Targeting MHC Regulation Using Polycyclic Polyprenylated Acylphloroglucinols Isolated from *Garcinia bancana*

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**Abstract:** Modulation of major histocompatibility complex (MHC) expression using drugs has been proposed to control immunity. Phytochemical investigations on *Garcinia* species have allowed the isolation of bioactive compounds such as polycyclic polyprenylated acylphloroglucinols (PPAPs). PPAPs such as guttiferone J (1), display anti-inflammatory and immunoregulatory activities while garcinol (4) is a histone acetyltransferases (HAT) p300 inhibitor. This study reports on the isolation, identification and biological characterization of two other PPAPs, i.e., xanthochymol (2) and guttiferone F (3) from *Garcinia bancana*, sharing structural analogy with guttiferone J (1) and garcinol (4). We show that PPAPs 1–4 efficiently downregulated the expression of several MHC molecules (HLA-class I, -class II, MICA/B and HLA-E) at the surface of human primary endothelial cells upon inflammation. Mechanistically, PPAPs 1–4 reduce MHC proteins by decreasing the expression and phosphorylation of the transcription factor STAT1 involved in MHC upregulation mediated by IFN-γ. Loss of STAT1 activity results from inhibition of HAT CBP/p300 activity reflected by a hypoacetylation state. The binding interactions to p300 were confirmed through molecular docking. Loss of STAT1 impairs the expression of CIITA and GATA2 but also TAP1 and Tapasin required for peptide loading and transport of MHC. Overall, we identified new PPAPs issued from *Garcinia bancana* with potential immunoregulatory properties.

**Keywords:** endothelium; Clusiaceae; *Garcinia bancana*; guttiferone F; guttiferone J; major histocompatibility complex; HLA-E; polycyclic polyprenylated acylphloroglucinols; xanthochymol; histone acetyltransferase