



# Pycnogenol inhibits tumor necrosis factor- $\alpha$ -induced nuclear factor kappa B activation and adhesion molecule expression in human vascular endothelial cells

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## Abstract

The transcriptional regulatory protein nuclear factor kappa B (NF-kappa B) participates in the control of gene expression of many modulators of inflammatory and immune responses, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). The heightened expression of these adhesion molecules has been reported to play a critical role in atherosclerosis, inflammation, ischemic vascular disorders, diabetes, and cancer metastasis. In the present study, we investigated the effect of pycnogenol, an antioxidant phytochemical, on the activation of NF-kappa B and the induction of VCAM-1 and ICAM-1 in tumor necrosis factor (TNF)- $\alpha$ -treated human umbilical vein endothelial cells (HUVECs). Gel-shift analysis of HUVEC demonstrated that pretreatment with pycnogenol exhibited a concentration-dependent suppression of TNF- $\alpha$ -induced activation of NF-kappa B. Induction of VCAM-1 and ICAM-1 surface expression by TNF- $\alpha$  was dose-

independently reduced by pycnogenol. TNF-alpha significantly increased the release of superoxide anion and hydrogen peroxide from HUVECs. Pycnogenol dose-dependently inhibited their release. The ability of pycnogenol to inhibit NF-kappa B activation and VCAM-1 and ICAM-1 expression suggests that this phytochemical may play an important role in halting or preventing the atherogenic process.

Pycnogenol affects the transactivation capacity of NF-κB, thus reducing expression of the inflammatory genes regulated by this transcription factor.<sup>17</sup> However, Pycnogenol does not prevent NF-κB from binding to DNA, suggesting that its mechanism of action is different from that of progesterone, which acts by preventing translocation of the activated NF-κB subunit to the cell nucleus and its consequent binding to DNA, where it will activate translation of genes such as Cox-2 that are involved in the inflammatory cascade.<sup>17</sup> Cox-2 will stimulate prostaglandin production, which in turn will activate the aromatase gene, thus stimulating local estrogen synthesis in the endometrium and enhancing the inflammatory reaction, as occurs in the breast.<sup>1,18</sup> Although both progestins and Pycnogenol reduce inflammation by modulating NF-κB-induced gene transcription, they act on different steps in this mechanism, which explains the greater efficacy of the combination therapy for the control of endometriosis-related pain. When given together with an oral contraceptive, not only is the DNA binding activity reduced but also the trans-activation capacity of the bound NF-κB.<sup>13,14,17</sup> This distinctive effect on the NF-κB activation pathway may provide a plausible explanation at the molecular level for the results reported here. It is also noteworthy that the increased efficacy in terms of pain control in endometriosis is not accompanied by any increase in incidence of side effects.

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