Methylated metabolites of the cocoa polyphenols catechin and epicatechin modulate expression of adhesion molecules and inflammatory cytokines in TNFα-stimulated human endothelial cells

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Numerous epidemiological studies suggest an association between intake of flavonoid-rich foods and beverages and reduced risk of CVD1–9, and many human intervention studies have reported positive effects of high-flavonol cocoa on endothelial function, in both healthy individuals and those with risk factors for CVD10–17. Plasma soluble adhesion molecules are a strong predictor of CVD risk, and consumption of a high flavanol cocoa beverage over 6 weeks has been reported to improve vascular reactivity in post-menopausal women who are hypercholesterolaemic, and furthermore this response was accompanied by reductions in plasma soluble VCAM-118. Cellular adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule (ICAM-1) and E-selectin, and inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) are up regulated in endothelial cells in response to inflammatory stimuli, such as TNFα. This process occurs in endothelial dysfunction, and their increased expression results in recruitment of leucocytes to the endothelium, their activation and their infiltration into the blood vessel wall, a key early stage in atherogenesis. The potential of the physiologically-relevant methylated metabolites of the cocoa polyphenols (+)-catechin (cat) and (−)-epicatechin (epi) to attenuate the TNFα-induced expression of VCAM-1, ICAM-1, E-selectin and MCP-1 have been investigated in human umbilical vein endothelial cells (HUVEC), by exposing the cells to the flavanols for 18 h before 4 h TNFα treatment, extracting RNA from the cells and performing real-time RT–PCR. To date it has been found (Figure) that physiological concentrations of 3′-O-methyl- (+)-catechin (3 cat) and 4′-O-methyl- (+)-catechin (4 cat) result in significant (P<0.05) decreases in VCAM-1 and ICAM-1 expression, and preliminary data suggest similar changes for 3′-O-methyl- (−)-epicatechin (3 epi) and 4′-O-methyl- (−)-epicatechin (4 epi). It has also been found that the aglycones cat and epi do not significantly reduce the TNFα-induced up-regulation of the genes studied. The results suggest that these in vivo metabolites could improve endothelial function, a risk factor for CVD, by attenuating inflammation-induced up-regulation of adhesion molecules and cytokines. This finding could go some way to explain the beneficial effects of flavonoid-rich foods, and specifically cocoa, on cardiovascular health. The present study also demonstrates the importance of using physiologically-relevant compounds in in vitro studies, as these species will exert bioactivity in vivo and, as has been shown, can have markedly different effects from the parent compound.

![Figure](https://www.cambridge.org/core). Modulation of MCP-1, E-selectin, ICAM-1 and VCAM-1 expression by 18 h treatment (0.3 µM) with cat, 3 cat, 4 cat, epi, 3 epi and 4 epi before stimulation of HUVEC for 4 h with TNFα. Values are means with their standard errors represented by vertical bars. *P<0.05.