



Anti-adipogenic and anti-diabetic effects of *cis*-3',4'-diisovalerylhellactone isolated from *Peucedanum japonicum* Thunb leaves in vitro



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ABSTRACT

Peucedanum japonicum Thunb is a medicinal plant belonging to the family Umbelliferae. This study evaluated the anti-diabetic and anti-obesity effects of *cis*-3',4'-diisovalerylhellactone (cDIVK) isolated from *Peucedanum japonicum* Thunb leaves. cDIVK (30 and 50 μ M) effectively inhibited adipocyte differentiation and fat accumulation, whereas it stimulated glucose uptake compared with the control in 3T3-L1 cells. cDIVK significantly increased AMPK activation and suppressed protein and mRNA expression of major adipogenic transcriptional factors such as C/EBP α , PPAR γ and SREBP-1c in 3T3-L1 cells. In addition, cDIVK had potential α -glucosidase inhibitory activity. These results indicated that cDIVK may act as a natural dual therapeutic agent for diabetes and obesity.

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Obesity is increasing at an alarming rate worldwide and has been implicated as a serious health risk because of the high correlation between obesity and various metabolic syndromes including diabetes mellitus, cardiovascular disease, hyperlipidemia and hypertension.¹ Obesity has been recognized as a major causative factor of insulin resistance and hyperglycemia associated with diabetes.² Insulin resistance is a major predictor in the progression of type 2 diabetes that is defined as diminished ability of tissues by reduced glucose uptake in response to normal insulin action.³ There are available pharmacologic agents such as anti-obesity and anti-diabetes medication, but they often cause adverse effects.⁴ As a result, natural products attract great attention for treating obesity and diabetes because they have fewer side effects.

Peucedanum japonicum Thunb (PJT) is a medicinal plant belonging to the family Umbelliferae that is cultivated in Japan, China and Taiwan. In Japan, PJT leaves have traditionally been used as

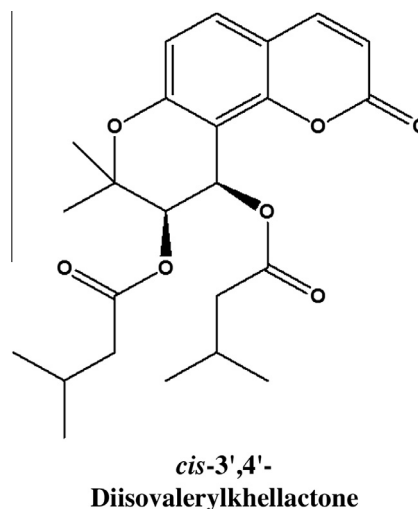


Figure 1. Chemical structure of cDIVK isolated from *Peucedanum japonicum* Thunb leaves.

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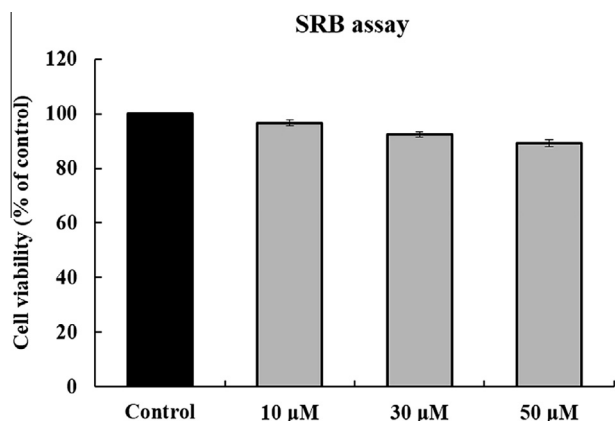


Figure 2. Effects of cDIVK on cell viability in 3T3-L1 adipocytes. Data are expressed as means \pm SE ($n = 9$).

medicinal herbs for the treatment of cough.⁵ Previous studies have demonstrated that PJT powder or the PJT hexane fraction has anti-obesity properties in mice fed a high-fat diet^{5,6} and in cells such as 3T3-L1, HepG2 and C2C12.⁷ Several coumarin compounds including *trans*- and *cis*-khellactone and khellactone esters purified from PJT have been shown to possess physiological activities, including antiplatelet aggregation,⁸ antioxidant⁹ and antagonistic effects.¹⁰ In addition, 3',4'-diisovalerylkhellactone diester has been reported to possess antiplatelet action;¹¹ however, it is still not clear if khellactone coumarins have beneficial effects on obesity and diabetes. Therefore, we investigated whether isolated *cis*-3',4'-diisovalerylkhellactone (cDIVK) as an active single compound from PJT leaves can be used as a natural therapeutic agent for obesity or diabetes using 3T3-L1 cells.

In this study, PJT leaves were obtained from Geumodo Island, Yeosu, Republic of Korea in May of 2013. Leaves of PJT were immersed in 50% methanol (MeOH) and 50% dichloromethane (1:1) for 24 h at room temperature. The extraction was repeated

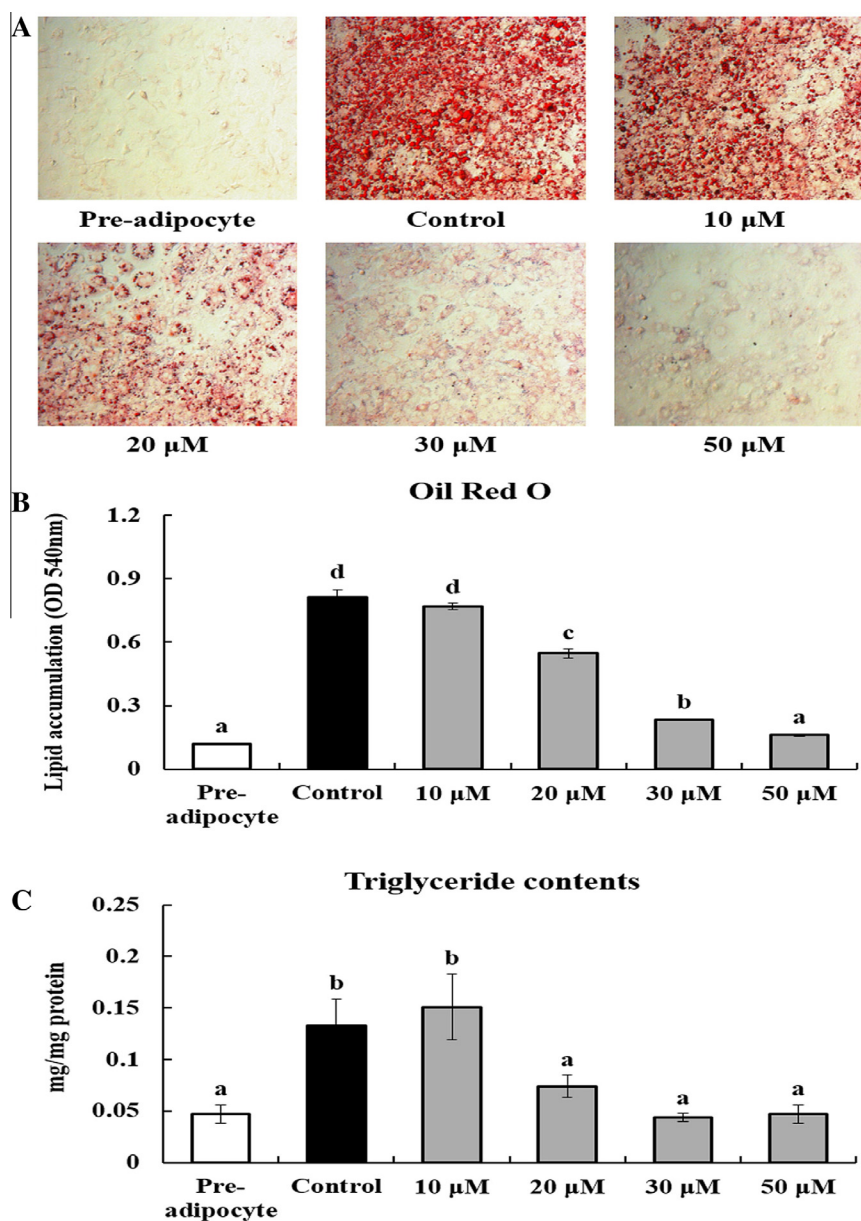


Figure 3. Effects of cDIVK on adipocyte differentiation in 3T3-L1 cells; (A) representative photographs of lipid droplets stained with Oil Red O, (B) corresponding absorbance levels of Oil Red O staining and (C) triglyceride contents. Data are expressed as means \pm SE ($n = 9$). ^{abcd}The means not sharing a common letter are significantly different among groups at $p < 0.05$ by Duncan's multiple range test.

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