Orange Polymethoxylated Flavones Suppress scavenger Receptor Expression in THP-1 Cells and Alter Lipid homeostasis in HepG2 Liver Cells

Jui-Hung Yen (顏瑞鴻)[1], Ching-Yi Weng (翁菁憶)[2], Shiming Li[3], Ya-Hsuan Lo (駱雅萱)[2], Min-Hsiung Pan (潘敏雄)[4], Shih-Hang Fu (傅士航)[2], Chi-Tang Ho (何其儻)[3], Ming-Jiuan Wu (吳明娟)[2]*

[1]*Department of Molecular Biology and Human Genetics, Tzu Chi University*
[2]*Department of Biotechnology, Chia Nan University of Pharmacy and Science*
[3]*Department of Food Science, Rutgers University*
[4]*Department of Seafood Science, National Kaohsiung Marine University*

Nobiletin, a polymethoxyflavone (PMF) from the peel of Citrus fruit, has been reported to inhibit modified LDL uptake in macrophages and enhance hepatic LDL receptor expression and activity. We report the anti-atherogenic effect and mechanism of 5-demethylnobiletin, an auto-hydrolysis product of nobiletin. 5-demethylnobiletin significantly attenuated PMA-induced gene expression and activity of scavenger receptors, CD36, SR-A and LOX-1. The inhibitory effect is partly associated with the inhibition of PKC activity and JNK 1/2 phosphorylation, thereby inhibiting the activation of AP-1 and NF-κB. 5-demethylnobiletin treatment also led to reduction of oxLDL-induced CD36 mRNA expression and blockade of DiI-modified LDL uptake in THP-1-derived macrophages. In human hepatoma cell line HepG2, 5-demethylnobiletin significantly induced LDLR activity and transcription, at least in part, through SREBP-2 activation. 5-demethylnobiletin also decreased the mRNA expression of DGAT2, the key enzyme involved in the hepatic triacylglycerol biosyntheses. Current results suggest that 5-demethylnobiletin has diverse anti-atherogenic bioactivities. It is more potent in inhibiting monocyte-to-macrophage differentiation and foam cell formation than its permethoxylated counterpart, nobiletin. It exhibits similar hypolipidemic activity as nobiletin and both can enhance LDLR gene expression and activity and decreased DGAT2 expression.