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**FILE: ■ French Maritime Pine (*Pinus pinaster*) Bark  
■ Pycnogenol®  
■ Endothelial Function**

**HC 010584-350**

**Date: April 15, 2008**

**RE: Pycnogenol® Facilitation of Vasodilation via Nitric Oxide Production**

Nishioka K, Hidaka T, Nakamura S, et al. Pycnogenol®, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans. *Hypertens Res*. September 2007;30(9):775-780.

Impaired function of the endothelium, which is the innermost cell layer of the arteries, is an initial step in the development of atherosclerosis. The degree of endothelial dysfunction is believed to predict future cardiovascular events such as heart attack and stroke. Pycnogenol® is an extract from the bark of the French maritime pine (*Pinus pinaster*). It is rich in water-soluble polyphenol compounds including procyanidins, catechin, taxifolin and phenolcarboxylic acids that have antioxidant and anti-inflammatory activity. Pycnogenol may influence endothelial function by stimulating endothelial nitric oxide synthase with the result of elevated nitric oxide levels. The purpose of this clinical trial was to investigate the effects of Pycnogenol on endothelial function in healthy men.

This randomized, double-blind, placebo-controlled trial was conducted at the Hiroshima University Graduate School of Biomedical Sciences in Hiroshima, Japan. The subjects were 16 healthy young men. The subjects were randomly assigned to take either 180 mg Pycnogenol (Horphag Research, Ltd., Geneva, Switzerland) or a placebo every morning for 2 weeks. Changes in basal forearm blood flow (vasodilation) were measured after subjects were given infusions of acetylcholine, which is an endothelium-dependent vasodilator, and sodium nitroprusside, which is an endothelium-independent vasodilator. Forearm blood flow was measured by strain-gauge plethysmography at baseline and after 2 weeks of treatment with Pycnogenol or placebo. To evaluate the effect of Pycnogenol on the release of nitric oxide, subjects were given an infusion of N-monomethyl-L-arginine (L-NMMA) along with acetylcholine. L-NMMA blocks the nitric oxide synthase enzyme that produces nitric oxide. Plasma levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) were measured as a marker of oxidative stress.

Basal forearm blood flow was unaffected after two weeks in both groups. Infusion of acetylcholine increased forearm blood flow before and after treatment in both groups. Pycnogenol significantly enhanced the vasodilation response to acetylcholine ( $P < 0.05$ ), whereas the placebo had no effect. Infusion of sodium nitroprusside also increased forearm blood flow before and after treatment in both groups, but neither Pycnogenol nor placebo had any additional effect. The infusion of L-NMMA with acetylcholine blocked the vasodilating effect of acetylcholine and decreased forearm blood flow. L-NMMA also eliminated the enhancement of acetylcholine-induced vasodilation by Pycnogenol. No significant changes in arterial blood pressure or heart rate occurred in the subjects during any of the infusions. Plasma levels of 8-OhdG were unchanged in both groups.

These results demonstrate that Pycnogenol enhances endothelium-dependent vasodilation but not endothelium-independent vasodilation. The blunting of Pycnogenol-stimulated vasodilation by a substance that inhibits nitric synthase suggests that the mechanism of action for Pycnogenol is augmented nitric oxide production. In vitro studies have shown that plant polyphenols enhance expression of nitric oxide synthase genes, resulting in release of nitric oxide from endothelial cells. Thus, Pycnogenol may have a direct ability to increase nitric oxide production.

The authors conclude that Pycnogenol augments endothelium-dependent vasodilation through an increase in nitric oxide production. Healthy endothelial function is dependent upon a balance between reactive oxygen species and nitric oxide, and therefore Pycnogenol may be useful in the treatment of cardiovascular disease and other diseases involving oxidative stress.

The authors recommend that future studies should measure urinary excretion of 8-OhdG, a more sensitive marker of oxidative stress than plasma levels, to provide more information about the antioxidant effects of Pycnogenol. Future studies should also involve a larger number of subjects and study populations other than healthy young men, particularly those with greater oxidative stress demonstrated by higher basal 8-OhdG levels.

—*Heather S. Oliff, PhD*

The American Botanical Council has chosen not to reprint the original article.

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