中文題目：查耳酮衍生物透由促進膽固醇排出與抑制發炎引起之內皮功能違常達抗動脈硬化保護作用

英文題目：A chalcone derivative, Im-6, exhibits athero-protective effects by promoting cholesterol efflux and lessening inflammation-induced endothelial dysfunction

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***Background**:* Atherosclerosis, resulting from lipid dysregulation and vascular inflammation, causes atherosclerotic cardiovascular diseases (ASCVD), which mainly contributes to the morbidities and mortalities worldwide. Chalcone and its derivatives possess several pharmaceutical benefits, including anti-inflammation, anti-oxidants, and anti-tumor activities with unknown cardioprotective effects. In this study, we aimed to develop an effective chalcone derivative with anti-atherogenesis potential.

***Method**:* Human THP-1 cells and human umbilical vein endothelial cells (HUVEC) were used as *in vitro* models. Western blots and real-time PCR were performed to quantify the expressions of protein, mRNA, and miRNA. The capacity of cholesterol efflux was assayed by ^{3}H-labeled cholesterol loading in THP-1 macrophages. The molecular mechanisms were evaluated by small interfering RNA technique. *Ldlr*$^{-/-}$ mice fed with high-fat-diet were used as *in vivo* atherogenesis model. Hematoxylin & Eosin and Oil red O staining were applied to analyze the plaque formation.

Results: By comprehensively screening the effects of chalcone derivatives on ATP binding cassette subfamily A member 1 (ABCA1) expressions, we identified the most effective and nontoxic chalcone derivative, Im-6, which enhanced ABCA-1 expression and promoted cholesterol efflux in THP-1 macrophages. Im-6 activated liver X receptors α (LXRα) signaling, stabilized the ABCA1 mRNA and suppressed the expressions of the potential ABCA-1 regulating miRNAs through heme oxygenase-1 (HO-1) signaling. Additionally, Im-6 significantly inhibited tumor necrosis factor α (TNFα)-induced adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), expression, and pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8, and monocyte chemoattractant protein–1 (MCP-1), production through the modulation of HO-1 signaling and inhibition of signal transducer and activator of transcription 3 (STAT3) activation in HUVECs. Importantly, in atherogenesis-prone mice, treatment with Im-6 significantly reduced lipid accumulation and atherosclerotic plaques.

Conclusion: Our study demonstrated the promising athero-protective effects of Im-6 through enhancing cholesterol efflux and suppressing inflammation-induced endothelial dysfunction, which

opens a new avenue in treating ASCVD.

Keywords: Atherosclerosis, ABCA1, cholesterol efflux, endothelial inflammation, HO-1, STAT3, chalcone derivative