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미리세틴이 자외선에 의해 유도된 신생혈관을 PI3K를 타겟하여 억제

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Myricetin inhibits UVB-induced angiogeneiss by directly regulating PI3 kinase *in vivo*

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Objectives

In our present study showed that myricetin, naturally occuring phytochemicals in berry, red wine, and onino, inhibited UVB-induced skin cancer formation in SKH-1 hailrless mouse by regulating Fyn kinase activity. This results showed the myricetin is a potent chemopreventive agent. However, there isn't direct result on inhibitory effect of myricetin on UVB-induced angiogenesis. The present study investigated the effect of myricetin on UVB-induced angiogenesis in SKH-1 hairless mouse skin tumorigenesis model.

Materials and Methods

Materials : myricetin (95%) was purchased from Sigma-Aldrich (St. Louis, MO).
Animals : SKH-1 hairless mice (6 weeks of age; mean body weight, 25 g) were purchased from the Institute of Laboratory Animal Resources, Seoul National University (Seoul, Korea).
UVB irradiation : UVB irradiation was performed using a UVB irradiation system. The spectral peak of the UVB source (Bio-LinkCrosslinker; VilberLourmat, Torcy, France) was at 312 nm.

Results

Topical treatment with myricetin inhibited repetitive UVB-induced neovascularization and platelet/endothelial cell adhesion molecule-1 expression in SKH-1 hailress mouse skin, The induction of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-9, and MMP-13 expression by chronic UVB irradiation was significantly suppressed by myricetin treatment. Immunohistochemical and western blot analyses revealed that myricetin inhibited UVB-induced hypoxia inducible factor-1α expression in mouse skin. Western blot analysis and kinase assay revelaed that myricetin suppressed UVB-induced phophatidylinositol-3 kinase (PI-3K) activity

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and subsequently attenuated the UVB-induced phosphorylation of Akt/p70S6K in mouse skin lysates. A pull-down assay revealed the direct binding of PI-3K and myricetin in mouse skin lysates. Our results indicate that myricetin suppreses UVB-induced angiogenesis by regulating PI-3K activity in vivo in mouse skin.

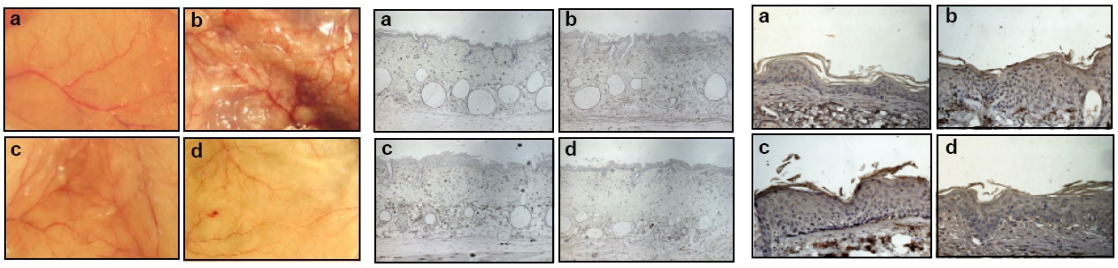

Fig. 1. Effects of myricetin on UVB-induced blood vessel formation, PECAM-1, and HIF-α expression in SKH-1 hairless mice. (A) Myricetin inhibits UVB-induced neovascularization in SKH-1 hairless mouse skin. (a) Vehicle-treated control, (b) UVB-irradiated (0.18 J/cm2), and UVB plus (c) 8 nmol of myricetin or (d) 20 nmol of myricetin-treated mice. (B) Myricetin inhibits UVB-induced PECAM-1 expression in SKH-1 hairless mouse skin. (C) Myricetin inhibits UVB-induced HIF-α expression in SKH-1 hairless mouse skin.

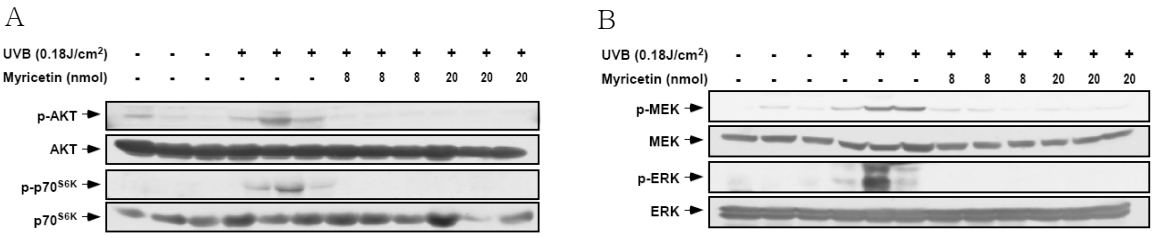

Fig. 2. Effects of myricetin on UVB-induced signaling in SKH-1 hairless mice. (A) Myricetin inhibits UVB-induced phosphorylation of Akt and $p70^{S6K}$ in SKH-1 hairless mouse skin. (B) Myricetin inhibits UVB-induced phosphorylation of MEK and ERK in SKH-1 hairless mouse skin.

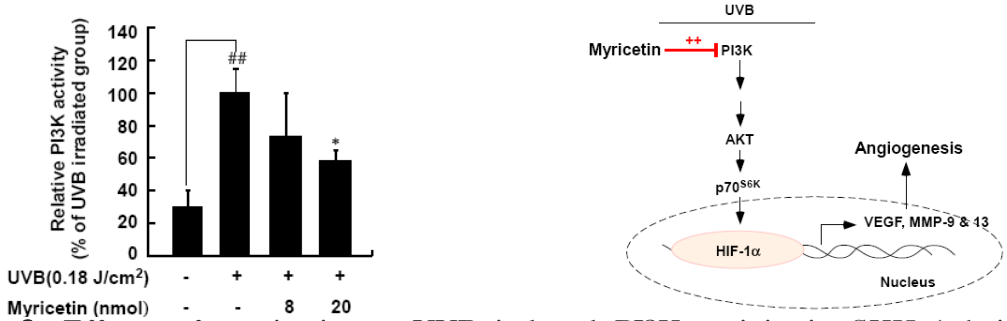

Fig. 3. Effects of myricetin on UVB-induced PI3K activiy in SKH-1 hairless mice. (A) Myricetin inhibits UVB-induced phosphorylation of Akt and $p70^{S6K}$ in SKH-1 hairless mouse skin. (B) The proposed anti-angiogenic mechanism of myricetin.