Non-pharma therapy for glaucoma and other ocular diseases (Consensus document 2010)

Ginkgo biloba extract (GBE)

Ginkgo biloba extract contains over 60 known bioactive compounds, about 30 of which are found nowhere else in nature. The standardized extract used most widely in clinical research, EGb 761 (Dr Willmar Schwabe GmbH & Co, Karlsruhe, Germany), contains 24% ginkgo flavone glycosides (flavonoids), 6% terpene lactones (ginkgolides and bilobalide), approximately 7% proanthocyanidines, and other, uncharacterized compounds. (De Feudis 1991)

GBE has been claimed effective in a variety of disorders associated with aging, including cerebrovascular disease, peripheral vascular disease, dementia, tinnitus, bronchoconstriction, and sexual dysfunction. GBE appears to have many properties applicable to the treatment of non-IOP-dependent risk factors for glaucomatous damage. (Ritch 2000) GBE exerts significant protective effects against free radical damage and lipid peroxidation in various tissues and experimental systems. Its antioxidant potential is comparable to water soluble antioxidants such as ascorbic acid and glutathione and lipid soluble ones such as alpha-tocopherol and retinol acetate. (Köse & Dogan 1995) The antioxidant properties of are due to its direct free radical scavenging activity. Proteasome inhibitory properties of anthocyanins may contribute to their antioxidative, anti-inflammatory and neuroprotective activities, rationalizing their use in neurodegenerative disorders. (Dreiseitel et al. 2008)

GBE preserves mitochondrial metabolism and ATP production in various tissues and partially prevents morphologic changes and indices of oxidative damage associated with mitochondrial aging. (Pierre et al. 1999; Janssens et al. 2000; Sastre et al. 2002; Eckert et al. 2003; Eckert et al. 2005) In contrast to other antioxidants, gingko has the capacity to enter the inner mitochondrial membrane, thus making it an effective antioxidant at the mitochondrial level. (Hirooka et al. 2004) It can scavenge nitric oxide (Marcocci et al. 1994) and possibly inhibit its production. (Kobuchi et al. 1997)

Substantial experimental evidence exists to support the view that GBE has neuroprotective properties in conditions such as hypoxia/ischemia, seizure activity, cerebral edema, and peripheral nerve damage. (Smith et al. 1996; Ahlemeyer & Krieglstein 2003) GBE protects against glutamate toxicity. (Chandrasekaran et al. 2002; Chandrasekaran et al. 2003) It can reduce glutamate-induced elevation of calcium concentrations (Zhu et al. 1997) and can reduce oxidative metabolism in both resting and calcium-loaded neurons. (Oyama et al. 1994) Neurons in tissue culture are protected from a variety of toxic insults by GBE, which inhibits apoptosis. (Ahlemeyer et al. 1999; Zhou & Zhu 2000; Guidetti et al. 2001; Lu et al. 2006)

GBE improves both peripheral and cerebral blood flow. It is effective in treating Raynaud's disease, which is strongly associated with normal-tension glaucoma. (Muir et al. 2002; Choi et al. 2009) It has been reported to protect myocardium against hypoxia and ischemia-reperfusion injury (Haramaki et al. 1994; Punkt et al. 1995) and to relax blood vessel walls. (Satoh & Nishida 2004) GBE is a strong inhibitor of platelet activating factor. (Koch 2005) There is mixed evidence for functional improvement in patients with Alzheimer's-type and multi-infarct dementias. Preliminary data suggest that GBE may increase the probability of survival in the elderly population. (Dartigues et al. 2007)

It has been suggested that alterations in systemic NO and ET-1 activity (endothelial dysfunction) are involved in vascular dysregulation in glaucoma. (Nicolela et al. 2003; Grieshaber & Flammer 2005; Henry et al. 2006; Su et al. 2006) Ginkgo biloba extract reportedly attenuates endothelial dysfunction (Zhou et al. 2006) and improvement of peripheral circulation by GBE is at least partly attributable to its effects on the NO-pathway or endothelium-dependent vasodilation. (Chen et al. 1997; Wu & Zhu 1999) Further studies of GBE on the ocular circulation and progression of normal-tension glaucoma are warranted.

In the eye, GBE may have a protective effect against the progression of diabetic retinopathy (Droy-Lefaix et al. 1996) and reduces ischemia-reperfusion injury in rat retina. (Szabo et al. 1993) GBE protects retinal photoreceptors against light-induced damage by preventing oxidative stress in the retina. (Ranchon et al. 1999; Xie et al. 2007) Chloroquine-induced ERG changes were prevented by simultaneous treatment with GBE. (Meyniel et al. 1992) In a rat model of central retinal artery occlusion, GBE reduced edema and necrosis and blocked the reduction in b-wave amplitude. (Droy-Lefaix et al. 1993)

Jia et al found that GBE suppressed dexamethasone-induced IOP elevation in rabbits. (Jia et al. 2008) It reduced the dexamethasone-associated accumulation of extracellular materials

within the cribriform layers of the trabecular meshwork and achieved better meshwork cellularity. In cultured human trabecular cells, GBE substantially reduced dexamethasone-induced myocilin expression. (Jia et al. 2008) Ma et al investigated the dosage dependence of intragastral GBE versus saline on RGC survival in the rat optic nerve crush model. The mean survival rate increased significantly ($P<0.001$) from 58.4±9.0% in the saline group to 74.2±6.8% in the high-dosage GBE group. The same group found that intraperitoneal administration gave similar results. (Ma et al. 2009)

GBE has been reported to improve automated visual field indices. (Raabe et al. 1991; Quaranta et al. 2003) In one clinical cross-over study of low-dose, short-term treatment in normal volunteers, GBE increased ophthalmic artery blood flow by a mean of 24%. (Chung et al. 1999) A more recent study, however, failed to confirm these results. (Wimpissinger et al. 2007)

A systematic review of case reports concluded that the causality between ginkgo intake and bleeding is unlikely''. (Ernst et al. 2005) A systematic review of eight randomized controlled trials concluded that the available evidence does not demonstrate that GBE causes significant changes in blood coagulation parameters''. (Savovic´ et al. 2005) The idea that the combination of ginkgo and anticoagulant or antiplatelet drugs might represent a serious health risk is based on several case reports but not supported by clinical trials. (Izzo & Ernst 2009)

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Grape seed extract

Grape seed proanthocyanidins have a broad spectrum of pharmacological and medicinal properties against oxidative stress. Grape seed proanthocyanidin extract (GSE) provides excellent protection against free radicals in both in vitro and in vivo models. (Bagchi et al. 2002) GSE-induced improvement in myocardial ischemia-reperfusion injury in vitro has been reported. (Pataki et al. 2002; Bagchi et al. 2003; Shao et al. 2003) Activin, a new generation antioxidant derived from grape seed proanthocyanidins, reduces plasma levels of oxidative stress and adhesion molecules (ICAM-1, VCAM-1 and E-selectin) in patients with systemic sclerosis. (Kalin et al. 2002) Supplementation of a meal with GSE minimizes postprandial oxidative stress by increasing the antioxidant levels in plasma, and, as a consequence, enhancing the resistance to oxidative modification of low density lipoproteins. (Natella et al. 2002) Grape seed proanthocyanidins have also been reported to have activity against HIV-1 entry into cells. (Nair et

al. 2002) Grape seed extract has recently been shown to inhibit the growth of prostate cancer cells in mice. (Raina et al. 2007) In the eye, GSE inhibits key components of cataractogenesis by reducing oxidative stress within lens epithelial cells. (Barden et al. 2008) and significantly prevents and postpones development of cataract formation in rats with hereditary cataracts. (Yamakoshi et al. 2002)

Resveratrol

Resveratrol (3,5,40-trihydroxystilbene), a powerful polyphenolic antioxidant, is found largely in the skins of red grapes and berries and came to scientific attention as a possible explanation for the low incidence of heart disease among the French, who eat a relatively high-fat diet (the French paradox). Many studies suggest that consuming alcohol (especially red wine) may reduce the incidence of coronary heart disease (CHD). Grape juice, which is not a fermented beverage, is not a significant source of resveratrol. A large number of studies in the past few years suggests its benefit in vitro and in vivo in a variety of human disease models, including cardioprotection, neuroprotection, immune regulation, and cancer chemoprevention. For an extensive review, see (Pervaiz & Holme 2009). Substantial data show that actions of resveratrol include inhibition of lipid peroxidation and platelet aggregation, metal chelating (primarilycopper), free radical'scavenging activity, antiinflammatory activity, modulation of lipid metabolism, antifungal properties, and anticancer and estrogen-like activity. (Pervaiz & Holme 2009)

Resveratrol increases the lifespan of the yeast, Saccharomyces cerevisiae, the nematode, Caenorhabditis elegans, and the fruitfly, Drosophila melanogaster. It was later shown to extend the lifespan of the short-lived fish, Nothobranchius furzeri, (Valenzano & Cellerino 2006) and has now been shown to significantly increase the health and survival of mice on a high-calorie diet, pointing to a new approach to treating diseases of aging. (Baur et al. 2006) Among its multiple functions, resveratrol activates sirtuins (silent information regulator proteins), a family of proteins that play an important role in DNA repair, gene silencing, chromosomal stability and longevity. (Michan & Sinclair 2007)

The physiologic effects of resveratrol appear to be related to its ability to regulate nutrition and longevity genes. (Pervaiz & Holme 2009) Resveratrol is an effective antioxidant. (Frankel et al. 1993; Chanvitayapongs et al. 1997; Shigematsu et al. 2003) It inhibits lipid peroxidation of low-density lipoprotein (LDL), prevents the cytotoxicity ofoxidized LDL, and protects cells against lipid peroxidation. (Chanvitayapongs et al. 1997) Resveratrol protects against the degeneration of neurons afteraxotomy. (Araki et al. 2004) A single infusion of resveratrol can elicit neuroprotective effects on cerebral ischemia-induced neuron damage through free radical scavenging and cerebral blood elevation due to nitric oxide release. (Lu et al. 2006) Its antiapoptotic activity has led to the suggestion that resveratrol may make a useful dietary supplement for minimizing oxidative injury in immune-perturbed states and human chronic degenerative diseases. (Losa 2003)

Levels of intracellular heme (iron-protoporphyrin IX), a pro-oxidant, increase after stroke. In neuronal cell cultures, resveratrol induces heme oxygenase 1, suggesting that increased heme oxygenase activity is a unique pathway by which resveratrol can exert its neuroprotective actions. (Zhuang et al. 2003)

Resveratrol directly inhibits CYP1B1. The versatility of RSV lies in its diverse targeting of membrane and intracellular receptors, signaling molecules, biogenesis enzymes, oxidative systems, DNA-repair mechanisms, and transcription factors, and it can activate or repress a number of signal-transducing pathways found throughout the cell (Pervaiz & Holme 2009)

There appears to be an association between aging and neurodegenerative diseases, such as Alzheimer's, and that modulation by both caloric restriction and drugs which mimic caloric restriction, such as resveratrol, can ameliorate these diseases. (Liu et al. 2007) Resveratrol reduces the levels of secreted and intracellular amyloid-ß peptides by proteosomal degradation. (Marambaud et al. 2005)

In the eye, resveratrol suppresses selenite-induced oxidative stress and cataract formation in rats. (Doganay et al. 2006) The authors suggested that the presence of oxidative stress in selenite cataract development and its prevention by resveratrol support the possibility that high natural consumption of resveratrol in food can help prevent human senile cataract. Resveratrol also induces dilation of retinal arterioles, suggesting a potential benefit for this compound in the treatment of retinal vascular disease. (Nagaoka et al. 2007) Sirtuin-1 activators (such as resveratrol) demonstrate neuroprotective properties in mouse models of optic neuritis and multiple sclerosis. (Shindler et al. 2007)

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Pycnogenol

Pycnogenol, an extract of French maritime pine bark (Pinus pinaster), is primarily composed of procyanidins and phenolic acids and is a potent antioxidant with strong free radical-scavenging activity against reactive oxygen and nitrogen species. Procyanidins are biopolymers of catechin and epicatechin subunits, which are important in human nutrition. (Rohdewald 2002)

Pycnogenol is effective in patients with venous microangiopathy (Cesarone et al. 2006)and accelerates healing in leg ulcerations from chronic venous insufficiency (Belcaro et al. 2005) and diabetes. (Belcaro et al. 2006) In chronic venous insufficiency, pycnogenol reduced lower leg circumference and symptoms of pain, cramps, nighttime swelling, feeling of ‘heaviness", and reddening of the skin. (Koch 2002) Pycnogenol can protect vascular endothelial cells from Aß-induced injury. (Liu et al. 2000) It reversed elevation of serum creatinine, BUN, LDH, IL-1beta, IL-6, and TNF-alpha levels in ischemia reperfusion injury in unilaterally nephrectomized rats. (Ozer Sehirli et al. 2009)

Pretreatment with pycnogenol reduces smoke-induced platelet aggregation. (Araghi-Niknam et al. 2000) Pycnogenol significantly reduces LDL-cholesterol levels. (Devaraj et al. 2002; Koch 2002) A randomized controlled trial reported it effective for erectile dysfunction. (Stanislavov et al. 2007) It has also been reported to improve symptoms of jetlag. (Belcaro et al. 2008) It inhibits not only HIV-1 binding to host cells, but also its replication after entry in susceptible cells in vitro. (Feng et al. 2008) It has been reported to increase urinary catecholamines and ameliorate attention deficit hyperactivity disorder in children. (Dvoráková et al. 2007)

After oral administration of pycnogenol, plasma samples significantly inhibited NFkB activation and MMP-9 release from human monocytes, indicating that it exerts anti-inflammatory effects by inhibiting proinflammatory gene expression. (Grimm et al. 2006) Glutamate inhibits cyclo-oxygenases 1 and 2. (Schafer et al. 2006) This cytotoxicity was inhibited by both GBE and pycnogenol. (Kobayashi et al. 2000) Pycnogenol not only suppresses the generation of reactive oxygen species, but also attenuates caspase-3 activation and DNA fragmentation, suggesting protection against Aß-induced apoptosis. (Peng et al. 2002)

Pycnogenol has also been reported to inhibit angiotensin-converting enzyme and to enhance the microcirculation by increasing capillary permeability. (Packer et al. 1999) It inhibits progression of preproliferative diabetic retinopathy (Schonlau & Rohdewald 2001) and may reduce the risk of formation of both diabetic retinopathy and cataract. (Kamuren et al. 2006) More recently, in patients with mild to moderate retinal edema, pycnogenol treatment significantly improved both the edema and retinal thickness as measured by high resolution ultrasound. (Steigerwalt et al. 2009) Laser Doppler flow velocity measurements at the central retinal artery showed a statistically significant increase from 34 to 44 cm/s in the Pycnogenol group as compared to marginal effects in the control group. (Steigerwalt et al. 2009)

Steigerwalt et al (Steigerwalt et al. 2008) evaluated the effects of the food supplement Mirtogenol (Mirtoselect and Pycnogenol) on IOP and ocular blood flow in 20 subjects versus 18 controls. After three months of treatment, the IOP was lowered compared to that of untreated controls from a baseline of 25.2 mmHg to 22.0 mmHg ($p<0.05$). Ocular blood flow (central retinal, ophthalmic, and posterior ciliary arteries) improved both in the systolic and diastolic components as measured by Color Doppler imaging.

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