Simons AL, Renouf M, Hendrich S, et al. Metabolism of glycitein (7,4′-dihydroxy-6-methoxy-isoflavone) by human gut microflora. *J Agric Food Chem.* 2005;53(22):8519-8525.

Song TT, Hendrich S, Murphy PA. Estrogenic activity of glycitein, a soy isoflavone. *J Agric Food Chem.* 1999; 47:1607-1610.

Zhang Y, Wang G-J, Song TT, et al. Urinary disposition of the soybean isoflavones daidzein, genistein and glycitein differs among humans with moderate fecal isoflavone degradation activity. *J Nutr.* 1999; 129:957-962.

For additional references, see Soy Isoflavones.

Grape Seed Proanthocyanidins

DESCRIPTION

Grape seed proanthocyanidins refer to procyanidin mixtures extracted from grape (*Vitis vinifera*) seeds. Procyanidins are derivatives of the flavan-3-o1 class of flavonoids. This class includes (+)-catechin, commonly referred to as catechin, and (-)-epicatechin, commonly referred to as epicatechin. Procyanidins are dimers and oligomers of catechin and epicatechin and their gallic acid esters. Procyanidins are widely distributed in the plant kingdom and, in addition to being found in grape seeds, are found in cocoa and chocolate, apples, peanuts, almonds, cranberries, blueberries and in the bark of pines, among other plant sources.

Grape seed proanthocyanidins are mainly comprised of dimers, trimers and tetramers of catechin and epicatechin and their gallates. They also contain smaller amounts of pentamers, hexamers and heptamers of these flavan-3-o1s and their gallates. The procyanidin dimers and oligomers are also known as oligomeric procyanidins (OPCs) and procyanidolic oligomers or PCOs. Grape seed proanthocyanidins comprise approximately 60 to 70% of the polyphenol content of grapes. The procyanidins are colorless in their pure state.

See also Cocoa Flavonoids and Pycnogenol.

ACTIONS AND PHARMACOLOGY

ACTIONS

Grape seed proanthocyanidins have antioxidant activity. They may also have anti-inflammatory, anticarcinogenic and anti-atherogenic activities.

MECHANISM OF ACTION

Grape seed proanthocyanidins have been found to have a number of antioxidant activities in the laboratory. These include scavenging of hydroxyl and peroxyl radicals, and inhibition of the oxidation of low-density lipoprotein (LDL). The inhibitory potential related to lipid peroxidation appears to increase with the degree of polymerization of the molecules. That is, grape seed proanthocyanidins with a greater number of catechin and epicatechin units appear to have more potent inhibitory activity than those with fewer catechin and epicatechin units. Further, the position of linkage between inter-flavan units also appears to influence lipid peroxidation inhibitory activity. Procyanidin isomers with a 4-6 inter-flavan linkage appear to show stronger inhibitory activity than those with a 4-8 linkage. Finally, the presence of a gallate group also appears to affect the inhibitory activity of the procyanidins with respect to lipid peroxidation. A procyanidin dimer with a gallate group linked at the 3-hydroxy position appears to show much greater inhibition of lipid peroxidation than a dimer without such a group.

Grape seed proanthocyanidins have shown anti-inflammatory, anticarcinogenic and anti-atherogenic activities, again in the laboratory. These activities are thought to be due, in large part, to the antioxidant activities of these molecules. These proanthocyanidins have been found to be cytotoxic for some human cancer lines in culture. Upregulation of apoptosis by the proanthocyanidins in these cancer lines is another possible mechanism for their possible anticarcinogenic activity.

PHARMACOKINETICS

Little is known about the pharmacokinetics of grape seed proanthocyanidins in humans. It appears that they do, at least in part, get absorbed. However, the extent of absorption appears to vary widely, not only among the various components of the grape seed proanthocyanidins, but also among subjects.

INDICATIONS AND USAGE

Experimental data suggest that grape seed proanthocyanidins may have anticancer activity, that they protect against some forms of lipid peroxidation and that they may be cardioprotective, hepatoprotective and capillary protective. They appear to have anti-inflammatory activity. Claims that they are useful in the treatment of arthritis, varicose veins, diabetic retinopathy and some allergies are largely based upon anecdotal testimony; clinical trials are lacking.

RESEARCH SUMMARY

Antitumor-promoting activity, described as highly significant, has been observed in animals treated with topical grape seed proanthocyanidins. Skin tumor incidence, multiplicity and volume were all significantly inhibited. These effects were attributed to inhibition of epidermal lipid peroxidation. Higher doses resulted in greater degrees of cancer inhibition.

An extract of grape seed proanthocyanidins has significantly inhibited human breast cancer, lung cancer and gastric adenocarcinoma cells *in vitro*. The extract did not inhibit

neoplastic K562 myelogenous leukemic cells. In the same experiment, the extract enhanced growth and viability of normal human gastric mucosal cells and J774A.1 murine macrophage cells. These promising preliminary findings warrant more research.

Grape seed proanthocyanidins have been shown to significantly inhibit the peroxidation of polyunsaturated fatty acids and some other lipids in animal and *in vitro* studies. Some experimental data suggest that these effects might help protect capillaries, heart, brain and liver tissues in some circumstances. In one study, a grape seed proanthocyanidin extract more potently protected brain and hepatic tissues from the damage of experimentally induced reactive oxygen species damage than did other antioxidants (vitamin C, vitamin E succinate and beta-carotene). In other *in vitro* experiments, grape seed proanthocyanidins have strongly inhibited reactive oxygen species activities implicated in microvascular injury.

Acetaminophen-induced programmed and unprogrammed liver-cell death was dramatically prevented and reduced in mice treated with a grape seed proanthocyanidin extract. Exposure to the extract for seven days prior to acetaminophen administration was notably more effective than pretreatment for three days. The extract significantly counteracted acetaminophen-promoted apoptotic DNA fragmentation.

In another animal model, grape seed proanthocyanidins were shown to increase resistance to myocardial ischemia reperfusion injury. And in a recent experiment utilizing cholesterol-fed rabbits, an extract of grape seed proanthocyanidins significantly attenuated the development of aortic atherosclerosis compared with controls that did not receive the extract.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Grape seed proanthocyanidins are contraindicated in those with a known hypersensitivity to any of the ingredients in a grape seed proanthocyanidin-containing product.

PRECAUTIONS

Grape seed proanthocyanidin supplementation should be avoided by pregnant women and nursing mothers.

DOSAGE AND ADMINISTRATION

Grape seed proanthocyanidins are available in products called grape seed extracts. These products contain grape seed procyanidins as well as catechin and epicatechin. Typical doses are 50 to 100 mg daily. Products called OPCs or PCOs (procyanidolic oligomers) are typically grape seed extracts.

LITERATURE

Bagchi D, Garg A, Krohn RL, et al. Protective effects of grape seed proanthocyanidins and selected antioxidants against TPA-induced hepatic and brain lipid peroxidation and DNA fragmentation, and peritoneal macrophage activation in mice. *Gen Pharmacol.* 1998; 30:771-776.

Gabetta B, Fuzzati N, Griffini A, et al. Characterization of proanthocyanidins from grape seeds. *Fitoterapia.* 2000; 71:162-175.

Sato M, Maulik G, Ray PS, et al. Cardioprotective effects of grape seed proanthocyanidins against ischemic reperfusion injury. *J Mol Cell Cardiol.* 1999; 31:1289-1297.

Yamakoshi J, Kataoka S, Koga T, Ariga T. Proanthocyanidin-rich extract from grape seed attenuates the development of aortic atherosclerosis in cholesterol-fed rabbis. *Atherosclerosis.* 1999; 142:139-149.

Ye X, Krohn RL, Liu W, et al. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. *Mol Cell Biochem.* 1999; 196:99-108.

Zhao J, Wang J, Chen Y, Agarwal R. Anti-tumor-promoting activity of a polyphenolic fraction isolated from grape seed in the mouse skin two-stage initiation-promotion protocol and identification of procyanidin B5-3′ -gallate as the most effective antioxidant constituent. *Carcinogenesis.* 1999; 20:1737-1745.

Green Tea Catechins

DESCRIPTION

Catechins belong to the flavan-3-ol class of flavonoids. Green tea catechins are the flavan-3-ols found in green tea leaves (*Camellia sinensis*). The major four catechins in green tea leaves are (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epicatechin (EC). They are all polyphenolic substances. Black tea leaves have a much lower content of these catechins. That's because black tea leaves undergo extensive fermentation, during which the majority of the catechins are enzymatically oxidized to the major pigments of black tea leaves, theaflavin and thearubigen.

The green tea catechins make up approximately 30% of the dry weight of green tea leaves. Of the catechins, EGCG is the most abundant one in green tea leaves. Green tea, an aqueous infusion of green tea leaves, has been a popular beverage in China and Japan for centuries. In these countries, it is thought that green tea has a number of health-promoting benefits, and it is used in the management of various disorders. Epidemiological studies suggest that green tea may have cancer chemopreventive, as well as anti-atherogenic, properties.

The possible health benefits of green tea are attributed to the catechins. These polyphenolic substances are antioxidants. EGCG appears to be the most potent antioxidant of all the green tea catechins.