



Oligomeric Proanthocyanidins (OPCs)

Introduction

Oligomeric proanthocyanidins (OPCs) are some of the most abundant polyphenolic substances in the plant kingdom. Proanthocyanidins are an integral part of the human diet, found in high concentrations in fruits such as apple, pear, and grapes, and in chocolate, wine, and tea. OPCs in nutritional supplements are generally extracted from grape seeds or pine bark. Due to potent antioxidant activity, OPCs have been the subject of recent research,

demonstrating anticarcinogenic, anti-inflammatory, antimicrobial, and vasodilatory properties, making them a potentially valuable therapeutic tool for the treatment of a variety of conditions.

Synonyms for oligomeric proanthocyanidins include procyanidins, procyanidolic oligomers (PCOs), leucoanthocyanins, condensed tannins, and pycnogenols, although the latter term is no longer used. Pycnogenol® is the trade name for an OPC extract from the bark of the French maritime pine tree.

Jacques Masquelier of the University of Bordeaux, France, first studied OPCs in depth after reading of explorer Jacques Cartier's 1534 expedition up the St. Lawrence River, in which Cartier's crew, trapped in ice flows and dying of scurvy, survived after Native Americans gave them a tea brewed from the bark and needles of the native pine. Masquelier later postulated the pine constituents contained vitamin C and flavonoids that aided in the crew's recovery. Today, dietary intake of OPCs varies from tens to hundreds of milligrams per day, depending on geographical and seasonal dietary differences.¹

Biochemistry

Proanthocyanidins are high-molecular weight oligomers or polymers of a basic flavan-3-ol unit, with an average degree of polymerization between 4 and 11. Proanthocyanidin mixtures from grapes are a combination of dimers, trimers, tetramers, oligomers, and polymers. The reducing capacity of OPCs is thought to be proportional to weight concentration rather than the degree of polymerization.^{2,3} The polymeric nature of proanthocyanidins is unique among polyphenols; they complex and precipitate proteins and inhibit enzymes involved in vascular tissue degradation. The ability of OPCs to complex proteins is referred to as astringency and is responsible for the "puckery" sensation when tea or red wine comes in contact with saliva and buccal tissue.⁴

Pharmacokinetics

Human studies of polyphenol absorption are limited and results have varied depending on the structure and solubility of the phenolic compound. Available research has demonstrated the acidic environment of the human stomach does not readily degrade proanthocyanidins; therefore, absorption rates in the upper

gastrointestinal tract are not high. It appears, however, that even the low amounts observed in urine after an oral dose (usually <25 percent of original dose) are enough to significantly increase plasma/serum antioxidant capacity.⁵⁻⁷ OPCs reaching the colon undergo extensive degradation by the colonic flora. The metabolites and biological properties of this process have not yet been explored, but it has been suggested they may also have direct antioxidant and protective effects on colonic tissue.^{3,8}

Mechanisms of Action

OPCs possess antioxidant, antimutagenic, anticarcinogenic, anti-inflammatory, and antiviral properties.

Antioxidant

The potent antioxidative properties of OPCs account for their therapeutic benefit in disease states characterized by oxidative stress. OPCs also demonstrate potent, concentration-dependent, free radical scavenging ability.⁹ Studies in mice show OPCs inhibit chemically-induced lipid peroxidation, DNA fragmentation, and subsequent apoptosis (indicators of oxidative tissue damage) in a dose-dependent manner in hepatic and brain tissue.¹⁰ Human studies also demonstrate an antioxidative mechanism as evidenced by decreased lipid peroxidation of LDL cholesterol^{11,12} and increased free-radical trapping capacity after consumption of red wine containing OPCs.⁷

OPCs appear to have an affinity for vascular tissue and strongly inhibit several enzymes involved in degradation of collagen, elastin, and hyaluronic acid, the main structural components of the extravascular matrix.¹³ These effects are perhaps attributable to trapping reactive oxygen species and preventing oxidative injury to vascular endothelium. *In vitro* studies have also found OPCs increase resistance of cell membranes to injury and degradation.^{14,15}

Proanthocyanidins possess endothelium-dependent relaxing (EDR) activity in blood vessels by increasing nitric oxide production,¹⁶ and stimulate vascular endothelial growth factor, a signaling factor involved in initiation of wound

healing. OPCs may also protect the microvasculature of the retina and increase visual acuity, possibly by increasing the rate of rhodopsin regeneration.¹⁷⁻¹⁹ In a rabbit model of ischemia/reperfusion, OPCs' beneficial effects were attributed to binding of copper and iron liberated from myocardial tissue, thereby reducing their oxidative effects.²⁰ The positive effects of OPCs on microcirculation are also attributed to their inhibition of LDL oxidation^{11,12,21} and decreased incidence of foam cells, markers of early stage atherosclerosis.²² Grape seed proanthocyanidins may have a vitamin E-sparing effect.²³ A clinical study of 10 healthy volunteers examining the effect of OPC supplementation on markers of oxidative stress showed significantly increased levels of alpha-tocopherol in red cell membranes.²⁴

Anti-inflammatory

OPCs from pine bark decrease symptoms of chronic inflammation. *In vitro* studies demonstrate anti-inflammatory effects may be due to inhibition of peroxide generation by macrophages.^{25,26} In addition, animal studies demonstrate OPCs from grape seed significantly inhibit formation of proinflammatory cytokines, interleukin 1-beta, and tumor necrosis factor-alpha.²⁷

Antimutagenic/Anticarcinogenic

OPCs possess natural antimutagenic properties when exposed to certain strains of bacteria.²⁸ Although the exact mechanism is not known, an *in vitro* study found OPCs exhibit selective cytotoxicity for certain cancerous cell lines, while remaining non-toxic to normal human gastric mucosal cells and macrophages.²⁹ An *in vitro* study in a mouse skin tumor model demonstrated OPCs' inhibition of two markers of tumor promotion.³⁰

Antimicrobial Effects

Flavonoids and associated polyphenols, particularly OPCs, elicit an inhibitory effect on human immunodeficiency virus (HIV). A possible mechanism may be inhibition of gene expression regulating virus binding to cell receptors on normal lymphocytes, thus preventing infection.³¹

Clinical Indications

Vascular Conditions: Peripheral Vascular Insufficiency/Lymphedema

Because of affinity of OPCs for vascular tissue, the basal membrane of the skin, and gastrointestinal mucosa, the preponderance of research has focused on conditions affecting these tissues. Europeans use OPCs to treat various vascular disorders, including varicose veins, venous insufficiency, capillary fragility, and retinopathies. Several clinical trials have confirmed the beneficial effects of OPC use in treating vascular disorders.³²⁻³⁵

A double-blind study of 50 patients with chronic venous insufficiency manifesting as varicose veins revealed 150 mg proanthocyanidins daily for one month had a more rapid and lasting effect on symptom alleviation than 450 mg daily of diosmin (a flavonoid known for its therapeutic efficacy in vascular insufficiency).³²

A double-blind, placebo-controlled study of 92 patients with peripheral venous insufficiency demonstrated improved venous function at a dose of 300 mg OPCs daily for 28 days. Sixty-nine patients reported 50-percent reduction in clinical parameter scores for pain, paresthesias, nocturnal cramps, and edema. Seventy-five percent of patients felt the treatment was effective, compared to 41 percent of the placebo group.³³

The use of grape seed OPCs in patients with venous and lymphatic edema was examined in a multicenter study of 165 patients with premenstrual symptoms, including breast tenderness, abdominal swelling, and pelvic pain. Sixty percent of patients reported improvement in, or cessation of, symptoms after initial treatment; when treatment duration doubled, that number increased to 78 percent.³⁴

A double-blind, randomized, placebo-controlled study of 63 patients undergoing treatment for lymphedema resulting from breast cancer surgery found six months of OPCs (600 mg daily) was superior to placebo in improving pain, skin tension, and arm and shoulder movements.³⁵

Skin Conditions

Skin conditions secondary to excessive exposure to ultraviolet rays (UVR) benefit from oral administration of proanthocyanidins. Twenty-one volunteer subjects were given 1.10 mg/kg OPCs daily for four weeks followed by 1.66 mg/kg OPCs daily for a second four-week period. UV sensitivity, expressed as minimal erythema dose (MED), was measured twice prior to OPC supplementation to establish a baseline, and again at the end of each four-week period. The UVR dose required to induce minimal erythema increased significantly (in a dose-dependent manner) in subjects supplemented with OPCs.³⁶ OPC supplementation at the higher dose resulted in nearly twice the mean baseline MED. Activation of nuclear factor-kappaB is believed to play a key role in UVR-induced erythema.³⁷

Melasma is a skin condition characterized by hyperpigmentation of the face and neck and is attributed to UV radiation, genetic factors, pregnancy, and various phototoxic drugs. OPCs from pine bark have been shown to be beneficial in treating melasma in women.³⁸

Cardiovascular Disease

One explanation for the “French Paradox” – relatively low rates of cardiovascular disease in France despite a diet of rich foods – is that OPCs in red wine offer protection by reducing LDL oxidation, inhibiting cyclooxygenase and lipoxygenase in platelets and macrophages, and decreasing thrombotic events.³⁹ Epidemiological studies support this theory, indicating red wine consumption reduces the incidence of coronary heart disease.^{40,41}

Several clinical trials have examined the effect of proanthocyanidins in red wine on lipid peroxidation and cardiovascular disease. In a two-week study of 17 healthy men, nine consumed 400 mL red wine daily with meals, while the remaining eight men consumed the same amount of white wine. Red wine consumption resulted in a 20-percent reduction of lipid peroxidation in plasma, while increased lipid peroxidation was observed in the men who drank white wine, suggesting phenolic substances present in red wine may be

responsible for the observed antioxidant effects.¹² Red wine polyphenols also significantly increase plasma high-density lipoprotein (HDL) cholesterol and plasma apolipoprotein A-I concentrations in humans.⁴²

Natella et al investigated the effect of grape seed proanthocyanidins on plasma postprandial oxidative stress. Eight healthy volunteers consumed a lipid-rich test meal with or without OPCs. OPC supplementation resulted in decreased lipid peroxidation, increased plasma antioxidant levels, and improved resistance of LDL to oxidation.⁴³ A larger, randomized, double-blind, placebo-controlled study of 40 hypercholesterolemic patients examined the effects of supplementation of niacin-bound chromium, grape seed extract, or a combination on total cholesterol, LDL, and autoantibodies to oxidized LDL. Grape seed extract administration did not result in statistically significant improvement in total cholesterol or LDL levels compared to placebo; however, the chromium/grape seed extract combination resulted in significant improvements in both parameters, superior to results with either substance alone. The group receiving grape seed extract alone demonstrated a greater than 50-percent decrease in autoantibodies to oxidized LDL.²¹

Retinopathies/Ophthalmologic Conditions

Numerous clinical trials in France support the protective benefit of OPCs on retinal health. In a randomized, double-blind, placebo-controlled study, 75 patients experiencing visual stress from video-display units were given either an OPC extract from grape seed, a *Vaccinium myrtillus* (bilberry) extract, or placebo. Dosage in all groups was 100 mg three times daily for 60 days. Assessments at trial conclusion showed subjects given either OPCs or bilberry had significant improvement in contrast sensitivity and subjective visual disturbances, compared to placebo. Subjects in the OPC group showed improvement superior to those in the bilberry group.⁴⁴

In additional studies of patients without retinal or ophthalmologic pathologies, proanthocyanidins administered at 150-300 mg

daily for 30-60 days improved visual acuity, contrast sensitivity in patients with ocular stress due to video display unit use, and visual performance after glare exposure.^{17,18} In another study 91 patients with bilateral myopia and associated ocular disorders demonstrated 100 mg OPCs given three times daily for 30 days improved retinal sensitivity during dark adaptation in 72 of the patients (79%). Subjective improvement was even greater, with 90 percent of patients reporting symptom improvement.⁴⁵ In the case of retinopathy, a review of 26 case studies reveals OPCs significantly improved vascular lesions, microaneurisms, and exudates associated with diabetic retinopathy.¹⁹

Cancer

OPCs incubated with several human cancer cell lines (breast, lung, and gastric) revealed a selective cytotoxicity for the cancerous cells, but not normal gastric mucosal cells or macrophages. It is postulated that in addition to selective cytotoxicity, OPCs may up-regulate certain apoptosis-promoter genes and down-regulate apoptosis-inhibitor genes in cancerous cells.²⁹

An *in vitro* study explored the chemopreventive effects of an OPC extract on cultured, non-malignant human Chang liver cells treated with the chemotherapeutic agents idarubicin or 4-hydroxyperoxycyclophosphamide; both agents induce apoptosis in normal cells. Incubation of either chemotherapeutic agent with non-malignant Chang liver cells resulted in growth inhibition significantly reversed with addition of OPC extract.⁴⁶ This suggests OPCs could be helpful adjuncts in managing the cytotoxicity of chemotherapeutic agents to normal human cells.

HIV Infection

Grape seed proanthocyanidins elicit an inhibitory effect on HIV infection *in vitro*. Recent research indicates chemokine receptors 3 and 5 expression on Th-2 lymphocytes is a prerequisite for HIV infection of the central nervous system.⁴⁷ An OPC extract incubated with immunocompetent peripheral blood mononuclear cells (PBMC) resulted in a significant dose-dependent suppression of HIV-1 chemokine co-receptor gene

expression (chemokine receptors 2b, 3, and 5) in normal PBMC. This inhibition may prevent binding of the HIV virus to cell receptor sites on normal white blood cells, thereby preventing infection.³¹

Wound Healing

Nitric oxide stimulates collagen synthesis and subsequent healing at wound sites.^{48,49} In addition, the induction of vascular endothelial growth factor (VEGF) is a crucial step in the re-epithelialization phase of skin repair.^{50,51} Extracts of grape seed proanthocyanidins appear to stimulate the expression of VEGF in cultured keratinocytes, making OPCs a potential therapeutic tool in dermal wound healing.^{52,53}

Insulin Resistance

Preliminary research in animals indicates OPCs may have potential in the treatment of insulin resistance. A short-term study in rats revealed grape seed extract decreased circulating insulin levels and systolic blood pressure. A one-year study also revealed significantly lower glycosylated hemoglobin levels in animals receiving a combination of grape seed extract, niacin-bound chromium, and a zinc methionine complex, compared to controls, although the effects of the single ingredients were not evaluated.⁵⁴⁻⁵⁶

Protection from Drug Toxicity

Animal studies indicate OPC administration is beneficial in preventing hepatic and renal toxicity in instances of acetaminophen and other drug poisonings. This protection may be attributable to detoxification of cytotoxic free radicals or facilitation of DNA repair.^{57,58} A study in rats with experimentally-induced myoglobinuric acute renal failure showed OPC administration to be of benefit in reducing blood urea nitrogen and serum creatinine; histological improvement was also noted.⁵⁹

Pancreatitis

A daily dose of 200-300 mg of a grape seed extract was given to three patients with chronic pancreatitis, characterized by epigastric pain with radiation to the back. All three patients reported a significant reduction in pain severity and frequency of painful episodes, and two of three patients reported a significant reduction in use of narcotic analgesics. The third patient, vomiting almost daily, reported resolution of vomiting after taking the OPC extract. All three patients reported a return of symptoms upon cessation of treatment.⁶⁰

Attention Deficit/Hyperactivity Disorder (ADHD) and Cognitive Dysfunction

Anecdotal reports of OPC use in ADHD describe improvement in symptoms that worsened upon discontinuation of treatment and improved again when treatment was restarted.^{61,62} In a study of age-accelerated mice, oral dosing of an OPC extract for two months resulted in significant improvement in age-related memory decline and learning impairments.⁶³

Systemic Lupus Erythematosus

In a pilot study of 11 patients with systemic lupus erythematosus (SLE), six were given an OPC extract (120 mg daily for 30 days, then 60 mg daily for 30 days) in addition to usual medications; the other five patients received placebo with their usual medications. Patients in the treatment group showed reductions in spontaneous lymphocyte apoptosis, T-lymphocyte activation, reduced generation of reactive oxygen species, lower erythrocyte sedimentation rates, and a decrease in the SLE disease activity index compared to the placebo group. The mechanism may be attributable to OPCs' antioxidant effect, resulting in reduced inflammatory activity.⁶⁴

Asthma

In a pilot study of 26 patients with varying degrees of asthma severity, an OPC dosage of 1 mg/lb/day for four weeks, at which time patients in the treatment group were crossed over to the placebo group for another four weeks, resulted in statistically significant improvements in forced expiratory volume (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratios. A significant reduction in serum leukotriene levels was also observed in patients receiving OPCs when compared to control and baseline values, and patients in the OPC group reported significant improvements in asthma symptom scores.⁶⁵

Drug Interactions

There are no known interactions between OPC extracts and other medications; however, data from *in vitro* and human studies indicate OPCs have an inhibitory effect on platelet aggregation similar to aspirin.^{66,67} Therefore, caution is suggested in patients taking anticoagulant medication.

Side Effects and Toxicity

OPCs have an excellent safety profile, with no known side effects, toxicity, or drug interactions. Rat studies have demonstrated OPCs to be nonmutagenic and nontoxic at high levels. The no-observed-adverse-effect level (NOAEL) of a chronic toxicity study of grape seed extract in rats was 1400-1500 mg/kg body wt/day,⁶⁸ which translates to 93-100 g grape seed extract daily for an average 150-pound adult. Human safety and toxicity studies for OPCs are limited, but no side effects are reported in the literature.

Dosage

Suggested dosages for OPCs generally range from 50-150 mg daily, although in some studies dosages of 300 mg daily were used. A dosage of 1 mg/kg/body wt has also been suggested.

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