PROGRESSION OF ATHEROSCLEROTIC LESION IN THE ARTERIES AND RELATED GENE EXPRESSION: PROTECTIVE EFFECT FROM A PHYTOTHERAPEUTIC AGENT

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The inflammatory nature of atherosclerosis has prompted efforts to prevent development and/or progression of disease by targeting inflammatory mediators, including cytokines, chemokines, and MMPs. Indeed, endothelial cell dysfunction in eNOS expression by TNF-α is involved in the pathogenesis of vascular diseases with related pathologic changes such as increased expression of adhesion ICAM-1, VCAM-1 and E-selectin. Moreover, oxidative modification of LDL is thought to play a key role in the pathogenesis of atherosclerosis. Consumption of nutrients rich in phenolic antioxidants has been shown to be associated with attenuation of development of atherosclerosis. The aim of this study was to investigate the ex vivo effect of DTS (panax pseudoginseng, eucommia ulmoides, ginseng radix, Institute of Health Care Oriental Herbs and Medicine, Tokyo, Japan) on the development of atherosclerosis in atherosclerosis-susceptible apoE-/-/LDL receptor-/- mice (E0) mice, in relation to the resistance of LDL to oxidation and aggregation. E0 mice (n 5 60; 6-wk-old) were divided into three groups of 15 and fed for 16 wk via their drinking water with the following: group A) placebo (control group), 1.1% alcohol and water (11 mL of alcohol in 1 L of water); group B) 10 mg DTS/d in 1.1% alcohol and water and group C) 50 mg of DTS/day in 1.1% alcohol and water. Aortic atherosclerotic lesion areas were reduced 38% ($p< 0.01$) in mice that consumed 50 mg of DTS/day. DTS did not significantly change cholesterol or triglyceride plasma level. However, peritoneal macrophages harvested from E0 mice after consumption of 25 or 50 mg of DTS/day had a lower ($p< 0.01$) capacity to oxidize LDL (by 45 and by 60%, respectively), and to take up and degrade oxidized LDL (by 41 and 68%, respectively). Consumption of either 25 and 50 mg of DTS/day also reduced the basal level of LDL-associated lipid peroxides by 26% and 62%, respectively ($p< 0.01$) with a 22% inhibition ($p<0.05$) in LDL aggregation. From ex-vivo study it appeared that the aortas of control 8 week old apoE-/-/LDLreceptor-/- mice displayed immunoreactivity for TNF-α as well as TNF p55 and p75 receptors (2.4 ± 1.2%, 5.1 ± 1.9% and 3.1 ± 1.6% of total media area, respectively). At 16 weeks TNF-α expression in the media was increased almost five-fold with widespread atherosclerosis and TNF-α immunoreactivity in all plaques and increased TNF-α mRNA levels. Both DTS-treated mice showed a significant (50mg > 10mg) decrease of TNF-α immunoreactivity and mRNA ($p<0.05$). These findings demonstrate that medial TNF-α and TNF receptor expression precedes lesion formation in apoE-/-/LDL receptor-/- mice and that dietary consumption of DTS by E0 mice significantly attenuates the development of atherosclerotic lesions with a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation.