

Waranya Chatuphonprasert. 2012. **Effect of Andrographolide on Synergism of CYP1A1 Induction.** Doctor of Philosophy Thesis in Research and Development in Pharmaceuticals, Graduate School, Khon Kaen University.
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ABSTRACT

Andrographolide is a major bioactive constituent in *Andrographis paniculata*, which has been employed as a folk remedy for centuries worldwide. Cytochrome P450 1A1 (CYP1A1) is a major hepatic enzyme for metabolizing procarcinogen into active form. In this study, impacts of andrographolide on expression of CYP1A1 in mouse hepatocytes in primary cultures and *in vivo* in C57BL/6 mice were determined. *In vitro* study in primary mouse hepatocytes, the synergistic CYP1A1 induction was observed after the co-treatment of andrographolide and beta-naphthoflavone (β -NF), a typical CYP1A1 inducer. From microarray analysis, besides induction of CYP1A1 mRNA, the combination of andrographolide and β -NF modified a large number of metabolism/oxidation/reduction related-genes. Additional glutathione modulators namely reduce glutathione, N-acetyl cysteine, or L-buthionine-(S,R)-sulfoximine, greatly altered the effects of andrographolide on CYP1A1 expression. Moreover, the synergistic effect of andrographolide on CYP1A1 expression by was further observed *in vivo* in C57BL/6 mice. Andrographolide showed the synergism of β -NF induced CYP1A1 expression only in the males, but not in the females. Orchiectomy clearly diminished the synergistic effect of andrographolide and β -NF on CYP1A1 mRNA expression in the males, while testosterone supplement restored this synergism in both orchiectomized and ovariectomized mice. These findings revealed that level of glutathione and the male sex hormone, testosterone, played important roles in regulatory mechanism of CYP1A1 expression by andrographolide plus typical CYP1A1 inducers, at least in part. In conclusion, the herb-drug interaction with use of andrographolide or *A. paniculata* containing health supplement-products should be concerned according to the potential to modify the expression of several CYPs and other metabolizing enzyme related-genes. Particularly, risk of carcinogenesis from the synergism of CYP1A1 activation by andrographolide with typical CYP1A1 inducers should be noted as an alert precaution for long-term use of andrographolide.