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Effect of cyanidin-glucoside and its metabolites on inflammatory biomarkers of vascular function

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Diet derived anthocyanins may have vasoprotective properties[1], however their low bioavailability suggests that their bioactivity is mediated by their degradants and/or metabolites[2]. Endothelial expression of cell adhesion molecules (CAMs) and cytokines can be activated through ligation of CD40L to its receptor or injury to the endothelium by oxidised low-density lipoprotein (oxLDL)[3], and is an initiating step in the pathogenesis of atherosclerosis. The present study aimed to investigate the ability of cyanidin-glucoside (C3G), the most abundant dietary anthocyanin, and its metabolites to modulate the expression of CAMs and cytokines in cultured human umbilical vein endothelial cells (HUVECs) challenged with either CD40L or oxLDL.

Compounds selected for bioactivity screening were C3G, its degradant, protocatechuic acid (PCA), and a methylated metabolite of PCA, vanillic acid (VA). HUVEC were treated with either CD40L expressing Jurkat cells (D1.1 cells, 1×10^6 cell/well) or oxLDL (5 μg/mL), with or without C3G, PCA or VA at 0.1 to 10 μM concentrations for 24 hours. Vascular cell adhesion molecule-1 (VCAM-1) and interleukin-6 (IL6) were then measured by ELISA (table below).

Compound	Concentration	CD40 induced				oxLDL induced	
		VCAM-1		IL6		IL6	
		Mean	SD	Mean	SD	Mean	SD
Cyanidin-3 glucoside	0.1 μM	67.4*	10.1	39.5	4.6	71.0	16.5
	1 μM	70.7*	6.3	29.6*	12.3	68.6	20.1
	10 μM	95.3	5.4	63.9	22.8	78.0	10.5
Protocatachuic acid	0.1 μM	81.2*	1.7	69.6	17.5	35.8*	14.8
	1 μM	73.8*	8.8	49.4	7.3	46.4*	7.6
	10 μM	71.2*	1.0	55.4	23.0	39.7*	11.6
Vanillic acid	0.1 μM	69.7*	4.5	47.7*	9.9	9.6*	4.7
	1 μM	46.4*	11.1	49.0*	6.4	27.5*	7.5
	10 μM	35.9*	3.4	49.9*	6.0	16.7*	6.3

Data expressed as percentage relative to control (without treatment compounds) VCAM-1 and IL6 expression was induced via D1.1 cells or oxLDL. *Significant difference versus control ($P < 0.05$; ANOVA with Tukey Kramer test, $n = 3$).

VCAM-1 expression by CD40L challenged HUVECs was significantly decreased ($P < 0.05$) by C3G (except at 10 μM), PCA and VA. IL6 levels were significantly reduced ($P < 0.05$) in CD40L treated HUVECs by C3G at 1 μM and VA at all concentration tested but not by PCA. IL6 expression was significantly reduced when HUVECs were challenged with oxLDL in the presence of PCA and VA at all concentrations tested, but not in the presence of C3G. This data suggests that C3G and its degradants/metabolites reduce CD40L induced expression of VCAM-1 and IL6. However, in oxLDL challenged HUVECs only degradants/metabolites of C3G reduced IL6, suggesting C3G and its degradants/metabolites may act differently under various inflammatory stimuli. In conclusion, C3G and its degradants/metabolites appear to have protective properties against proinflammatory mediators of cardiovascular disease.

1. Cassidy A, O'Reilly EJ, Kay C *et al.* (2010) *Am J Clin Nutr.* **93**, 338–47.
2. Williamson G & Clifford MN (2010) *Br J Nutr.* **104**, S48–S66.
3. Granger DN, Vowinkel T & Petnehazy T (2004) *Hypertension.* **43**, 924–31.