

## MEDOX, Purified Anthocyanins: Antioxidant power with many biological effects. SCIENTIFIC REVIEW

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The advantages of an antioxidative diet are well accepted today. However, new research shows that the term antioxidant is far from being specific. Thought antioxidants are present in many foods including wines, fruits, nuts, olive oil, cocoa, honey, some vegetables, green tea and cereals, dietary supplements (including vitamins E, C or A), oligoelements (like zinc and selenium), and carotenoids (like beta carotene, lutein and zeaxanthin), new biological and chemical characteristics of this compounds have been discovered indicating that there are different types of antioxidants, some of them with different free-radical scavenging capacities (indicating their potency), and even more important, with different mechanisms of action.

**Description:** One important family among antioxidants is the flavonoid group, which comprise the most abundant group of plant polyphenols. The flavonoid group includes the anthocyanins, the flavonols, the flavones, the flavanones, the proanthocyanidines, the flavan-3-ols and isoflavones. From these, anthocyanins have received special attention because a long tradition of beneficial effects. Thought other antioxidants have been tested in clinical trials that have given conflicting results; new research has been done recently and clinical trials are ongoing to test the specific effect of anthocyanins *in vitro* and *in vivo*. MEDOX (also identified as MP865) is a unique combination of anthocyanins obtained by purification from black currants (*Ribes nigrum L.*) and from bilberries (*Vaccinium myrtillus*). The purification process (MEDOX is made in an in-house developed, high tech., patented, chromatographic process) yields highly purified anthocyanines presented as capsules of 80 mg pure anthocyanins plus 115 mg polyphenols. Next, scientific evidence demonstrating important biological effects of specific anthocyanins (as well as the synergistic effect of the natural anthocyanin mixture) that compose MEDOX is presented.

**Absorption and metabolism:** Anthocyanins are hydro-soluble plant pigments that usually have an attached sugar (glycosides) or less frequently, do not have it (aglycones). Both forms have particular characteristics in reference to absorption and antioxidant capabilities. Although some generalizations are possible, new evidence suggest that the biological properties are different, and some times unique, among different anthocyanines (for review see Prior et al. 2006). As an example, now it is accepted that anthocyanines can be absorbed intact as glycosides (in contraposition to other hydro-soluble compounds), though still the aglycones present easier absorption. Several mechanisms are involved in absorption to explain why anthocyanines can be detected in plasma as soon as 6 minutes after ingestion, and the maximum concentration in plasma (C<sub>max</sub>) can be reached 30 to 120 minutes after ingestion (Prior 2006). Surprisingly, one of

those mechanisms has been determined to be direct gastric absorption using a bilitraslocase-type enzyme (Passamonti 2003) at the gastric mucosa; the highest absorption seems to be at the jejunum. Though the absorbed fraction of anthocyanins, determined by measuring plasma levels and excretion, is around 0.1 (1%), the process of absorption and metabolism is still under active investigation. In particular, the fraction of anthocyanins that is collected in feces after ingestion, has turned out to be very important because this fraction comprise intact anthocyanins and metabolized anthocyanins excreted in the bile together with phenolic acids which are products of bacterial degradation. This mixture is biologically active and is responsible for the reported protective antioxidant effect over colonic mucosa mediated by inhibition of malignant transformation and/or invasion (Coates 2007, Cooke 2006, Prior 2006). The most abundant anthocyanins in blackcurrants are Cyanidin-3-rutinoside, Delphinidin-3-rutinoside, Delphinidin-3-glucoside and Cyanidin-3-glucoside and their aglycones cyanidin and delphinidin (Slimestad and Solheim 2002, Prior 2006). The most abundant anthocyanins in bilberries are, in order of percentage composition, Delphinidin-3-galactoside, Delphinidin-3-glucoside, Delphinidin-3-arabinoside, Cyanidin-3-glucoside, Cyanidin-3-galactoside, Cyanidin-3-arabinoside, Malvidin-3-glucoside, Petunidin-3-glucoside, Malvidin-3-galactoside, Petunidin-3-galactoside, Peonidin-3-glucoside, Petunidin-3-arabinoside, Malvidin-3-arabinoside, Peonidin-3-galactoside and Peonidin-3-arabinoside (Rahman 2006, Cooke 2006(b)). This composition gives MEDOX unique characteristics, not only for the highly purified amount of anthocyanins, but also because the superoxide radical-scavenging activity is synergic among different anthocyanins (Rahman 2006). Anthocyanins from bilberries and black currants (which are the prime material in MEDOX) are rapidly absorbed after ingestion (facilitated by specific transporters and the aglycone part), Keep their antioxidant ability during the process (reinforced in part by the stability of the rutenoside compounds (Rubinskiene 2005)), and have a longer half life in human plasma due to the presence of glycosides which are metabolized in part to anthocyanidins, which are suspected to exert even more potent biological activities (Cooke 2006, Cooke 2006(b)). The last feature is particularly important because is an *in vivo* demonstration about the presence of aglycones in human plasma which can then undergo further biotransformation, asseveration that has been subject of controversy.

**Antioxidant activity:** The antioxidant properties of anthocyanins have been extensively demonstrated *in vivo* and *in vitro* and only specific mechanisms are considered here. In addition to the higher superoxide-scavenging activity and peroxy nitrite-scavenging activity in the natural or reconstituted mix of anthocyanins (Rahman 2006); other biological effects of anthocyanins have been demonstrated, some of which are not directly related to their antioxidant capacity. Below, some of those effects will be described.

**Aging and exercise-induced oxidative stress:** Starting with the general antioxidant ability of anthocyanins, some human studies can be cited. In one

study, healthy volunteers received berry juice or the same juice after anthocyanins-polyphenols extraction during three weeks; during intervention with the fruit juice blood and urine samples were collected; a decrease of oxidative DNA damage ( $p < 5 \times 10^{-4}$ ) (determined by the comet assay) and an increase of reduced glutathione ( $p < 5 \times 10^{-4}$ ) and of glutathione status ( $p < 0.05$ ) were observed (Weisel 2006). Elevation of glutathione S-transferase P1 (hGSTP1) protein expression in human leucocytes of healthy volunteers has also been demonstrated after two two-weeks period of berry juice consumption when compared with controls; hGSTP1 has been shown to prevent DNA damage and mutagenesis (Hofmann 2006). Interestingly, *in vitro* polyphenol mixtures up-regulated other biotransformation enzymes (*e. g.*, members of the cytochrom P450 and the sulphotransferase family) and treatment of leucocytes led to a modulated mRNA expression of selected genes, not directly related to oxidative defense systems (Hofmann 2006). According to another study, this antioxidant protection seems to be extended in individuals performing physical exercise as determined by analyzing the levels of lipid peroxidation (TBARS) in blood samples from rowers (with or without berry juice supplementation) performing a daily physical exercise during 1 month training camp. In the group supplemented with berry juice, glutathione peroxidase activity was lower in the samples collected 1 min after the exercise test, superoxide dismutase activity was lower in the samples taken following a 24-h recovery, and TBARS were lower at both times when compared to the subjects receiving placebo. The authors of this study suggest that an increased intake of anthocyanins limits the exercise-induced oxidative damage to red blood cells, most probably by enhancing the endogenous antioxidant defense (Pilaczynska-Szczesniak 2005). The protection against exercise-induced oxidative damage is further supported by a double-blind, placebo-controlled, crossover study that assesses peripheral circulation using near-infrared spectroscopy (NIRS). Forearm blood flow (FBF) is measured after venous occlusion prior to and hourly for 4 h after ingestion of blackcurrant anthocyanins (BCA). FBF increases significantly 2 h after BCA ingestion [BCA 1.22 (0.13)-fold increase relative to pre-values vs. placebo 0.83 (0.06) of pre-values;  $P < 0.05$ ] and then tended to increase for a further 3 h after ingestion [BCA 1.26 (0.15)-fold increase relative to pre-values vs. placebo 0.82 (0.07) of pre-values;  $P = 0.078$ ]. The protective effect is also observed if intermittent typing workload is performed for 30 min in order to induce acute shoulder stiffness. BCA intake prevented the decrease in oxy-Hb significantly ( $P < 0.05$ ), and also tended to alleviate the increase in root mean square (RMS) of the EMG during the typing workload and muscle stiffness after the workload, in this way, reducing muscle fatigue (Matsumoto 2005).

**Anti-inflammatory activity:** The mechanisms mediating the anti-inflammatory effect of anthocyanins are under continuous investigation. It has been shown that anthocyanins have ability to inhibit cyclooxygenase-2 (COX-2) at the same amount that NSAIDs do (Seeram 2001). Among the molecular mechanisms involved in this response it has been shown in murine lipopolysaccharide-activated macrophages, that anthocyanidins, specially Delphinidin, suppressed

COX-2 by blocking the mitogen-activated protein kinase (MAPK) pathway, with simultaneous modulation of the nuclear factor-kB (NF-kB) pathway, activator protein-1 (AP-1) and C/EBP $\delta$  (Hou 2005). Other related anti-inflammatory mechanisms have been invoked, including inhibition of interleukin-6 related also with inhibition of the NF-kB pathway (Omoigui 2007); and the modulatory effect in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Xu J-W 2006). A clinical study showed that proanthocyanidins reduced inflammation and oxidative stress plasma levels and adhesion molecules (ICAM-1, VCAM-1 and E-selectin) in systemic sclerosis (Kalin 2002).

**Cardiovascular System:** In reference to the cardiovascular system it is clear now that atherosclerosis is an inflammatory disorder; also that lipid peroxidation as well as alterations in nitric oxide-mediated vasodilatation are relevant pathogenic events. This circumstances put anthocyanins in a privileged position since they are able to positively influence all three factors. Xia et al. (Xia 2007) reported a novel mechanism how anthocyanins can attenuate atherosclerotic plaque formation in apolipoprotein E (ApoE)-deficient mice. It has been published that hyperactivation of the pro-inflammatory CD40 receptor is greatly amplified by hipercholesterolemia and other pro-inflammatory stimulus including its ligation to CD40 ligand (CD40L) and traslocation of tumor necrosis factor receptor-associated factors (TRAF-2) to the membrane (Lutgens 2000, Frolov and Hui 2007); CD40 activation strongly depends on the cholesterol domain (raft) structure of the cell plasma membrane. Xia et al showed that anthocyanins, specifically Cyanidin-3-glucoside or peonidin-3-glucoside, reduced raft cholesterol levels by up-regulation of ABCA1-mediated cholesterol efflux to Apo A-I, in this way, inhibiting the formation of a CD40/TRAF-2 complex (formed after traslocation of TRAF-2 to the lipid raft) able to activate NF-kB and inhibiting also subsequent up-regulation of pro-inflammatory citokines IL-1, IL-8 and monocyte chemoattractant protein-1 (MCP-1) in human endothelial cells. Te authors conclude that anthocyanin protects from CD40-induced proinflammatory signaling by preventing TRAF-2 translocation to lipid rafts through regulation of cholesterol distribution (Xia 2007). A positive role of anthocyanins in preventing endothelial cell death has been also demonstrated. TNF- $\alpha$  is involved in inflammation-mediated vascular damage by inducing apoptosis (associated with cleaved caspase-3 and cleaved poly(ADP-ribose) polymerase) of endothelial cells. Anthocyanins inhibit this effect of TNF- $\alpha$  through multiple signaling pathways which include elevation of endothelial nitric oxide synthase (eNOS) and thioredoxin (Trx); this is related to activation of AKT, decrease in lipid peroxidation products and modulation of the tumor suppressor gene P53 (Xu J-W 2006). It is well accepted that eNOS promote endothelium-dependent relaxation of blood vessels, and this is consistent with the vasodilatation produced by anthocyanins. Lazze et al (Lazze 2006) showed that anthocyanidins (aglycones delphinidin and cyanidin) at the physiological concentration that could be observed *in vivo*, decreased endothelin-1 production and increased endothelial nitric oxide synthase in cultured human endothelial cells. As an example of anthocyanins diversity, Bell et al (Bell 2006) applied extracts from three different

berries (bilberry, chokeberry or elderberry) to coronary arterial rings isolated from 64 pigs. Bilberry and chokeberry extracts, but not elderberry extract, produced dose and endothelium-dependent vasorelaxation; at lower concentration bilberry and chokeberry extracts did not induce vasorelaxation but protected against ROS-induced (pyrogallol-induced) vasoconstriction.

**Prevention of malignant transformation:** Anthocyanins prevent cellular malignant transformation. Moreover, anthocyanins have been probed to induce apoptosis in some malignant cells. This characteristic is extremely important since, as was shown above, anthocyanins are protective for normal cells. A recent publication from Feng et al (Feng 2007) brings light over this apparent contradiction and reinforces the selectivity of anthocyanins anti-tumorous activity. Feng found that Cyanidin-3-rutenoside selectively kills leukemic cells (HL-60 cells) by induction of oxidative stress. Anthocyanins induce peroxide accumulation and apoptosis in HL-60 cells. In addition, cyanidin-3-rutinoside treatment resulted in reactive oxygen species (ROS)-dependent activation of p38 MAPK and c-jun NH2-terminal kinase (JNK), which contributed to cell death by activating the mitochondrial pathway mediated by Bim. Notably, cyanidin-3-rutinoside treatment did not lead to increased ROS accumulation in normal human peripheral blood mononuclear cells and had no cytotoxic effects on these cells (Feng 2007). Molecular mechanisms behind the chemoprotective effects of anthocyanins can be inferred from all the biological effects already mentioned. Hou et al (Hou 2004) proposed similar mechanisms including modulation of MAPK pathway, AP-1 factor, NF- $\kappa$ B pathway, Cyclooxygenase-2 gene and JNK-mediated caspase activation. Though more information is available every day; the current information should be enough to support the use of anthocyanines. Block et al (Block 2007) performed a systematic review of the literature in order to compile results from randomized trials that evaluate concurrent use of antioxidants with chemotherapy. Anthocyanins were not used in any of this trials. Still, Block et al. concluded that the review “ provides suggestive evidence that antioxidant supplementation helps reduce some adverse reactions including neurotoxicity, thrombocytopenia, diarrhea, thus enabling increased or uninterrupted dosing in patients who otherwise may discontinue treatment due to side effects”. The review did not detect diminished chemotherapeutic efficacy in patients receiving antioxidant supplementation in randomized trials and suggest that “the clinical application of antioxidant supplementation during chemotherapy should be further explored” (Block 2007). The link between the inhibitory effect of anthocyanins over the epidermal growth factor receptor (EGFR) and their effect on phosphodiesterase modulation, was proposed by Marko et al (Marko 2004) to be the common end point modulation of the MAPK pathway that regulates cell proliferation.

**The visual system:** The eye is a biological system relying significantly in pigment function, and it seems that the anthocyanin pigments have important beneficial effects in the eye. It has been shown that bilberry anthocyanins protect human retinal pigment epithelial cells in culture (ARPE-19 cells) from pyridinium bisretinoid (A2E) photooxidation and membrane permeabilization; A2E is a pigment that accumulates in retinal pigment epithelial cells with age and also in “Stargardt” and “Best” retinal disorders, A2E mediate a detergent-like permeabilization of cell membranes and light-induced damage. Anthocyanines quenched singlet oxygen which mediated the photooxidation process and improved survival of RPE cells by 60% (Jang 2005). The effects of anthocyanin-enriched bilberry extracts were also analyzed in ARPE-19 cells oxidatively challenged with hydrogen peroxide. The same extract after phenolic removal was used as control. Anthocyanines from bilberry up-regulated the oxidative stress defensive enzymes Heme Oxygenase-1 and Glutathion S-Transferase-pi. Indicating this way, that anthocyanins have effect in gene expression of cell-endogenous antioxidant mediators (Milbury 2007). In the rd1 mouse model of retinitis pigmentosa (RP) a cocktail of antioxidants (not including anthocyanins) was administered. Carbonyl adducts and immunohistochemical staining for acrolein were measured as markers for oxidative damage. “the staining for acrolein in remaining cones at day 35 of life was eliminated in antioxidant-treated *rd1* mice, confirming that the treatment markedly reduced oxidative damage in cones; this was accompanied by a 2-fold increase in cone cell density and a 50% increase in medium-wavelength cone opsin mRNA. Antioxidants also caused some preservation of cone function based upon photopic electroretinograms”(Komeima 2006).

**Neuroprotection:** Finally, it is important to mention the possible role of anthocyanins in the brain. 6-hydroxy dopamine is a neurotoxic metabolite of dopamine. Both can be oxidized to generate ROS, which has been implicated in dopaminergic neurodegeneration; this could be also related to abnormal redox state and cytoplasmic release of cytochrome c (Cytc) leading to neuronal apoptosis. Purified anthocyanins and *Vaccinium* extracts were tested for their effect to protect against Cytc-enhanced 6-hydroxy DA oxidation. The most potent protector was *Vaccinium myrtillus* (bilberry) with a 50% inhibition (Yao 2007). This study provide strong support for testing anthocyanins as neuronal and mitochondrial protectors.

At this point, it could be undoubtedly concluded that there is a big amount of evidence about the biological mechanisms mediating the beneficial effects of the anthocyanins that compose MEDOX. MEDOX provides a unique opportunity to supplement high quality anthocyanins.

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