A unique, clinically documented Nutraceutical

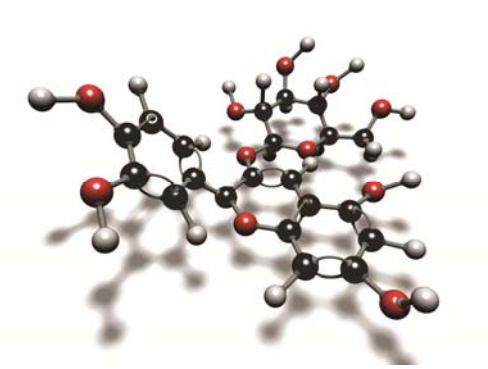
MEDOX®

The artery to lasting health

Medox® is anthocyanins. The size of the anthocyanin molecules makes them able easily to penetrate cell membranes and the "Blood-Brain-Barrier". As a sample, Cyanidin-3β-Glucopyranoside = 484g/mol.

Medox® is an absolute unique product developed to fit into the coming, exploding, novel Nutraceutical market for health promoting products, defined as:

> "*Any substance that may be considered a food or a part of food and at the same time provides medical or health benefits, including the prevention and treatment of disease*".



As opposed to Nutrition Supplements, Medox® has been documented by multiple published, independent clinical trials at university hospitals and universities in Norway, EU, PR China, Canada, USA, and Australia since entering the market early 2000.

The scientific background for Medox® was many years of research at the University of Bergen since the early eighties.

Anthocyanins possess strong documented characteristics that:

- "Trigger" genes, proteins & hormones
- Modulate the endocrine system (Elevates eNOS, Lower iNOS,)
- Lower Chronic Inflammation (NF-κB, IFNα, IL-4, ----)
- Modulates/improve the immune system showing strong synergistic effects with Glutathione (GSH)
- Impede growth/spread of cancer cells (Apoptosis, MMP, COX-2, NF-κB, VEGF, VEGFR, EGFR, I□B PDGFR, p38, p53, TNF-α, CETP, . .)
- Reduce risk of cardiovascular diseases (Increase HDL & decrease LDL balance by ~ 30 %, modulating CETP)
- Stimulates insulin production, counteract insulin resistance
- Have strong virus-fighting properties
- Neuro-protective effects (Pre-treatment of SH-SY5Y cells with Cy-3G inhibits H2O2-induced ROS, +++)

Medox® entered the market in the year 2000. Ever since then Medox® and its anthocyanin molecules, have been subject to clinical cell line and animal trials, also including several larger human randomized, double-blind placebo-controlled studies.

Trials on Medox® are all independent. The trials have taken place on Universities and University Hospitals and Pharmaceutical Companies in Norway, EU, PR China, Canada, USA, and Australia since entering the market early 2000.

Samples of published clinical studies on Medox®

- documenting sensational health-promoting properties

Purified Anthocyanin Supplementation Reduces Dyslipidemia, Enhances Antioxidant Capacity, and Prevents Insulin Resistance in Diabetic Patients [1–3]:

DanLi, [4,5] Yuhua Zhang, [5] YanLiu, [4,5] Ruifang Sun, [4,5] and Min Xia [4,5*]
[4]Guangdong Provincial Key Laboratory of Food, Nutrition, and Health, Guangzhou, China; and [5]Department of Nutrition, School of Public Health, Sun Yat-sen University, Guangzhou, China.

Conclusion: These findings demonstrate that anthocyanin supplementation exerts beneficial metabolic effects in subjects with type 2 diabetes by improving dyslipidemia, enhancing antioxidant capacity, and preventing insulin resistance.

Funded by: Grants from the National Natural Science Foundation of China and the National Natural Science Foundation from Guangdong Province.

Published: "The Journal of Nutrition", USA 2015.

From one of Biolink Group's research laboratories.

Anthocyanins Inhibit Nuclear Factor-kB Activation in Monocytes and Reduce Plasma Concentrations of Pro-Inflammatory Mediators in Healthy Adults1–3:

Anette Karlsen,4 Lars Retterstøl,6 Petter Laake,5 Ingvild Paur,4 Siv Kjølsrud-Bøhn,4 Leiv Sandvik,7 and Rune Blomhoff4*4Department of Nutrition, and 5Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway N-0316 and 6Department of Medical Genetics and 7Research Centre, Ullevaal University Hospital, Oslo, Norway N-0407.

Conclusion: Medox efficiently suppressed LPS-induced activation of NF-κB related inflammation. Furthermore these data suggest that anthocyanin supplementation may have a role in the prevention or treatment of chronic inflammatory diseases by inhibition of NF-κB transactivation and decreased plasma concentration of pro-inflammatory chemokines, cytokines, and inflammatory mediators.

Funded by: The Norwegian Cancer Society, The Throne Holst Foundation, The Norwegian Research Council.

Published: "The Journal of Nutrition", USA 2007.

Columns involved in the patented process of Medox®.

Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects[1,2,3,]

Yu Qin, Min Xia, Jing Ma, YuanTao Hao, Jing Liu, HaiYing Mou, Li Cao and WenHua Ling [1] From the Departments of Nutrition (YQ, MX, JM, JL, HYM, LC, and WHL) and Statistics (YTH), School of Public Health, Sun Yat-Sen University (Northern Campus), Guangzhou, China. [2]

YQ and MX contributed equally to this work. [3] Supported by research grants from the National Natural Science Foundation of China (30730079) and the China Medical Board of New York Inc (CMB 98-677). The treated capsules, including the anthocyanin (Medox) and the placebo, were gifts from Polyphenols AS (Sandnes, Norway).

Conclusion: Anthocyanin supplementation in humans improves LDL- and HDL-cholesterol concentrations and enhances the cellular cholesterol efflux to serum. These benefits may be due to the inhibition of CETP. Furthermore: The 13,6% decrease in LDL and 13,7% increase in HDL observed in the present study would result in a nearly 27,3% reduction in coronary heart disease risk which is meaningful and greatly promising.

Funded by: A medical research foundation in New York, USA and PR China

Published: "The American journal of Clinical Nutrition" USA 2009.

Anthocyanin supplementation improves HDL associated paraoxonase 1 activity and enhances cholesterol efflux capacity in subjects with hypercholestrolemia

Yanna XZhu, Xiuwei Huang, Yuhua Zhang, Yun Wang, Yan Liu, Ruifang Sun, Min Xia. Guangdon provincial Key Laboratory of Food, Nutrition and Health; department of nutrition, School of Public Health, Sun Yat-sen University(Northrern Campus), Guangzhou, Guangzhou province, P.R. China

Conclusions: Our observations suggest that the alterations of PON1 activity by anthocyanin (Medox®) observed in hypercholesterolemic HDL reflect a shift to an improvement in cholesterol efflux capacity of HDL and may provide a link between anthocyanion and cardioprotective effects.

Our results suggest that anthocyanin supplementation (Medox®) in dyslipidemic patients has a beneficial effect on the lipoprotein profile, which include a decrease in LDL-cholesterol and an increase in HDHL-cholesterol concentrations. The beneficial effects may be partially explained by *the improvement of cholesterol efflux capacity*, a key metric of HDL function, via enhancing HDL-PON1 activity. These findings reinforce the concept that assessment of *HDL function rather than HDL level* may prove informative in refining our understanding of anthocyanin mediated athero-protection.

Published: "The Journal of Clinical Endocrinology & Metabolism", USA 2013.

Effects of anthocyanins on cardiovascular risk factors and inflammation in pre hypertensive men; a double-blind randomized placebo-controlled crossover study.

SS Hassellund, A Flaa, SE kjeldsen, Seljeflot, A karlsen I Erlund and R Rostrup

Conclusion: The present study strengthens the evidence that anthocyanins (Medox®) may increase HDL-cholesterol levels, and this is demonstrated for the first time in prehypertencive and non-dyslipidemic men. Other beneficial effects, including modulating effects on Chronic Inflammation were not registered in this short trial time.

Published: "The Journal of Human Hypertension", USA, 2013.

Anthocyanins protect human endothelial cells from mild hyperoxia damage through modulation of Nrf2 pathway

Francesco Cimino, Antonio Speciale, Sirajudheen Anwar, Raffaela Canali, Elisabeth Ricciardi, Fabio Virgili, Domenico Trommbetta, Antonia Saila

Conclusion: This study confirms that dietary anthocyanins (Medox®) and/or their metabolites can protect endothelial cells against mild hyperoxia-induced alterations acting as cell signaling modulators.

In other words: This study shows that anthocyanins and/or their metabolites, present in human serum after oral administration of a dietary plant-derived supplementation (Medox®), can protect HUVECs against mild hyperoxia-induced alterations acting as cell signaling modulators and inducing activation of the Nrf2/ARE pathway.

Published online: Springer Verlag Berlin Heidelberg Germany 2012

Spray-drier at the manufacturing plant for Medox®

Anti-inflammatory effect of purified dietary anthocyanin in adults with hypercholesterolemia: A randomized controlled trial

Y. Zhu, W. Ling, H. Guo, F. Song, Q. Ye, T. Zhou, D. Li, Y. Zhang, G. Li, Y. Xiao, F. liu, Z. LI, Z. Shi, Y. Yang
Guangdong Provincial Key Laboratory of Food, Nutrition and health, Department of Nutrition, Scool of Public Health, Sun Yat-sen University, Guangzhou, Guangdong Province, PR China. Department of Material and Child Health, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong Province, PR China. Department of Food Science, Yingdong College of Bioengineering, Shaoguan University, Shaoguan, Guangdong Province, PR China. School of Public Health, Guangdong Medical College, Dongguan 523808, PR China. Department of Cardiovascular Disease, Guangzhou General Hospital, Guangzhou Military Region, Guangzhou, Guangdong Province, PR China.

Conclusion: Anthocyanin consumption (Medox®) significantly decreased the levels of serum high sensitivity C-reactive protein (hsCRP) (-21,6% vs -2,5% placebo, P=0.001) and plasma IL-1ß(-12,8% vs -1,3% placebo, P= 0.019).

We also found a significant difference in the LDL cholesterol (-10,4% verses -0,3% placebo, P= 0.030, and HDL cholesterol level changes (-14,0% vs -0,9% placebo, P=0.036) between the two groups.

In cell culture assays in vitro, purified anthocyanin mixture of Delphinidin-3-ß-glucoside, and cyanidin-3-ß-glucoside (from Polyphenols/Biolink Group, Norway) inhibited IL-6 and IL-1ß-induced CRP production (P<0.05) in HepG2 cell line and LPS-induced VCAM-1 secretion (P=<0.05) in porcine iliac artery endothelial cell line respectively in a dose-dependent manner.

In other words: The supplementation of anthocyanin mixture (Medox® and Medox® pure single molecules) to hypercholesterolemia subjects for 24 weeks reduced serum levels of CRP, VCAM-1 and IL-1ß, which involved the improvement of the lipid profile, In addition, different anthocyanin compounds (Polyphenols, Norway) were found to have additive or synergistic effects in mediating anti-inflammatory responses in vitro cell culture assays.

Published in: Nutrition, Metabolism & Cardiovascular Diseases, USA, 2012

Years of scientific research in our laboratories is the fundament of Medox®.

Purified Anthocyanin Supplementation Improves Endothelial Function via NO-cGMP Activation in Hypercholesterolemic Individuals

Yanna Zhu,1,2 Min Xia,1,2 Yan Yang,1,2 Fengqiong Liu,1,2 Zhongxia Li,1,2 Yuantao Hao,1,3 Mantian Mi,4 Tianru Jin,1,2,5 and Wenhua Ling1,2*

Conclusions: Anthocyanin supplementation improves endothelium-dependent vasodilation in hypercholesterolemic individuals. This effect involves activation of the NO-cGMP signaling pathway, improvements in the serum lipid profile, and decreased inflammation.

In other words: Significant increases of FMD from 8.3% (0.6%) at baseline to 11.0% (0.8%) at 1 h and 10.1% (0.9%) at 2 h were observed after short-term anthocyanin consumption, concomitantly with increases of plasma anthocyanin concentrations ($P < 0.05$). In the study participants who received long term anthocyanin intervention, compared with the control group, we observed significant increases in the FMD (28.4% vs 2.2%), cGMP (12.6% vs -1.2%), and HDL-cholesterol concentrations, but decreases in the serum soluble vascular adhesion molecule-1 and LDL cholesterol concentrations ($P < 0.05$).

The changes in the cGMP and HDL cholesterol concentrations positively correlated with FMD in the anthocyanin group ($P < 0.05$). In the presence of NO-cGMP inhibitors, the effects of anthocyanin on endothelial function were abolished in human participants and in a rat aortic ring model.

We have demonstrated for the first time that dietary anthocyanin supplementation improves endothelium-dependent vasodilation through the activation of the NO-cGMP signaling pathway in hypercholesterolemic individuals. Additional investigations are needed to assess the causative relationship between the beneficial effect of anthocyanins on the lipid profile and the reduction in inflammatory molecule release.

Funding: National Natural Science Foundation of China (30730079) and the Supporting Program of the “Eleventh Five-Year Plan” for Science and Technology Research of China (2008BAI58B06).

Published: Clinical Chemistry 57:11 Lipids, Lipoproteins, and Cardiovascular Risk Factors 1524–1533, USA, 2011.

High increase in demand for Medox®

The nutraceutical Medox®

Medox® is anthocyanins

Model, cell-line and animal trials on Medox®

- type single main molecules, C-3G and/or D-3G supplied by the Biolink Group owned company Polyphenols AS, Norway

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Plant Food Delphinidin-3-Glucoside Significantly Inhibits Platelet Activation and Thrombosis: Novel Protective Roles against Cardiovascular Diseases

Yan Yang1,2,3,4*, Zhenyin Shi2, Adili Reheman3, Joseph W. Jin1,3, Conglei Li3,4, Yiming Wang1,3,4, Marc C. Andrews3,5, Pingguo Chen1,3, Guangheng Zhu3, Wenhua Ling2, Heyu Ni1,3,4,5,6*

Physiology, University of Toronto, Toronto, Ontario, Canada, 6 Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

1 Canadian Blood Services, Toronto, Ontario, Canada, 2 Department of Nutrition, School of Public Health, Sun Yat-sen University (Northern Campus), Guangzhou, People's Republic of China, 3 Toronto Platelet Immunobiology Group, Department of Laboratory Medicine, and Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada, 4 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada, 5 Department of Physiology, University of Toronto, Toronto, Ontario, Canada, 6 Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Conclusion: We found that Dp-3-g reduced phosphorylation of adenosine monophosphate-activated protein kinase, which may contribute to the observed inhibitory effects on platelet activation. Thus, Dp-3-g significantly inhibits platelet activation and attenuates thrombus growth at both arterial and venous shear stresses, which likely contributes to its protective roles against thrombosis and CVDs.

Funding: This work was supported by Canadian Institutes of Health Research and National Natural Science Foundation of China (China-Canada Joint Health Research Initiative Program), Heart and Stroke Foundation of Canada (Ontario), and National Natural Science Foundation of China Research Grants (No. 30972481). Equipment Funds from St. Michael's Hospital, Canadian Blood Services and Canada Foundation for Innovation. YY is a recipient of the Canadian Blood Services postdoctoral fellowship award. YW is a recipient of a Ph.D. Graduate Fellowship from Canadian Blood Services. CL is a recipient of Connaught Scholarships, University of Toronto. JWJ is a recipient of the Canadian Blood Services postdoctoral fellowship award, and the Heart and Stroke Foundation of Canada postdoctoral fellowship. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

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Supplementation with Cyanidin-3-O-b-Glucoside Protects against Hypercholesterolemia- Mediated Endothelial Dysfunction and Attenuates Atherosclerosis in Apolipoprotein E–Deficient Mice 1–3

Yun Wang,4,5 Yuhua Zhang,4,5 Xiaoming Wang,4,5 Yan Liu,4,5 and Min Xia4,5*
4Guangdong Provincial Key Laboratory of Food, Nutrition and Health, and 5Department of Nutrition, School of Public Health, Sun Yat-sen University (Northern Campus), Guangzhou, Guangdong Province, P.R. China

Conclusion: Taken together, this study indicates that the mechanism of action of the anthocyanin, C3G, is to ameliorate hypercholes- terolemia-induced endothelial dysfunction and atherosclerosis by reducing cholesterol and 7-oxysterols levels via the ABCG1 pathway, thus decreasing superoxide production and enhancing eNOS activity and NO bioavailability.

Funded by: Supported by grants from the National Natural Science Foundation of China (81172663), the Foundation for the Author of National Excellent Doctoral Dissertation of PR China (200978), Guangdong Province Universities and Colleges Funded Scheme (2011), and the Fundamental Research Funds for the Central Universities of Sun Yat-sen University (09ykpy59).

Published: "The Journal of Nutrition", 142: 1033–1037, USA, 2012

One of the Rotavapors used in an early generation of our patented Medox® manufacturing plant is still in use.

Gut Microbiota Metabolism of Anthocyanin Promotes Reverse Cholesterol Transport in Mice Via Repressing miRNA-10b

Dongliang Wang, Min Xia, Xiao Yan, Dan Li, Lei Wang, Yuxuan Xu, Tianru Jin, Wenhua Ling

Conclusions: PCA, as the gut microbiota metabolite of Cy-3-G, exerts the antiatherogenic effect partially through this newly defined miRNA-10b-ABCA1/ABCG1-cholesterol efflux signaling cascade. Thus, gut microbiota is a potential novel target for atherosclerosis prevention and treatment. (Circ Res. 2012;111:967-981.)

From the Department of Nutrition, School of Public Health, Sun Yat-Sen University, Guangzhou, PR China (D.W., M.X., X.Y., D.L., L.W., Y.X., T.J., W.L.); the Department of Physiology, University of Toronto, Toronto, Canada (T.J.); and Guangdong Provincial Key Laboratory of Food, Nutrition, and Health, Guangzhou, PR China (W.L.).

Funding: This work was supported by grants from the National Natural Science Foundation of China (81130052), the Joint project of NSFC, China-CIHR, Canada (81010017), and the Medical Scientific Research Foundation of Guangdong Province (B2012074).

Published: The Journal of The American Heart Association; Circulation Research is available at http://circres.ahajournals.org

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Cyanidin-3-glucoside suppresses TNF-a-induced cell proliferation through the repression of Nox activator 1 in mouse vascular smooth muscle cells: involvement of the STAT3 signaling

Xiaoqin Luo • Shi Fang • Yunjun Xiao • Fenglin Song • Tangbin Zou • Min Wang • Min Xia • Wenhua Ling

Conclusion: Administration of the ROS scavenger catalase (2,000 U/ml) remarkably inhibited TNF-a-induced cell proliferation and STAT3 activation. These data suggest that C3G exerts its antiproliferative effect on TNF-a-induced VSMCs proliferation through inhibiting STAT3 activation by attenuating NoxA1-derived ROS over production.'

In other words: In conclusion, the present findings demonstrate that C3G inhibits TNF-a-induced VSMCs proliferation through down regulating of the NoxA1-ROS-STAT3 pathway. It is noteworthy that NoxA1 is a potential target for modulation of vascular ROS in atherosclerotic arteries. Hence, further understanding of the antioxidative property of C3G in NoxA1-containing NADPH oxidase and the detailed mechanisms should provide the basis for devising novel therapies in cardiovascular disorders.

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Published: Molecular Cell & Biochemistry DOI 10.1007/s11010-011-1144-3, USA, 2011

Differentiation of human melanoma cells induced by cyanidin-3-O-β-glucopyranoside

Annalucia Serafino,* Paola Sinibaldi Vallebona,† Giuseppe Lazzarino,‡ Barbara Tavazzi,§ Guido Rasi,* Pasquale Pierimarchi,* Federica Andreola,* Gabriella Moroni,†
Giacomo Galvano, ‖ Fabio Galvano,¶ and Enrico Garaci †

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Conclusion: Data obtained provide evidence that a single treatment with C-3-G is able to revert the human melanoma cells from the proliferating to the differentiated state. We conclude that C-3-G is a very promising molecule to include in the strategies for treatment of melanoma; also because of its nutritional relevance.

In other words: Our results provide morphological and functional evidence that a single treatment with the anthocyanin C-3-G is able to revert human melanoma cells from the proliferating to the differentiated state. What is particularly encouraging is that C-3-G is active at concentrations corresponding to those achieved with food intake (range of μM) and without any toxicity.

Although further studies will be necessary to understand the molecular mechanism underlying the differentiating effect induced by C-3-G on human melanoma cells, our results provide a new perspective in the development of novel strategies for the prevention and treatment of melanoma through consumption of C-3-G in an appropriate cancer prevention diet.

Funded by: "Contributo per Progetti di Ricerca anno 2003- Università Cattolica del Sacro Cuore, Roma" Grant Number 7020269; by "Funds of Provincia Regionale di Catania," Research Contract on "Antioxidant properties of sicilian pigmented oranges"; and by Ministero della Salute: Progetto ricerca finalizzata 2002; Project title: "Sviluppo di nuove strategie di immunoterapia e terapie combinate contro i tumori" Grant Number 3AO/F5 and Progetto ricerca finalizzata 2003: Sviluppo di nuove strategie antitumorali: identificazione dei target subcellulari mediante l'applicazione di metodologie avanzate" Grant Number 4AA/F8.

Published: The FASEB Journal express article 10.1096/fj.04-1925fje. USA, 2004. Published online September 27, 2004.

Cyanidin-3-O-β-glucoside improves obesity and triglyceride metabolism in KK-Ay mice by regulating lipoprotein lipase activity

Xiaoyi Wei, Dongliang Wang, Yan Yang, Min Xia, Dan Li, Guilan Li, Yanna Zhu, Yunjun Xiao and Wenhua Ling∗

Conclusions: Our present data thus demonstrate that Cy-3-g improves obesity and triglyceride metabolism in KK-Ay mice. The underlying mechanism is found to be partly related to the activation of LPL in plasma and skeletal muscle, and inhibition of LPL in adipose tissue following the activation of pAMPK.

In other words: Cy-3-g improves TG metabolism and decreases adipose storage in VAT, leading to body weight loss. These actions may be mediated by an increase in LPL activity in plasma and skeletal muscle, and decreased LPL expression in VAT, through the activation of pAMPK. This study will provide a biochemical and nutritional basis for the use of Cy-3-g anthocyanin as a functional food factor, which may be beneficial in the prevention of obesity and the amelioration of hypertriglyceridemia.

Funding: This study was supported in part by the National Natural Science Foundation of China (Grant No. 30730079), the National Natural Science Foundation of Guangdong province (Grant No. 7117377), and by the 11th Five-year Project of China (2008BAI58B06). We particularly thank J Ha in the Department of Molecular Biology, Kyunghee University College of Medicine, Seoul, Korea, for providing dominant-negative AMPK α1 construct.

Published: "Society of Chemical Industry"; USA, 2011

Cyanidin-3-O-b-glucoside, a typical anthocyanin, exhibits antilipolytic effects in 3T3-L1 adipocytes during hyperglycemia: Involvement of FoxO1-mediated transcription of adipose triglyceride lipase

Honghui Guo a,⇑, Jiebiao Guo a, Xinwei Jiang b, Zhen Li b, Wenhua Ling b.
a Department of Food Science, Yingdong College of Bioengineering, Shaoguan University, 512005 Shaoguan, China. b Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Department of Nutrition, School of Public Health, Sun Yat-Sen University (Northern Campus), Guangzhou 510080, China

Conclusion: Our findings reveal a novel mechanism by which anthocyanin regulates FoxO1-mediated transcription of ATGL and thus inhibits adipocyte lipolysis, suggesting its potential therapeutic application in diabetes-associated hyperlipidemia.

In other words: Taken together, our results indicated that anthocyanin C3G apparently eliminated the impacts of high-glucose on the induction of adipocytes lipolysis by reducing FoxO1 GlcNAcylation and suppressing gene expression of ATGL. Although it appears hard to get the concentration of anthocyanin shown in this study from daily consumed foods, our findings provide a novel insight into the potential implications of anthocyanin in preventing and/or treating diabetes-associated hyperlipidemia in humans.

Funding: This work was supported by grants from the National Natural Science Foundation (30800913; 81172655), the National Basic Research Program (973 Program, 2012CB517506), the Foundation for Qualified Personnel in Colleges and Universities in Guangdong Province (2011-128), and Natural Science Foundation of Guangdong Province China (8451200501000168).

Published: Food and Chemical Toxicology 50 (2012) 3040–3047, USA, 2012

Cyanidin-3-O-ß-glucoside upregulates hepatic cholesterol 7Î±-hydroxylase expression and reduces hypercholesterolemia in mice

Dongliang Wang1, Min Xia1, Song Gao2,3, Dan Li1, Yuan Zhang1, Tianru Jin1,2,3 and Wenhua Ling1,4. 1 Department of Nutrition, School of Public Health, Sun Yat-Sen University, Guangzhou, P. R. China 2 Department of Physiology, University of Toronto, Toronto, Canada. 3 Department of Medicine, University of Toronto, Toronto, Canada. 4 Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Guangzhou, P. R. China

Conclusion: Our results indicate that the hypocholesterolemic activity of cyanidin-3-O-ß -glucoside was, at least in part, mediated by activating the potential LXRConclusion: Our results indicate that the hypocholesterolemic activity of cyanidin-3-O-ß- glucoside was, at least in part, mediated by activating the potential LXRα-CYP7A1-bile acid excretion pathway, thus contributing to the antiatherogenic effect of cyanidin-3-O-ß-glucoside. Importantly, cyanidin-3-O-ß-glucoside could activate LXRα in an agonist-dependent manner.

In other words: The present study has clearly shown that Cy- 3-G possesses the antiatherogenic and hypocholesterolemic effects in the ApoE-deficient mouse model. Mechanistically, the hypocholesterolemic effect of Cy-3-G may be through ac- tivating the potential LXRα-CYP7A1-bile acid excretion path- way in vivo. More importantly, we demonstrated for the first time that Cy-3-G could activate LXRα in an agonist-dependent manner.

Funding: This work was supported by grants from the National Natural Science Foundation of China (30730079) and the Joint project of NSFC, China-CIHR, Canada, 2010-2012.

Published: Molecules, Nutrition & Food Research. 56, 610–621, USA, 2012; WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim www.mnf-journal.com

Bilberry and black currant skin dissolved in tanks before being moved to the next step in our patented manufacturing.

Cyanidin-3-O-glucoside counters the response to TNF-alpha of endothelial cells by activating Nrf2 pathway

Antonio Speciale1, Sirajudheen Anwar1, Raffaella Canali2, Joselita Chirafisi1, Antonella Saija1, Fabio Virgili2 and Francesco Cimino1. 1 Department of Drug Sciences and Health Products, University of Messina, Messina, Italy 2 National Research Institute for Food and Nutrition, Rome, Italy.

Conclusion: Our data confirm the hypothesis that natural Nrf2 and HO-1 inducers, such as C3G and other dietary phytochemicals, might be a potential therapeutic strategy to protect vascular system against various stressors preventing several pathological conditions.

In other words: Our results strongly support the hypothesis that C3G, as well as other dietary plant polyphenols, can play an important role in the prevention of pathological conditions associated with inflammation and oxidative stress. This protective role is likely to be due to activities and roles totally independent of their chemical reactivity toward free radicals and their capacity to prevent the oxidation of important intracellular components.

A possible molecular mechanism of these natural compounds is the ability to induce Nrf2 activation, which in turn regulates a number of detoxification enzyme pathways, and in particular, as indicated by our study, HO-1. In this context, natural Nrf2 and HO-1 inducers, such as C3G, might be a potential therapeutic–preventive strategy to protect vascular system against various stressors in several pathological conditions.

Funding: Department of Drug Sciences and Health Products, University of Messina, Messina, Italy; National Research Institute for Food and Nutrition, Rome, Italy

Published: Molecular Nutrition & Food Research, 57, 1979–1987, USA, 2013

Anticancer Activities of an Anthocyanin-Rich Extract From Black Rice Against Breast Cancer Cells In Vitro and In Vivo

Chang Huia; Yu Bina; Yu Xiaopinga; Yi Longa; Chen Chunyea; Mi Mantiana; Ling Wenhuab.a Chongqing Key Laboratory of Nutrition and Food Safety, Third Military University, Chongqing, China b Public Health School, Sun Yet-sen University, Guangzhou, China.

This study investigates the anticancer effects of an anthocyanin-rich extract from black rice (AEBR) on breast cancer cells in vitro and in vivo. AEBR reduced the viability of breast cancer cell lines MCF-7 (ER+, HER2/neu−), MDA-MB-231 (ER−, HER2/neu−), and MDA-MB-453 (ER−, HER2/neu+) and induced apoptosis in MDA-MB-453 cells via the intrinsic pathway in vitro by activating caspase cascade, cleaving poly (ADP-ribose) polymerase (PARP), depolarizing mitochondrial membrane potential, and releasing cytochrome C. Oral administration of AEBR (100 mg/kg/day) to BALB/c nude mice bearing MDA-MB-453 cell xenografts significantly suppressed tumor growth and angiogenesis by suppressing the expression of angiogenesis factors MMP-9, MMP-2, and uPA in tumor tissue.

Conclusion: This study suggests the anticancer effects of AEBR against human breast cancer cells in vitro and in vivo by inducing apoptosis and suppressing angiogenesis.

Funding: This work was supported by the research grants from National Natural Science Foundation of China (30771794), the "Eleventh Five-Year Plan" for National Key Technology R & D Program (2008BAI58B06). Chang Hui and Yu Bin contributed equally to this work. Authors do not have a conflict of interest.

Published: Nutrition and Cancer; Volume 62, Issue 8, 2010, USA, 2010

Anthocyanin Extract from Black Rice Significantly Ameliorates Platelet Hyperactivity and Hypertriglyceridemia in Dyslipidemic Rats Induced by High Fat Diets

Yan Yang,*,†,‡,§ Marc C. Andrews,|| Yan Hu,† Dongliang Wang,† Yu Qin,† Yanna Zhu,† Heyu Ni,‡,§,|| and Wenhua Ling†

†Department of Nutrition, School of Public Health, Sun Yat-sen University (Northern Campus), Guangzhou 510080, People's Republic of China, ‡Canadian Blood Services, Toronto, Ontario M5G 2M1, Canada, §Department of Laboratory Medicine and Pathobiology and Department of Physiology, University of Toronto, Ontario M5S 1A8,Canada

Conclusion: These findings suggest that dietary intake of anthocyanins reduces platelet hyperactivity, hypertriglyceridemia, and body weight gain, and facilitates in the maintenance of optimal platelet function in dyslipidemic rats induced by high fat diets.

In other words: The present study shows that, in rats fed a high fat diet, anthocyanins supplementation was able to significantly reduce body weight gain, and rescue serum TG levels and platelet function by restoring CaM and sP-selectin levels, TXA2 production and TXA2:PGI2 ratio back to that of controls. This is also the first study that shows the beneficial effects of anthocyanins on in vivo platelet function. While several mechanisms are proposed, the exact mechanism by which anthocyanins improves platelet function, hyper-triglyceridemia and weight gain seen in high fat diets, and how these results are implicated in the development of CVD, requires further investigation.

Funding: This study was supported by National Science Foundation of China Research Grants (30972481), Laboratory Funding of Sun Yat-sen University (KF200824), and Canadian Blood Services Postdoctoral Fellowship.

Published: The Journal of Agricultural and Food Chemistry. 59, 6759–6764 dx.doi.org/10.1021/jf201079h, USA, 2011

Medox® is a 100% natural product based on bilberries and black currants.

Cyanidin-3-glucoside suppresses TNF-?-induced cell proliferation through the repression of Nox activator 1 in mouse vascular smooth muscle cells: involvement of the STAT3 signaling

Xiaoqin Luo, Shi Fang, Yunjun Xiao, Fenglin Song, Tangbin Zou, Min Wang, Min Xia, Wenhua Ling

Conclusion: These data suggest that C3G exerts its anti-proliferative effects on TNF-α-induced vascular smooth muscle cells proliferation through inhibiting signal transducer and activator of transcription 3 activation by attenuating NoxA1-derived reactive oxygen species

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Differentiation of human melanoma cells induced by cyanidin-3-O-β-glucopyranoside

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Conclusion: C C-3-G treatment induced, in a dose- and time-dependent manner, melanoma cell differentiation characterized by a strong increase in dendrite outgrowth accompanied with a remodeling of the microtubular network, a dramatic increase of focal adhesion and an increased expression of "brain specific" cytoskeletal components such as NF-160 and NF-200 neurofilament proteins. C-3-G treatment also induced increase of cAMP levels and up-regulation of tyrosinase expression and activity resulting in an enhanced melanin synthesis and melanosome maturation.

Up-regulation of the melanoma differentiation antigen Melan-A/MART-1 in treated cells respect to the untreated control was also recorded. Data obtained provide evidence that a single treatment with C-3-G is able to revert the human melanoma cells from the proliferating to the differentiated state.

We conclude that C-3-G is a very promising molecule to include in the strategies for treatment of melanoma; also because of its nutritional relevance.onclusion:

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Published: The FASEB Journal express article 10.1096/fj.04-1925fje. Published online September 27, USA, 2004.

Summary of some acknowledged international nutrition- and medicine journals in which clinical studies on Medox® and its two main anthocyanin molecules C 3G and D 3G have been published:

- ”The Journal of Nutrition”, USA-2007, Chronic Inflammation
- "The American Journal of Clinical Nutrition”, USA-2009, CVD, Cholesterol, CETP
- ”Clinical Chemistry”, USA-2011, CVD
- ”Arteriosclerosis, Thrombosis and Vascular Biology”, USA-2007, Chronic Inflammation
- ”The Journal of Federation of American Societies for Experimental Biology”, USA-2004, Cancer
- "The Journal of Lipid Research”, USA-2011, Diabetes
- “Molecular and Cellular Biochemistry”, USA-2011, CVD
- "Genes and Nutrition", USA-2012, CVD
- ”The Journal of Clinical Endocrinology & Metabolism”;USA-2013, Cholesterol & CVD
- ”The Journal of Human Hypertension”; USA-2013, Cholesterol & CVD
- ”Nutrition, Metabolism & Cardiovascular Diseases”; USA-2012, Cholesterol &CRP

Some non-published trials and articles

- on Medox® and/or Medox® single anthocyanin molecules C 3G and D 3G

Medox and possible mitigating effect on Cancer (in vitro, human brain-tumor): "Indremedisinsk Institutt", University of Bergen (UIB),Norway 2000-2002.

Conclusion: Medox® shows marked inhibitory effect on tumor growth and proliferation

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Pilot trial, 8 persons on Medox® and possible influence on Inflammation (CRP), Ullevål University hospital, Oslo.

Conclusion: Medox® lowered CRP

Pilot trial, 10 persons on Medox® and possible influence on Inflammation (CRP), Ullevål University hospital, Oslo.

Conclusion: Medox® lowered CRP

Pilot trial, Institute of Experimental Medical research on Medox®, resting pulse and Ischemia. Ullevål University hospital, Oslo.

Conclusion: Medox® lowered resting pulse.

Medox® and possible influence on resting pulse, immune defence, sedimentation and colds. Randomized, double blind, placebo controlled, n =120, Ullevål University Hospital, Oslo.

Conclusion: Medox lowered resting pulse and sedimentation rate

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Absorption, penetration and metabolism of Medox® in oral consumption, Stavanger University hospital.

Conclusion: Anthocyanins were found in serum already half an hour after consumption, and were even present more than 8 hours after consumption.

Medox® and oxidative stress on elderly female (small in vivo pilot trial), Dr. Med. M. Nylander, nutrition researcher, Stockholm, Sweden.

Conclusion: Medox® lowered oxsidative stress in 3 out of four cases

Effects of Medox® against oxidative stress on top ski cross country athlets during periods of vigorous exercise (small in vivo pilot trial), Dr. Med. M. Nylander, nutrition researcher, Stockholm, Sweden.

Conclusion: Medox® significantly lowered oxidative stress in all subjects with abnormal elevated oxidative stress

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Effects of Medox® against oxidative stress on rheumatics (small in vivo pilot trial), Dr. Med. M. Nylander, nutrition researcher, Stockholm, Sweden.

Conclusion: As opposed to high doses of C-vitamins, Medox® significant lowered oxidative stress in all cases.

Multiple studies on the effects of Medox on resting heart rate and blood pressure (in vivo pilot, rat study, placebo controlled), Ullevål University Hospital, Oslo.

Conclusions: Medox® lowered resting heart rate and blood pressure.

Study on the effect of Medox® single anthocyanin molecules C 3G/D 3G on resting heart rate and blood pressure (placebo controlled rat study), Ullevål University Hospital, Oslo.

Conclusions: Medox® lowered resting heart rate and blood pressure in the rats, while placebo rats had only negligible changes.

Study on the effect of Medox® single anthocyanin molecules C 3G/D 3G on: Prostate Cancer, Ovarian Cancer, Lung Cancer, Breast Cancer and Bladder Cancer(in vitro, humane cancer cell lines), Apoptosis, Necrosis and Autoschises.: Summa Health Center, Cleveland, Ohio, USA.

Conclusion: The Medox® molecules, C 3G and D 3G dampens growth and spread of the investigated cancers significantly in the following output sequence: Ovarian cancer = Bladder cancer = Prostate cancer >Breast cancer >Lung cancer.

New clinical studies being planned/taking place

- Medox® and Osteoporosis; Norway
- Medox® and Alzheimers/Dementia; Norway, Sweden, UK
- Medox® and Neurodegenerative diseases/Parkinson;* Norway
- Medox® and the Cardiovascular System; Germany
- Medox® and NAFL/Diabetes; PR China
- Medox® and Diabetes 2; PR China
- Medox® and Cancer; Italy
- Medox® and Lung Cancer; USA
- Medox® molecules C 3G/D 3G and Cancer; USA
- Medox® and the Cardiovascular System: Australia
- Synthetic Medox® type anthocyanin molecule C 3G and the Cardiovascular System; Australia
- Pharmacological/Medical oral & intravenous animal studies on natural & synthetic Medox® type anthocyanin molecule D 3G; Germany

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