Name of Supplement

Grape Seed

Scientific names[1,2]:

Vitis vinifera, Vitis coignetiae;
Family: Vitaceae

Common names[1,2]

grape seed, muskat, procyanidolic oligomers (PCO), proanthocyanidin, Oligomeric procyanidolic complexes (OPC), Activin, Extrait De Pepins De Raisin, Grape Seed Extract, Grape Seed Oil, Grapeseed, Leucoanthocyanin, Oligometric Procyanidins, OPCs, PCOs, Proanthodyn

Description of active ingredients

The active ingredients are compounds called oligometric proanthrocyanidins (OPCs) also known as procyanidinso or Procyanidolic oligomers (PCOs), which are responsible for its pharmacological effects[1,2]. These compounds belong to the bioflavonoid family.
The most potent or active proanthrocyanidins are those bound to other proanthrocyanidins, i.e. mixtures of proanthocyanidin molecules called PCOs[2,4]. Highest concentration PCOs are found in grape skin[2,3].

MOA[1]

Grape seed's antioxidant activity is exerted via inhibition of the several proteolyic enzymes (collagenase, elastase, hyaluronidase, and beta glucuronidase), which are involved in breakdown of structural components of the vasculature and skin. In addition, grape seed is also thought to have antilipoperoxidant activity.
Another mechanism of grape seed is the inhibitory effect on the growth of streptococcus mutants and prevention of glucan formation from sucrose. This effect can be beneficial in preventing dental caries; however, there is lack of human studies to show this benefit.

Current indications and efficacy

Grape seed is commonly used as an antioxidant, cytoprotective and for its vascular effects [2,3]. It is used in treatment and prevention vascular or circulatory disorders including venous insufficiency, varicose veins, atherosclerosis, peripheral vascular disease, and edema associated with injury or surgery, and myocardial or cerebral infarction [1]. However, most human studies are done to show its antioxidant effect; these studies are done in a very small population, but do show efficacy of grape seed.

Original Author Saba Gidey
Reviewed 5/12/03 Susan Paulsen Pharm D

Evidence[5]

Paolo Simonetii et al. did a study to show the effect of procyanidins, from Vitis vinifera seeds, on indicators of oxidative stress which included leukocyte DNA damage, plasma total radical-trapping antioxidant parameter, plasma and red blood cell α-tocopherol (also known as Vitamin E), and red blood cell (RBC) membrane phospholipids fatty acid composition. There were ten healthy volunteers in the study with a mean age of 40, and they were not taking additional drugs or supplements including phenolics-rich foods such as bran cereals and certain foods that may have antioxidant effects. The study group was given two capsules, each containing 110mg of procyanidins from grape seed extract for total of 30days. Blood samples were taken at the beginning of the study, at the end of the study (i.e. 30days) and then seven days after the study was completed. Computerized statistical tests were done using the Statistica RM-ANOVA module. The results of the study showed that, the average intake of procyanidins by patients was approximately 100mg. After 30days, there was a significant increase seen in RBC α-tocopherol levels (from 1.8 ± 0.1 to 2.8 ± 0.2mg/g; $p < 0.001$) indicating that the grape seed extract had some sparing effect on α-tocopherol (figure 3 of article). The lymphocyte oxidized DNA which was used to evaluate oxidative DNA damage, was also reduced from 7.23 ± 2.47 to 2.34 ± 0.51(figure 5 of article). In addition, there was an increase of polyunsaturated fatty acid in the phospholipids of RBC membranes. However, this was not considered statistically significant. Based on the results, the study concluded that, grape seed extract may have a significant sparing effect on α-tocopherol in RBC membranes, help reduce oxidative DNA damage, and also might increase the level of polyunsaturated fatty acid in RBC membranes.

Grape seed may also have some benefit in the prevention of the progression of atherosclerosis.

Evidence[6]

It has been suggested that an increase in plasma lipid hydroperoxides (LPO) is associated with imbalance between oxidant/antioxidant leading to an increase in the susceptibility of LDL (low density lipoprotein) to oxidation. This leads to postprandial hyperlipemia that is a risk factor for atherosclerosis. The effect of grape seed proanthocyanidins on plasma postprandial oxidative stress has been studied in humans. In a study by Natella F et al, there was a favorable effect of grape seed on reduction of oxidants and an increase in antioxidant levels in plasma. The study included eight healthy men between the ages of 25-40; they received either meal that is rich in oxidized and oxidizable lipids and 300mg of proanthocyanidin-rich grape seeds extract (GSE), or a placebo (without the 300mg GSE). The GSE was in a capsule form and study group took four capsules before and during the meal. The men were not allowed to take any drugs or vitamin supplements. They received the test meal, which contained "milanese" meat (beef, egg, and breadcrumbs, fried in corn oil) and fried potatoes, at two different occasions (two weeks apart) after a 16-hour fasting interval. Comparison of groups was done using the paired Student *t*-test. Outcomes measured were lipid hydroperoxide concentration, antioxidant status and LDL resistance to oxidative modification. Results of the study showed an increase in plasma LPO after ingestion of test meal (LPO in chylomicrons was 1.5 fold higher in control group), increased in antioxidant effect was seen in the postprandial phase only after GSE supplementation, and an increase in α-tocopherol and ascorbic acid

levels were also observed (total ascorbic acid at one hour was higher in GSE group, $P < 0.05$). LDL three hours after control meal was slightly more susceptible to oxidation than GSE group. However, this was not considered statistically significant (no P value given). The study concluded that supplementation of a meal with GSE helps reduce oxidants and increase antioxidant level in plasma; it increases LDL resistance to oxidation by decreasing postprandial oxidative stress.

The cytoprotective effect of grape seed has been demonstrated in vitro and vivo models. It is proposed that grape seed proanthocyanidin extract (GSPE) could have a better free radical scavenging ability and cytotoxicity towards cancer cells than vitamins C, E and beta-carotene; it may also provide better protection against chemotherapy induced cytotoxicity[7].

Other proposed benefits of grape seed include treatment of Fibromyalgia, Endometriosis (by preventing tissue damage, reducing inflammation and scarring[8]), anti-inflammatory effects (varicose veins, hemorrhoids, easy bruising, swelling after injury/surgery)[9], diabetic complications such as neuropathy or retinopathy, improving wound healing, preventing dental caries, cancer prevention, macular degeneration, poor night vision, liver cirrhosis, allergies, and prevention of collagen breakdown associated with collagen diseases and aging[1].

Contraindications/allergies

Hypersensitivity to grape seed[2]
Relative contraindication with anticoagulant therapy, pregnancy and lactation[1]

Dosage forms

Grape seed extract comes in tablet and capsule forms dosed at 50mg, 75mg, and 100mg*

Recommended doses and duration

The average recommended dose for antioxidant therapy is 50-100mg/day of proanthocyanidins[3]. Some sources recommend using 75-300mg for three days followed by maintenance dose of 40-80mg qd [1]. However, doses range from 40-600mg depending on use.

- Chronic venous insufficiency (varicose veins): 150-300mg qd[1,9]
- Ocular stress reduction due to glare: 200-300mg qd[1]
- Edema: 600mg/d x 6months[9]
- Night vision: 200mg/d[9]
- Endometriosis: 200-400mg[8]
- Fibromyalgia 50-300mg of OPCs/day[8]
- Gout and Parkinson's disease 50-200mg of procyanidins/day[8]
- Unable to find dosage information for cancer

* Commercially available products: dose information obtained from 'dealtime.com'

Original Author Saba Gidey
Reviewed 5/12/03 Susan Paulsen Pharm D

- Some recommend daily dose of 50mg qd as preventive measure and as antioxidant support; and daily dosage of 150-300mg for therapeutic purposes[4]

Drug interactions

Theoretically, concurrent use with warfarin may lead to an increase in warfarin's effects and the risk of bleeding[1, †]. Exact mechanism is unknown, possibly due to its effect on tocopherol. Grape seed may have sparing effect on the body's stores of vitamin C[3] and vitamin E.

Drug-disease interaction
There are no reported disease interactions with grape seed

Other safety issues

It is recommended that pregnant and lactating women do not exceed dose greater than those found in foods, as there is insufficient data to show the risk in these conditions[1,8] Only one source reported that possible GI distress may occur[9]. However, grape seed seems to be relatively safe. The hydrophilic effect of proanthrocyanidins allows for urinary excretion of the compound even with excess intake[3].

Other comments:

- Other products containing OPCs include wine, cranberries, bilberries, green and black teas, black currant, onions, legumes, parsley, and hawthorn[1]
- Studies that show benefits of grape seed other than the antioxidant effect are done either in vitro or in animal models (rats); or other benefits of grape seed are related to its antioxidant effect.
- There are a couple of the studies that looked at the antioxidant effects of grape seed, but these are written in Chinese

† There is drug interaction between tocopherol and warfarin. Mechanism is unknown.

Original Author Saba Gidey
Reviewed 5/12/03 Susan Paulsen Pharm D

References

1. Jellin JM, Gregory PJ, Batz F, Hitchens, K, et al. Pharmacist's Letter/Prescriber's Letters Natural Medicines Comprehensive Database. 5th ed. Stockton, CA. Therapeutic Research Faculty, 2003. pp. 653-4.

2.Facts and Comparisons. The Review of Natural Products: Grape Seed. By Facts and Comparsions. Aug 2002.

3. Lininger S, D.C. editor in chief, Wright J, M.D., Austin S, N.D., Gaby A, M.D. The Natural Pharmacy: Proanthocyanidins. Virtuaol Health, LLC. 1998. pp. 199-200.

4. Murray TM, N.D, Pizzorno J, N.D. Encyclopedia of Natural Medicine. Revised 2nd ed. Joseph Pizzorno and Michael T. Murray, 1998. pp. 94-5.

5. Simonetti P, Ciappellano S, Gardana C, Bramati L, and Peitta P. Procyanidins from Vitis vinifera Seeds: In Vivo Effects on Oxidative Stress. J. Agric. Food Chem. American Chemical Society, 2002. 50: 6217-3221.

6. natella G, Belelli F, Gentili V, Ursini F, and Scaccini, C. Grape Seed Proanthocyanidins Prevent Plasma Postprandial Oxidative Stress in Humans. J. Agric. Food Chem. American Chemical Society, 2002. 50: 7720-7725.

7. Bagchi D, Bagchi M, Stohs JS, Ray DS, Sen KC, and Preuss GH. Cellular Protection with Proanthocyanidins Derived from Grape Seeds. Ann. N.Y. Acad. Sci. New York Academy of Sciences, 2002. 957: 260-270.

8. Linda B. White, M.D., Foster S and the staff of Herbs for Health. The Herbal Drugstore: The Best Natural Alternatives to Over-the-Counter and Prescription medicines. Rodale INC, 2000. p. 232, 255, 276, 364, 452

9. Bratman S, M.D. and Kroll D, PhD. The Natural Pharmacist: your complete guide to herbs. Prima publishing, 1999. pp. 106-109.

Original Author Saba Gidey
Reviewed 5/12/03 Susan Paulsen Pharm D