVI range from 100 mg to 360 mg, with 100 mg three times daily as the typical dosing schedule.[2,18]

Safety Issues with HCSE and Pycnogenol

The German Commission E monograph notes that itching, nausea, and gastric complaints have occurred in isolated cases after oral use of HCSE.[1] Adverse drug reactions as documented in eight studies included GI symptoms, dizziness, nausea, headache, and itching, with a reported frequency between 0.9% and 3.0%. Three studies found no greater frequency than with placebo.[8] This extract is not recommended for use in children, since no data support its use in this population. Children have been poisoned after consuming the raw seeds.[19] No embryotoxic or teratogenic effects were found in rats or rabbits after intravenous doses of 30 mg/kg HCSE or oral doses of 100 or 300 mg/kg in rats. Only the 300 mg/kg dose in rabbits produced an undesirable effect: a mildly reduced average weight of the fetuses.[22] Though not generally recommended for pregnant or nursing women, a controlled double-blind study using 600 mg HCSE (100 mg escin) daily with 52 pregnant women found no serious adverse effects after two weeks.[19]

Due to their content of the antiplatelet coumarin derivative esculetin, the potentially toxic whole seeds or tea should not be consumed. HCSE does not contain this component and is considered safe with oral HCSE dosing unless a patient has a rare allergic sensitivity to it or its components. HCSE should not be used with hypoglycemic agents such as insulin, sulfonylureas, or metformin.[19] The escin fraction from the seeds has shown oral hypoglycemic activity in rats after a single 200 mg/kg dose, while its major components were active at 100 mg/kg.[23] Some speculate that since escin binds to plasma protein it may affect the binding of other drugs.[2]

Aside from reductions in cholesterol measurements[12,18] and platelet aggregation,[13,24] no significant differences in physiological, hematological, or biochemical parameters have been observed in clinical studies with Pycnogenol.[13,16,17] Pycnogenol has been associated with gastric upset, diarrhea, and constipation, so it is recommended that it be taken with meals. Based on reports from 2,000 patients, frequency of adverse drug effects including headaches and dizziness is 1.6% and is unrelated to dose or duration of treatment. It is not recommended during the first three months of pregnancy, though no mutagenic or teratogenic effects, perinatal toxicity, or antifertility effects have been shown in safety pharmacological studies.[2]

No drug interactions have been reported with Pycnogenol. However, it is recommended that combinations with antiplatelet drugs be avoided,[2] for when 60 patients were studied in a randomized, four-week, controlled, double-blind trial using 150 mg Pycnogenol three times daily, platelet aggregation and adhesion decreased compared to placebo.[13] On the other hand, this effect can provide beneficial consequences in regular tobacco use as seen in a series of studies with smokers. The smoking-induced increase in platelet aggregation was prevented with single doses of 500 mg aspirin = 100 mg < 150 mg < 200 mg Pycnogenol. While aspirin significantly increased bleeding time in the smokers, Pycnogenol did not.[24]

Conclusion

Chronic venous insufficiency is a common and progressive problem of the lower extremities that can lead to significant morbidity. Treatment with pharmaceutical grade botanical extracts has been shown to significantly improve clinical outcomes. Reduction of symptoms, such as heavy sensation, swelling, and pain in the legs, and objective decreases in leg volume and ankle circumference, have been documented after using standardized HCSE and Pycnogenol. Both appear to impact both causes and effects of inflammation as they act as free radical scavengers and inhibit enzymatic degradation of connective tissue. Consequently, they are able to reduce vascular permeability. In addition, the horse chestnut extract enhances vascular tone by influencing ion channel sensitization and prostaglandin production, while Pycnogenol improves microcirculation.

Reviews of multiple clinical trials indicate that each of these botanical products has been shown to be clinically safe and effective. In a comparative study with CVI, 40 patients using the standard HCSE daily dose (600 mg = 100 mg escin) and a relatively high Pycnogenol dose (360 mg), the Pycnogenol group experienced significant symptom relief and greater beneficial clinical outcomes than those using HCSE.

Recommendation

Pycnogenol appears to be the optimal first choice when instituting an oral phyto-pharmaceutical therapeutic trial to assist in the management of CVI and it sequellae. Often a single therapeutic approach is not completely effective on its own, and individual patient response ultimately determines which product will prove preferable. The focus thus far on botanical extract clinical studies has been the mono-treatment of patients having well-established pathologies. The possibility of combining Pycnogenol with HCSE, internally and/or topically, to improve therapeutic outcome is worthy of investigation. Regular walking and/or aquatic exercise help reduce distal fluid retention. Mechanical support from elastic stockings is an obvious useful adjunct. Other passive means such as tonic (cold water) hydrotherapy, massage, and postural elevation techniques for the lower extremities also can be considered.

One would expect the greatest benefit from employing a combination of internal and external medication together with patient-appropriate exercise and physical therapy, especially for patients with severe symptomatology who otherwise face the probability of surgical intervention. For those whose conditions have not reached such an extreme degree, prevention of pathological progression by the use of one or another of these botanical extracts along with physical adaptations remains a benefit well worth pursuing. ❖

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Rhodiola rosea: A Botanical Adaptogen

By Susan T. Marcolina, MD, FACP, and Claudia Petaccio, MD

In daily life, everyone deals with stress, the mental and physical imbalance that occurs when life's demands exceeds the ability to meet them. Physiologically, stress causes predictable systemic effects in immune function, hormone levels, and gastrointestinal and intellectual functioning.[1] A wide range of events including sleep deprivation, surgery, extremes of cold and heat exposure, and anguished mental states can induce a surge of cortisol and catecholamines. Such stressors, if intense and long-lasting enough, eventually result in a decline in performance and, indeed, are risk factors for significant medical illness such as coronary artery disease and myocardial infarction.[2]

Stress Mitigation

Stress management programs help individuals increase their adaptation response. One component of a comprehensive program could be the use of adaptogenic herbs. The term adaptogen, coined in 1947 by the Russian scientist Nicolai Lazarov and still in use today, refers

Table

Chemical compounds identified in *Rhodiola rosea*

Compounds	Classification	Comments
Cinnamyl alcohol glycosides: rosavin, rosin, rosarin, collectively rosavins	Phenylpropanoids	Standardization of RRRE based on rosavin content; Rosavins critical to RRRE's adaptogenic properties; Rosavin phytochemical unique to RRRE
Salidroside p-tyrosol	Phenylethanol derivatives	Salidroside present in all analyzed *Rhodiola* sp. and in a wide variety of non-*Rhodiola* sp.; p-tyrosol has significant antioxidant and modest 5-lipoxygenase inhibitory activity in vivo
Rodiolin, rodionin, rodiosin, acetylrodalgin, tricin	Flavonoids	Antioxidant properties
Rosiridol, rosavidin	Monoterpenes	Antioxidant properties
Daucosterol, β-sitosterol	Triterpenes	Antioxidant properties
Chlorogenic, caffeic, hydroxycinnamic, and gallic acids	Organic acids	Antioxidant properties

Adapted from: Brown RP, et al. *Rhodiola rosea*: A Phytomedicinal Overview. *HerbalGram* 2002;56:40-65.

to a substance that allows the body to adapt to a broad range of physical, chemical, and biological stresses and returns it to a balanced or homeostatic state. One such herb extensively studied for this purpose in Nordic countries and the countries comprising the former Soviet Union is *Rhodiola rosea*, also known as "golden root" and "rose root."

Taxonomy and Growth Characteristics

Rhodiola rosea L., is a member of the Crassulaceae family of plants native to circumpolar arctic alpine regions, particularly in Asia and Europe. Optimum growing conditions occur in dry sandy soils at altitudes of 5,000-18,000 feet above sea level. It is a perennial plant that grows to approximately 12-30 inches in height and bears yellow flower blossoms.[3] Its thick rhizome (a root-like, horizontal stem growing just below the surface of the soil) is the portion of the plant utilized for medicinal purposes. A minimum of five to six years of growth is required before the medicinal roots are ready for harvesting. Such harvesting should occur in autumn when the plant stops its vegetative growth and the dry-matter content of the root is greatest.[4]

Uses

The use of *R. rosea* root extract (RRRE) dates back to the ancient Greek physician Dioscorides, who recorded the first medicinal applications of rodia riza in 77 C.E. in *De Materia Medica*. It was renamed *Rhodiola rosea* by Linnaeus due to the fragrance of roses emitted from the freshly cut rootstock.[3,5]

Traditional Russian folk medicine used RRRE to increase physical endurance and work productivity, and to treat a variety of symptoms including fatigue, depression, anemia, and infertility. In Middle Asia, RRRE tea was utilized as a treatment for colds and flu during the severe winters. In the Nordic countries, Vikings used this herb to enhance their physical strength and endurance. Today *R. rosea* remains a popular plant in traditional Eastern European and Asian medical systems and is used primarily to mitigate stress-related declines in work performance and to improve depression, sleep, and fatigue.[1]

Phytochemistry

Although Hegi, in 1963, identified more than 50 species of rhodiola plants with morphological similarities, the pharmacologic and medicinal properties of *R. rosea* represent a species-dependent phenomenon. Biochemical investigations of the *R. rosea* root in countries of the former Soviet Union over the past 40 years have revealed the presence of six distinct groups of chemical compounds *(see Table)*.

Postulated Mechanisms for Adaptogenic Effect

Russian studies conducted primarily in animals show that RRRE stimulates norepinephrine (NE), dopamine (DA), serotonin (5-HT), and nicotinic cholinergic effects in the central nervous system (CNS). It also enhances the effects of these neurotransmitters on the brain by increasing blood-brain barrier permeability to DA and 5-HT precursors. In the brain stem, RRRE promotes the release of NE, 5-HT, and DA in ascending pathways that activate the cerebral cortex and the limbic system. This is the proposed mechanism whereby rhodiola enhances cognitive functions of the cerebral cortex and the attention, memory, and learning functions of the prefrontal and frontal cortices. The cholinergic system and the

acetylcholine (Ach) neurotransmitter also contribute to memory retrieval via pathways ascending from the memory storage systems of the limbic system to various areas of the cerebral cortex. Agents that block Ach suppress the activity of these ascending pathways and interfere with memory. RRRE reverses this blockade.[6,7]

RRRE also modulates the release of opioid peptides that occurs as part of the pituitary adrenal axis response to stress. RRRE alters the secretion of corticotrophin-releasing factor from the hypothalamus under stress. These actions prevent sudden increases in opioid, catecholamine (NE and DA), and glucocorticoid levels, and increases stress tolerance without damage to the CNS or cardiovascular system.

In addition to its effect on neurotransmitters, RRRE contains antioxidant compounds that help protect the nervous system from free radical oxidative damage.[8]

Clinical Studies

Shevtsov et al conducted a randomized, double-blind, parallel-group study with two verum groups (treated with SHR-5, a standardized extract of *R. rosea* root called Swedish Herbal Rhodiola manufactured by the Swedish Herbal Institute), one placebo group, and one control (non-treatment) group to study the antistress effects of a single dose of SHR-5 against a background of fatigue and stress.[9] The subjects were physically fit, healthy, young (age range 19-21 years) male cadets of the Russian Defense Ministry who were not heavy smokers. One treatment group took two 185 mg SHR-5 capsules and the other took three 185 mg SHR-5 capsules. Cognitive tests were used to assess mental work capacity before and after completion of night watch duty in each of the four groups.

The verum groups performed significantly better on the individual cognitive tests. A calculated total Antifatigue Index that combined measurements of work/unit time and quality of work (number of errors) showed the two rhodiola groups to perform significantly better than either the placebo or non-treatment groups ($P < 0.0001$).

Spasov et al performed a randomized, double-blind, placebo-controlled pilot study of a repeated, low-dose regimen of SHR-5 on a group of healthy, non-smoking 17- to 19-year-old east Indian male students during their first year medical school examination period.[10] Outcome measures included physical fitness, mental capacity, and well-being. The students were randomly divided into two parallel groups receiving either SHR-5 in a dose of 50 mg or placebo twice daily for 20 days.

All students completed the test protocol and no adverse effects were observed. Despite the low dosage, investigators found significant reductions in mental fatigue, improvements in general well-being and physical fitness, and in many but not all of the cognitive tests in students taking the *R. rosea* extract compared to students on the placebo.

Forty-two competitive skiers (20-25 years of age) took 100 mg of RRRE or placebo 30 minutes before 30 km training races and a biathlon (20 km race carrying a rifle while skiing and shooting targets at stops).[3] The athletes taking the *R. rosea* extract had statistically significantly increased shooting accuracy with less arm tremor and better coordination than those on placebo. Thirty minutes after the races, the heart rate in the *R. rosea* group was 104-106% of baseline vs. 128.7% in the placebo group ($P < 0.02$).

Darbinyan et al conducted a placebo-controlled, double-blind, crossover study of the effectiveness of a repeated low-dose regimen of SHR-5 (170 mg) for treating 56 healthy volunteer physicians experiencing work-related fatigue.[11] Mental fatigue following night duty was evaluated using five tests addressing complex cognitive functions. A fatigue index was calculated based on these measured parameters to compare the results in both groups.

Although significant improvement was seen in the fatigue index scores of the group who took the RRRE tablets during the first two-week period, this effect was not seen in the group who took the RRRE during the third two-week period. A possible reason for this difference may have been the cumulative fatigue incurred by the second group. Since the authors did not specify the frequency of night call performed during the study, it was difficult to determine the effect on these physicians.

Adverse Reactions

RRRE has demonstrated few side effects in clinical studies. RRRE should be taken early in the day as it may interfere with sleep or cause vivid dreams during initiation of therapy. It is contraindicated for people in excited states and in individuals with bipolar spectrum disorders, as it may precipitate manic episodes. Since blood pressure elevations have been observed with the use of RRRE, it should not be used in hypertensive individuals.[5,12] Because it has blood-thinning properties, RRRE should not be used prior to surgery or in those using anticoagulant medication.[13]

Since there are no data on RRRE's use in pregnant and nursing women, such patients should not be given this preparation.[1]

Dosage

R. rosea has a low level of toxicity. The LD_{50} (lethal dose at which 50% of animals die) was calculated to be

28.6 mL/kg, which is approximately 3,360 mg. An equivalent dose in a 70 kg man would be 235,000 mg. Since usual clinical doses range between 200 mg/d and 600 mg/d for chronic supplementation, there is a huge safety margin. When using RRRE as a single dose for acute purposes (exam or athletic competition), the suggested dose is three times that used for chronic supplementation.[3,6] It is best absorbed when taken on an empty stomach approximately 30 minutes prior to the morning or early afternoon meal.[3]

Standardization

The RRRE used in human clinical studies was standardized to a minimum of 3% rosavins and 0.8-1% salidroside, since this is the ratio of these compounds that occurs naturally in the plant root (i.e., about 3:1, respectively). For this reason, whole extracts of RRRE used for medicinal purposes are standardized to these concentrations and ratios. This new standard has been adopted by the Russian Pharmacopoeia Committee.[3,6,14]

Conclusion

Clinical studies suggest that RRRE is effective for enhancement of physical and mental performance during periods of stress for healthy individuals. Thus far, side effects appear to be negligible. RRRE should not be used in pregnant/nursing women.

Recommendation

More clinical research in the form of placebo-controlled, double-blind trials is necessary to confirm the beneficial effects of RRRE. RRRE may be useful as a component of a comprehensive program for stress management that includes a healthy diet, regular exercise, smoking and substance abuse cessation, weight management, relaxation therapies, and improvement in communication and relationship-building skills. ❖

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CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

20. In which of the following clinical conditions has coenzyme Q_{10} proven most beneficial?
a. Type 1 diabetes
b. Type 2 diabetes
c. Diabetes caused by mtDNA mutations

21. Which of the following appears to be the optimal botanical adjunct in managing CVI?
a. Horse chestnut seed extract
b. Pycnogenol

22. Pycnogenol should *not* be administered concomitantly with which class of drugs?
a. Anti-inflammatory drugs
b. Antipsychotic drugs
c. Antiplatelet drugs

23. *Rhodiola rosea* appears to enhance physical and mental performance during periods of stress in healthy individuals.
a. True
b. False

Answers: 20. c, 21. b, 22. c, 23. a.

different extent from the brain. In: Saratikov AS, ed. *Stimulants of the Central Nervous System.* Tomsk, Russia: Tomsk State University Press; 1968:27-31.
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Clinical Briefs

With Comments from Russell H. Greenfield, MD

Vegetarian Diet and Screening for Down Syndrome

Source: Cheng P-J, et al. Elevated maternal midtrimester serum free β-human chorionic gonadotropin levels in vegetarian pregnancies that cause increased false-positive Down syndrome screening results. *Am J Obstet Gynecol* 2004;190:442-447.

Goal: To determine the effect of a vegetarian diet on maternal serum levels of free β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) for Down syndrome screening.

Subjects: This study examined 98 lactovegetarian and 122 omnivore Taiwanese women with singleton pregnancies, and without maternal complication or abnormal outcomes.

Methods: Screening for Down syndrome was performed between 14 and 18 weeks of gestation via enzyme or radioimmunoassay. Results of free β-hCG and AFP levels were compared between groups and with reference levels. Serum B_{12} concentrations were also determined.

Results: Levels of free β-hCG were significantly higher in the lactovegetarian group as compared with reference levels. This resulted in a false-positive rate for the presence of Down syndrome of 17.3%. The vegetarian group also had a significantly lower mean serum vitamin B_{12} concentration. On further analysis, levels of free β-hCG were highest in the vegetarian pregnancies that also had the lowest serum levels of vitamin B_{12}. Those vegetarian pregnancies with normal B_{12} levels had free β-hCG levels comparable to those of the reference population. No differences were noted between groups with respect to AFP levels.

Conclusion: The false-positive rate with midtrimester screening for Down syndrome is higher than normal among vegetarian women with low serum levels of vitamin B_{12}. New reference levels for free serum β-hCG for vegetarian women should be established to correct this situation.

Study strengths: Sample size; degree of follow-up.

Study weaknesses: Inadequate discussion of sample size determination, including lack of exclusion criteria; no mention as to whether any subjects had access to prenatal vitamins.

Of note: A lactovegetarian was defined in this study as someone who eats eggs and dairy products, but no meat, fish, or poultry; the false-positive rates for the reference and omnivore groups were 5.3% and 5.7%, respectively; the authors recommend screening for Down syndrome using ultrasound markers and nuchal translucency measurement, rather than serum markers, for vegetarian women.

We knew that: Numerous other factors influence the accuracy of screening for Down syndrome, including maternal weight, smoking, and the presence of illnesses such as SLE and IDDM; most maternal serum AFP is of fetal origin, whereas hCG is of placental origin; adequate vitamin B_{12} is necessary for proper DNA synthesis.

Clinical import: The importance of folic acid supplementation during pregnancy has been recognized for some time, and in this regard public health initiatives have helped to lower the incidence of birth defects. It also has long been known that people adhering to a strict vegetarian/vegan diet often are deficient in specific nutrients, including zinc, calcium, iron, and vitamin B_{12}. It now appears that inadequate levels of vitamin B_{12} during pregnancy can complicate screening for Down syndrome, leading to unnecessary interventions. While the authors call for the development of new serum β-hCG reference levels for vegetarian women, the results also can be taken as further call to ensure that all pregnant women have access to both nutritious foods and prenatal vitamins.

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Supplement to *Alternative Medicine Alert*
June 2004

ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

Type 2 Diabetes and Risk Reduction

TYPE 2 DIABETES, FORMERLY CALLED ADULT-ONSET OR NON-INSULIN-DEPENDENT DIABETES, IS the most common form of diabetes. People can develop Type 2 diabetes at any age, even during childhood. This form of diabetes usually begins with insulin resistance, a condition in which fat, muscle, and liver cells do not use insulin properly. At first, the pancreas keeps up with the added demand by producing more insulin. In time, however, it loses the ability to secrete enough insulin in response to meals. Being overweight and inactive increases the chances of developing Type 2 diabetes. Treatment includes taking diabetes medicines, making wise food choices, exercising regularly, and controlling blood pressure and cholesterol.

What are the signs and symptoms of Type 2 diabetes?

Many people have no signs or symptoms. Symptoms can also be so mild that you might not even notice them. More than 5 million people in the United States have Type 2 diabetes and do not know it. Here is what to look for:

- Increased thirst
- Increased hunger
- Fatigue
- Increased urination, especially at night
- Weight loss
- Blurred vision
- Sores that do not heal

Sometimes people have symptoms but do not suspect diabetes. They delay scheduling a checkup because they do not feel sick. Many people do not find out they have the disease until they have diabetes complications, such as blurry vision or heart trouble. It is important to find out early if you have diabetes because treatment can prevent damage to the body from diabetes.

What does it mean to have pre-diabetes?

If you have been told that you have pre-diabetes, it means you are at risk for getting Type 2 diabetes and heart disease. The good news is if you have pre-diabetes you can reduce the risk of getting diabetes and even return to normal blood glucose levels. With modest weight loss and moderate physical activity, you can delay or prevent Type 2 diabetes. If your blood glucose is higher than normal but lower than the diabetes range (what is now called pre-diabetes), have your blood glucose checked in 1-2 years.

What can I do about my risk?

You can do a lot to lower your chances of getting diabetes. Exercising regularly, reducing fat and calorie intake, and losing weight can help you reduce your risk of developing Type 2 diabetes. Lowering blood pressure and cholesterol levels also helps you stay healthy.

Reach and maintain a reasonable body weight

Your weight affects your health in many ways. Being overweight can keep your body from making and using insulin properly. It can also cause high blood pressure. Losing even a few pounds can help reduce your risk of developing Type 2 diabetes because it helps your body use insulin more effectively. In the Diabetes Prevention Program (DPP), a study evaluating standard diabetes care, metformin, and lifestyle modification, people who lost 5-7% of their body weight significantly reduced their risk of Type 2 diabetes.

If you are overweight or obese, choose sensible ways to get in shape:

- Avoid crash diets. Instead, eat less of the foods you usually have. Limit the amount of fat you eat.
- Increase your physical activity. Aim for at least 30 minutes of exercise most days of the week.
- Set a reasonable weight-loss goal, such as losing 1 lb per week. Aim for a long-term goal of losing 5-7% of your total body weight.

Make wise food choices most of the time

What you eat has a big impact on your health. By making wise food choices, you can help control your body weight, blood pressure, and cholesterol.

- Take a hard look at the serving sizes of the foods you eat. Reduce serving sizes of main courses (such as meat), desserts, and foods high in fat. Increase the amount of fruits and vegetables.
- Limit your fat intake to about 25% of your total calories. For example, if your food choices add up to about 2,000 calories/d, try to eat no more than 56 g of fat. Your doctor or a dietitian can help you figure out how much fat to have. You can check food labels for fat content too.
- You may also wish to reduce the number of calories you have each day. People in the DPP lifestyle modification group lowered their daily calorie total by an average of about 450 calories. Your doctor or dietitian can help you with a meal plan that emphasizes weight loss.

Be physically active every day

Regular exercise tackles several risk factors at once. It helps you lose weight, keeps your cholesterol and blood pressure under control, and helps your body use insulin. People in the DPP who were physically active for 30 minutes a day five days a week reduced their risk of Type 2 diabetes. Many chose brisk walking for exercise.

If you are not very active, you should start slowly *(see sidebar)*, talking with your doctor first about what kinds of exercise would be safe for you. Make a plan to increase your activity level toward the goal of being active for at least 30 minutes a day most days of the week. When preparing to exercise, if you haven't eaten for more than an hour or if your blood glucose is less than 100-120, have a snack before you begin.

Source: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. For more information, please see: www.diabetes.niddk.nih.gov/dm/pubs/riskfortype2/index.htm.

Time Depends on Intensity

Higher intensity activities require less time spent. Lower intensity activities require more time spent.

Light-Intensity Activities

- Walking slowly
- Golf, powered cart
- Swimming, slow treading
- Gardening or pruning
- Bicycling, very light effort
- Dusting or vacuuming

Moderate-Intensity Activities

- Walking briskly
- Golf, pulling or carrying clubs
- Swimming, recreational
- Mowing lawn, power motor
- Tennis, doubles
- Bicycling 5-9 mph, level terrain, or with a few hills
- Scrubbing floors or washing windows
- Weight lifting, Nautilus machines, or free weights

Vigorous-Intensity Activities

- Race-walking, jogging, or running
- Swimming laps
- Mowing lawn, hand mower
- Tennis, singles
- Bicycling more than 10 mph, or on steep uphill terrain
- Circuit training

Source: Centers for Disease Control & Prevention. Available at: www.cdc.gov/nccdphp/dnpa/physical/measuring/examples.htm.