Development of anti-allergic lead(s) from Ayurvedic plants through the suppression of PKC- dependent signaling pathway.

( PKC-シグナルを抑制するアユルベーダ由来抗アレルギーリード化合物の開発 )

Up-regulation of histamine H1 receptor (H1R) was observed in Allergic rhinitis (AR) patients. A positive correlation between the expression of H1R mRNA and severity of allergic symptoms has also been reported in the patients with pollinosis and toluene-2,4-diisocyanate (TDI)-sensitized allergic model rats. Accordingly, compound(s) that suppress H1R gene expression might be a good therapeutics in AR. Although advances in biological and chemical technology have led to several modern medicines for palliative treatment of AR, no conclusive therapeutic agent for treating AR has yet been identified. We have studied six Ayurvedic plants and selected *Tephrosia purpurea* (TP) for the isolation of lead compound(s) through the suppression of H1R gene expression in a PKC- dependent signaling pathway. A novel naturally occurring compound 4-methoxybenzofuran-5-carboxamide (MBCA) was isolated from the plant TP. The chemical synthesis of this compound and its derivatives was carried out. MBCA dose dependently suppressed PMA- and histamine-induced H1R mRNA expression in-vitro. MBCA also dose-dependently suppressed PMA-induced up-regulation of H1R protein expression. Moreover, MBCA suppressed PMA-induced phosphorylation at PKC- Tyr311 and inhibit PMA-induced translocation of PKC- from cytosol to the Golgi. The compound improved allergic symptoms in TDI-sensitized rats and significantly suppressed the elevation of H1R mRNA and Th2 cytokine mRNAs (IL-4, IL-5, IL-9 and IL-13). The inhibition of PKC- activation played the underlying molecular mechanism for H1R gene expression.