The Longwood Herbal Task Force

(http://www.mcp.edu/herbal/default.htm) and

The Center for Holistic Pediatric Education and Research

(http://www.childrenshospital.org/holistic/)

Oligomeric Proanthocyanidin Complexes (OPCs)

(Pycnogenols, Pine Bark Extract, Grape Seed Extract)

Kathi J. Kemper, MD, MPH

Principal Proposed Uses: Edema and impaired capillary integrity, atherosclerosis, ADHD; antioxidant

Other Proposed Uses: Impaired night vision, diabetic retinopathy, macular degeneration, allergies, skin aging, cancer prevention

Overview

Oligomeric proanthocyanidin complexes (OPCs) or pycnogenols are extracted commercially from either grape seeds or maritime pine bark and sold under trade names such as Pycnogenol®. In Europe they are used to enhance capillary stability and enhance lymphatic drainage in diverse conditions; they are widely marketed in the US as a treatment for attention deficit hyperactivity disorder (ADHD). Data from *in vitro* and animal studies demonstrate OPCs' potent antioxidant and vasoprotective effects. At least eight double blind, placebo controlled trials have found significant benefits of OPCs in preventing and/or treating edema and chronic venous insufficiency. Several studies suggest that, like bilberry (which contains similar compounds), OPCs enhance night vision and recovery from glare. There are no randomized, controlled trials evaluating the effect of OPCs on atherosclerosis, ADHD, allergies, macular degeneration, diabetic retinopathy or aging skin. There are no reported allergies and no side effects with OPCs that exceed those found with placebo treatment. There are no data on safety during pregnancy, lactation or childhood, and no data on adverse interactions with other medications or dietary supplements.

Historical and Popular Uses

Oligomeric proanthocyanidin complexes (OPCs), pro-cyanidolic oligomers (PCOs) or pycnogenols are a family of chemicals found in a variety of plants, most prominently grape seeds and French maritime pine bark; they are widely sold under the brand name Pycnogenol®. Grape seeds offer a less expensive source of commercial OPCs than pine bark.

OPCs gained prominence in the 1990's. They were first extracted from pine bark in 1951 by a French investigator who found that they shared many biochemical and physiologic effects with Vitamin C. Subsequent research confirmed that OPCs are plentiful in and easily extracted from grape seeds. OPCs are also found in green tea (*Camellia sinensis*) and account for some of its antioxidant effects. Most of the research on OPCs has been done in Europe, primarily in France, where grape seeds are abundant. The French use OPCs to improve capillary stability, decrease venous stasis and bruising, enhance lymphatic drainage and reduce lymphedema. Based on their ability to improve night vision and recovery from glare (see also BILBERRY), OPCs are also used to treat macular degeneration and diabetic retinopathy.

Numerous sites on the World Wide Web market OPC products to American consumers. Controversy rages in the marketing literature about the benefits of products derived from pine bark vs. grape seed. Some brands, including Pycnogenol®, a patented extract from French maritime pine bark, are claimed to provide dramatic relief from and reduce the risk of heart disease, cancer, accelerated aging (including wrinkles, psoriasis and sun damage), arthritis and oxidative stress, and to strengthen blood vessels and reduce the risk of bruising, varicose veins, chronic venous insufficiency and phlebitis. Some OPC manufacturers also claim them to be a very effective natural treatment for attention deficit hyperactivity disorder (ADHD), hay fever, inflammation, diabetic retinopathy, chronic fatigue syndrome and stomach ulcers and to prevent upper respiratory tract infections.*

Most of the studies on OPC's have been conducted on products derived from grape seed extracts. Grape seed extracts tend to be less expensive than pine bark products.

OPCs have not been reviewed by the German Commission E, nor have they been rated for safety by the American Herbal Products Association (AHPA).†

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* www.nmia.com/~garcia/healthy/pyc.html, www.pycnogenol-usa.com/index.htm, www.nu-gen.com/add.htm

† http://www.ahpa.org/

Botany

Medicinal species:

Grape seed: *Vinis vinifera* Linne

French maritime pine bark: *Pinus maritima* or *P. pinaster* Soland

Common names: The naming of these compounds is complex and is made more confusing by the fact that one of the generic terms, pycnogenols, is also patented as a trade name for one particular product, Pycnogenol®. Other names include condensed tannins, grape seed extract, leucoanthocyanidins, nonhydrolyzable tannins, oligomeric proanthocyanidins, polyphenolic oligomers, and pycnogenols. Pycnogenol® is a brand name for a patented OPC made from maritime pine bark[1].

Where it's grown: French maritime pines are grown in the forest of Gascogne in southwest France and throughout Europe. Grapes are grown throughout Europe and North America.

Biochemistry

OPCs: Potentially Active Chemical Constituent
• Oligomeric proanthocyanidin complex (OPC), also known as pro-cyanidolic oligomers (PCOs), grape seed proanthocyanidin extract (GSPE), or pycnogenols

The biochemistry and nomenclature of this group of compounds are very confusing. Phenols are a large group of natural products derived from *p*-coumaric acid. The major groups of phenols are:

- simple phenols (e.g. capsicum)
- coumarins and their glycosides
- anthraquinones
- lignans and neolignans (e.g. etoposide)
- tannins
  - hydrolyzable tannins (e.g. gallic acid)
  - nonhydrolyzable or condensed tannins (e.g. proanthocyanidins, leucoanthocyanidins, OPCs, pycnogenols)
- flavones and flavonoids (e.g. apigenin, rutin, quercetin)
- anthocyanidins and their glycosides (e.g. anthocyanidin, cyanidin)*

Most phytopharmacologists classify OPCs as tannins, which are typically complex mixtures of polyphenols; they are closely related to flavonoids[2]. When treated with acid, proanthocyanidins break down into anthocyanidin monomers.

Different plants (e.g. pines and grapes) contain different concentrations of the various proanthocyanidins and tannins and have different physiologic effects[2]. Pine bark extract contains flavonoids, catechin, epicatechin, and taxifolin (proanthocyanidin monomers), as well as OPCs. Grape seed extract contains simple phenolic acids (e.g. *p*-coumaric, cinnamic, caffeic, gentisic, ferulic, and vanillic acids), trihydroxy stilbenes (e.g. resveratrol and polydatin), and flavonoids (catechin, epicatechin, and quercetin) in addition to OPCs. Polymeric aggregation gives rise in

* Some phytopharmacologists consider anthocyanidins a subcategory of flavones and flavonoids.

turn to the viniferins and procyanidins[4]. Red, but not white wine, contains abundant polyphenols, about one gram per liter; red wine's compounds have been associated with endothelium-dependent vasodilation, serum antioxidant activity, reduced platelet aggregation and decreased LDL oxidation[5,6,7,8,9,10]. The principal flavonoids in grape seeds are procyanidins (75% - 85%), while the principal flavonoids in grape skins are anthocyanidins.

OPCs are also found in many other plants including hawthorn flowers, berries, onions, peas, and parsley. Related compounds are found in bilberry, cranberry, uva ursi, green tea, coffee, chocolate, and peanut skins. Green tea, for example, contains up to 30% procyanidins by dry weight[11].

The antioxidant and free-radical scavenging effects of polyphenols such as OPCs have been demonstrated in many experimental systems; they are roughly twice as potent as Vitamin E and four times as potent as Vitamin C[12,13,14,15,16].

Procyanidins inhibit lipoxygenase and cyclo-oxygenase, thereby preventing lipid oxidation and platelet aggregation[17].

Several polyphenols found in grape seed extracts (notably catechin, quercetin, and resveratrol) promote nitric oxide production by vascular endothelium[18], inhibit the synthesis of thromboxane in platelets and leukotriene in neutrophils, modulate the synthesis and secretion of lipoproteins, arrest tumour growth, and inhibit carcinogenesis in different experimental models[4].

OPCs chelate free iron molecules, preventing iron-potentiated lipid peroxidation, and reduce the release and production of pro-inflammatory histamine and leukotrienes. OPCs enhance collagen cross-linking and reduce elastin's susceptibility to degradation by elastase[19,20]. These effects may contribute to OPCs beneficial effects on capillary stability[21].

Experimental Studies

OPCs: Potential Clinical Benefits

1. Cardiovascular: Edema and impaired capillary integrity, atherosclerosis
2. Pulmonary: none
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: Gastric ulcers
5. Neuropsychiatric: Impaired night vision and recovery from glare, diabetic retinopathy and macular degeneration, ADHD
6. Endocrine: Diabetic retinopathy: See Neuropsychiatric
7. Hematologic: Excessive platelet aggregation
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: Anti-inflammatory for allergic rhinitis
11. Antimicrobial: none
12. Antineoplastic: Antineoplastic
13. Antioxidant: Antioxidant
14. Skin and mucus membranes: Skin aging: see Antioxidant
15. Other/miscellaneous: none

1. **Cardiovascular:** Edema and impaired capillary integrity, atherosclerosis
   a. Edema and impaired capillary integrity
      i. *In vitro data:* OPCs enhanced collagen cross-linking and reduced elastin's susceptibility to degradation by elastase in rabbit skin[19,22]. Studies of tissue cultures of excised human veins from patients with and without peripheral edema support the notion that OPCs modulate the incorporation of glucosamine and the synthesis of glycoproteins and sulphated glycosaminoglycans, thereby affecting vascular integrity[23]. OPCs also modulated the attachment, proliferation and detachment of fibroblasts, enhancing the number of cell-fiber interactions and increasing resistance to degradation by elastase and collagenase[24,25,26] .

ii. *Animal data:* Treatment with OPCs (Endotelon®) for seven days before and after surgical interruption of the rat hindlimb's lymphatic drainage decreased peripheral edema by 47% compared with untreated control animals[17,27]. In rats, both oral and intraperitoneal administration of OPCs helped prevent capillary leaking in the brain, increasing the resistance of the tight junctions in the arteriolar capillaries[28].

iii. *Human data:* In France, OPCs are used to treat patients with a variety of peripheral circulatory problems characterized by capillary fragility and impaired venous drainage[29,30]. A small pilot study demonstrated that OPCs could significantly improve venous tone within two hours of administration in patients with severe varicose veins[31].

In a double-blind, placebo-controlled trial of 92 patients with chronic venous insufficiency, those randomized to an OPC product (Endotelon® 100 mg three times daily) had significantly reduced edema[32]. In another European trial of 50 patients with chronic venous insufficiency, Endotelon® (150 mg daily) was more effective than a semi-synthetic flavonoid (Diosmin®) in reducing peripheral edema[33]. A review of three small French double-blind clinical trials concluded that in patients with chronic venous insufficiency, grape seed extract was significantly more helpful than placebo in improving venous function in terms of edema, pain, paresthesias and nocturnal leg cramps[17,34]. A much larger French study of 4,729 women taking hormone therapy reported that OPCs (Endotelon, 300 mg daily for three months) produced significant benefits in terms of venous and lymphatic insufficiency[35].

In a double-blind, randomized, placebo controlled trial of 63 post-operative breast cancer patients, those treated with OPCs (600 mg daily for six months) had significantly less edema, pain and paresthesias than the placebo-treated patients[36]. Similarly, in a double-blind, controlled trial of 32 patients who had undergone facial cosmetic surgery, those given OPCs for ten days had significantly less edema than the placebo-treated group[37]. Finally, in a randomized, controlled trial of 50 adults who had sustained sports injuries, those treated with OPCs had significantly less swelling at the injured site over the next ten days than the placebo group[38].

In a double-blind placebo controlled trial of 20 patients with hepatic cirrhosis, supplementation with 300 mg daily of OPCs was associated with significantly reduced capillary fragility[39].

b. Atherosclerosis: Because dietary intake of antioxidant bioflavonoids is linked epidemiologically with a lower risk of coronary artery disease, some clinicians have inferred that OPCs may be useful in the prevention and treatment of atherosclerosis[40,41,42].

i. *In vitro data:* OPCs' use for cardiovascular disease is primarily based on their antioxidant and anticoagulant effects, but they also cause vasodilation, mildly inhibit angiotensin-converting enzyme, enhance microcirculation and modulate nitric oxide metabolism[43,44]. See also the **Hematologic** and **Antioxidant** sections below.

In the rat heart model of ischemia/reperfusion, OPCs had no significant effect on the resultant damage[45]. In intact rat aortic ring experiments, OPCs relaxed sympathomimetic-induced contractions in a concentration-dependent manner. OPCs also increased nitric oxide (NO) levels, counteracting the vasoconstrictor effects of sympathomimetics[18].

ii. *Animal data:* In both young and aged rats, procyanidin protected the heart against ischemia/reperfusion damage; this protection was positively associated with an increase in plasma antioxidant activity[46].

In cholesterol-fed rabbits, proanthocyanidin-rich extracts did not appreciably affect the serum lipid profile, but they did lower the level of cholesteryl ester hydroperoxides and significantly reduce severe aortic atherosclerosis[47].

In rabbits fed with normal or cholesterol rich diets who were randomized to OPC supplements or control, the cholesterol content of the excised aortic intima media and the serum were significantly increased in all animals; however, the interaction of cholesterol with macromolecules of the aorta was beneficially modulated by OPCs[48].

iii. *Human data:* Epidemiologic evidence links diets high in OPCs, such as those in red wine, with lower risks of cardiovascular disease[49]. The theory that red wine consumption reduces coronary heart disease mortality despite a high-fat diet is known

as the “French paradox.” However, there are no prospective randomized, controlled clinical trials evaluating the effects of OPCs on the prevention or treatment of cardiovascular disease in humans.

2. **Pulmonary:** none
3. **Renal and electrolyte balance:** none
4. **Gastrointestinal/hepatic:** Gastric ulcers. This is an experimental use.
   i. *In vitro data:* none
   ii. *Animal data:* In rats with experimentally-induced gastric mucosal ulcers, significant protection was afforded by treatment with 200 mg/kg of OPCs from grape seed extract[50].
   iii. *Human data:* none
5. **Neuropsychiatric**: Impaired night vision and recovery from glare, diabetic retinopathy and macular degeneration, ADHD
   a. Impaired night vision and recovery from glare
      i. *In vitro data:* In bovine or porcine retina, purified rod outer segments and retinal pigment epithelium were exposed to lipid peroxidation by ferric ions; lipid peroxidation was subsequently measured. Of the compounds tested as antioxidants, partial protection in the bovine retina was found at 10(-5) M levels for epigallocatechin gallate, quercetin, diosmetin and pycnogenol[51,52].
      ii. *Animal data:* none
      iii. *Human data:* In a French study of 100 healthy volunteers, those who received OPCs (200 mg daily for six weeks) had a marked improvement in dark vision and recovery from glare[53]. Similarly, in a multi-center study of 100 subjects without major ocular pathology, Endotelon treatment (200 mg of OPCs daily) for five weeks was associated with significant improvements in night vision and visual response to glare[54]. An Italian study in myopic patients indicated similar improvements in night vision with OPCs[55].

      In a double blind study of 75 patients with ocular fatigue, those treated with OPCs and bilberry extracts had significant improvement in symptoms compared with those treated with placebo preparations[56].

b. Diabetic retinopathy and macular degeneration: OPCs' use for these conditions is based on their effects on night vision. There are no clinical studies evaluating these uses.

c. ADHD: Although pycnogenols are widely marketed as natural remedies for attention deficit hyperactivity disorder (ADHD), there are no clinical trials evaluating their effectiveness or toxicity in treating this condition, either compared to placebo or standard medications[57].

6. **Endocrine:** none
7. **Hematologic:** Prevention of platelet aggregation
   i. *In vitro data:* Procyanidins inhibited platelet aggregation as effectively as aspirin. They specifically inhibited thromboxane formation by intact platelets[58].
   ii. *Animal data:* none
   iii. *Human data:* In a series of German and American experiments on adults who smoked at least 15 cigarettes daily, pretreatment with Pycnogenol® (100 mg) was as effective as aspirin (500 mg) in preventing the platelet reactivity and aggregation usually observed two hours after smoking; the 200 mg dose of Pycnogenol effectively inhibited smoking-induced platelet aggregation for more than six days[59]. Aspirin significantly increased bleeding time from 167 to 236 seconds, while Pycnogenol did not[59].
8. **Rheumatologic:** none
9. **Reproductive:** none
10. **Immune modulation:** Anti-inflammatory for allergic rhinitis
    i. *In vitro data:* In cells from immunosuppressed mice, OPCs enhanced IL-2 production by mitogen-stimulated splenocytes, decreased production of interleukin 6, and increased the cytotoxicity of natural killer cells[60].
    ii. *Animal data:* In mice with aging-associated immune deficits, supplementing the diet with OPCs for two months significantly improved T- and B-cell function[61]. In the rat paw model of inflammation, OPCs provided significant protection against edema[62].
    iii. *Human data:* Despite OPCs' popular use in the treatment of allergic disorders, there are no studies evaluating their anti-inflammatory effects for this condition.

11. **Antimicrobial**: none
12. **Antineoplastic**: Antineoplastic. Most of the claims that OPCs affect carcinogenesis have been inferred from studies on the antineoplastic effects of another constituent of red wine, the stilbene, resveratrol.
    i. *In vitro data:* In the liver and lung microsomes of six-month old rats, pycnogenols inhibited the carcinogenic response to the tobacco-specific nitrosamine NNK, a potent environmental carcinogen, in a dose-dependent manner[63,64].
    ii. *Animal data:* none
    iii. *Human data:* none
13. **Antioxidant**: Antioxidant. OPCs are potent antioxidants. Their antioxidant effects are presumed to account for many of their benefits on the cardiovascular and immune systems[21,44,65,66].
    i. *In vitro data:* Preincubation of bovine pulmonary artery endothelial cells with pycnogenol (10-80 micrograms/mL) before organic oxidant exposure significantly increased cell viability and decreased lipid peroxidation[67]. Further studies in this model suggest that OPCs exert their protective effect partially by increasing the activity of endogenous antioxidants such as glutathione and superoxide dismutase[68].

    Proanthocyanidin-rich extract added to human plasma inhibited the oxidation of cholesteryl linoleate in low density lipoproteins[47].

    In liver and brain microsomes from mice, grape seed OPCs effectively prevented peroxidation induced by UV-C radiation[69].

    In mouse endothelial cells challenged with reactive nitrogen species, OPCs protected against alpha tocopherol depletion, potentially protecting vascular endothelium from oxidative stress from reactive nitrogen species such as nitric oxide[70,71].

    OPCs inhibited the oxidative burst of mouse macrophages, the oxidation of LDL, and hydroxyl radical induced breakage of DNA[72].

    OPCs from grape seed extracts exhibited 78-81% inhibition of superoxide anion and hydroxyl radical, significantly more than seen with vitamin C (12- 19%) or vitamin E (36-44%)[12]. Similarly, normal human oral keratinocytes treated with smokeless tobacco extract had a 1.5- to 7.6-fold increase in lipid peroxidation, cytochrome c reduction, DNA

fragmentation and apoptotic cell death; antioxidants provided 10-54% decreases in the former parameters and a 51-85% decrease in apoptotic cell death. OPCs exhibited better protection than vitamins C and E, singly and in combination[14].

ii. *Animal data:* The comparative protective abilities of OPCs, vitamin C, vitamin E, and beta-carotene on experimentally-induced lipid peroxidation and DNA fragmentation in mouse hepatic and brain tissues were assessed; OPCs exhibited the most marked antioxidant activity and DNA protection of all substances tested[13].

iii. *Human data:* In a single-blinded randomized, placebo-controlled cross-over study in 20 young volunteers, those who received 600 mg of OPCs (Leucoselect-phytosome) for five days had similar serum levels of vitamins C and E as the placebo-treated group, but exhibited significantly increased serum total antioxidant activity[73].

14. **Skin and mucus membranes**: Skin aging: See **Antioxidant** effects. Benefits on dermatologic signs of aging (i.e. wrinkles) are presumed based on OPCs' antioxidant effects, but have not undergone evaluation in randomized, controlled trials. Despite the lack of clinical trials, a number of anti-aging and anti-wrinkle skin creams containing OPCs are sold in Europe and the US.
15. **Other/miscellaneous**: none

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals and pharmaceuticals.

Furthermore, allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions to OPCs have not been reported.

Potentially toxic compounds in OPCs: None

Acute toxicity: In double-blind controlled trials, acute toxicities have not been reported to differ from placebo treatment. Studies in rats suggest that OPCs are essentially non-toxic: the LD50 in rats was greater than 4000 mg/kg[11].

Chronic toxicity: None reported. OPCs demonstrate no significant mutagenicity[74]. Giving up to 60 mg/kg daily to rats and dogs for up to 12 months did not result in any significant toxicity[11].

Limitations during other illnesses or in patients with specific organ dysfunction: Effects on platelet coagulation suggest caution in patients with bleeding diatheses.

Interactions with other herbs or pharmaceuticals: Effects on platelet coagulation suggest caution for patients taking anticoagulant medication or anticipating surgery.

Safety during pregnancy, lactation and/or childhood: Unknown.

Typical Dosages

Provision of dosage information dose NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.

Doses are given for single herb use and must be adjusted when using herbs in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Adult doses of OPCs:

As a general health-promoting antioxidant: 50 – 100 milligrams daily[3,75]

To treat disease: 150 – 300 milligrams daily[3]. After acute treatment (three weeks), doses of 40 – 80 mg daily are often recommended for maintenance[76].

Pediatric dosages: Unknown

Availability of standardized preparations: Standardized grape seed extract products contain 95% polyphenols, while pine bark extracts vary from 80% -85% OPCs[77,78]

Dosages used in herbal combinations: Variable

Proprietary names: Endotelon, Indena's Grape Seed Standardized Extract, Leucoselect®, Masquelier's Original OPCs®[79], Pycnogenol®

See Also:

Clinician Information Summary: http://www.mcp.edu/herbal/opcs/opcs.cis.pdf

Patient Fact Sheet: http://www.mcp.edu/herbal/opcs/opcs.ph.pdf

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