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(−)-9′-*O*-(α-L-Rhamnopyranosyl)lyoniresinol from *Lespedeza cuneata* suppresses ovarian cancer cell proliferation through induction of apoptosis

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ABSTRACT

Lespedeza cuneata (Dum. Cours.) G. Don. (Fabaceae), known as Chinese bushclover or sericea lespedeza, has been used in traditional medicine to treat diabetes, hematuria, and insomnia, and it has been reported that bioactive compounds from *L. cuneata* possess various pharmacological properties. However, there has been no study to determine the active compounds from *L. cuneata* with potential activity against ovarian cancer. This study aimed to isolate cytotoxic compounds from *L. cuneata* and identify the molecular mechanisms underlying the apoptosis pathway in ovarian cancer cells. Based on cytotoxic activity identified in the screening test, chemical investigation of the active fraction of *L. cuneata* led to the isolation of nine compounds including four lignanosides (**1**–**4**), three flavonoid glycosides (**5**–**7**), and two phenolics (**8**–**9**). Cytotoxicity and the molecular mechanism were examined by methyl thiazolyl tetrazolium (MTT) assay and Western blot analysis. Of the isolated compounds, (−)-9′-*O*-(α-L-rhamnopyranosyl)lyoniresinol (**3**) demonstrated the strongest effect in suppressing A2780 human ovarian carcinoma cell proliferation in a dose-dependent manner, with an IC_{50} value of 35.40 ± 2.78 μM. Control A2780 cells had normal morphology, whereas cell blebbing, shrinkage, and condensation were observed after treatment with compound **3**. Western blotting analysis showed that compound **3** inhibited A2780 human ovarian cancer cell viability by activating caspase-8, caspase-3, and PARP, which contributed to apoptotic cell death. These results suggest that (−)-9′-*O*-(α-L-rhamnopyranosyl)lyoniresinol (**3**) has potent anticancer activities against A2780 human ovarian carcinoma cells through the extrinsic apoptotic pathway. Therefore, (−)-9′-*O*-(α-L-rhamnopyranosyl)lyoniresinol is an excellent candidate for the development of novel chemotherapeutics.

Globally, ovarian cancer is the seventh leading cancer diagnosis, the third leading gynecologic cancer, and the eighth leading cause of cancer mortality among women.[1,2] Most ovarian cancer patients receive surgery and paclitaxel and platinum-based chemotherapeutic drugs.[3,4] Over 90% of the mortality associated with ovarian cancer is caused by intrinsic or acquired drug resistance, dormant tumor cells, cancer metastasis, high cancer heterogeneity, late diagnosis, and rapid tumor progression.[5,6] These represent important reasons for the development of new effective drugs for ovarian cancer patients.[7,8] Natural products have enormous structural diversity, making them a novel source of effective pharmaceutical compounds for various diseases.[9,10]

Lespedeza cuneata (Dum. Cours.) G. Don. (Fabaceae), known by the common names of Chinese bushclover and sericea lespedeza,

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is widely distributed in many countries including Korea, China, India, and Australia.[11] It is a warm-season perennial legume that grows in various habitats including prairies, woodlands, and swamp and even in high drought and shade conditions.[12] *L. cuneata* has been used in traditional medicines to treat diabetes, hematuria, and insomnia and protect the kidney, liver, and lung.[13,14] *In vitro* and *in vivo* studies of this medicinal plant have demonstrated that *L. cuneata* showed hepatoprotective effects[13,15,16] and inhibition of nitric oxide (NO) production,[11,17] as well as antidiabetic effects.[11] Recent studies reported that extracts of *L. cuneata* showed inhibitory effects on inflammatory mediators in LPS-activated RAW264.7 cells and paw edema in carrageenan-stimulated rats,[18] as well as antioxidant, tyrosinase inhibition, and cytotoxic activities against several cancer cell lines including A549, HeLa, Hep3B, and Sarcoma180.[19] Previous phytochemical investigations on the aerial parts of *L. cuneata* led to the identification of various compounds such as steroids, phenolics, flavonoids,[14,17,20] phenylpropanoids,[13,21] lignans,[15,21] and phenyldilactones.[22] Several lignans in *L. cuneata* exhibited hepatoprotective[15] and anti-ulcerative colitis activities,[21] and flavonoids identified in *L. cuneata* are reported to have hepatoprotective[16] and NO inhibitory effects.[17] Although a recent pharmacological study of extract of *L. cuneata* reported its *in vitro* anti-cancer activity against several cancer cell lines, [19] there has been no study to determine the types of active compounds from *L. cuneata* with potential activity against ovarian cancer.

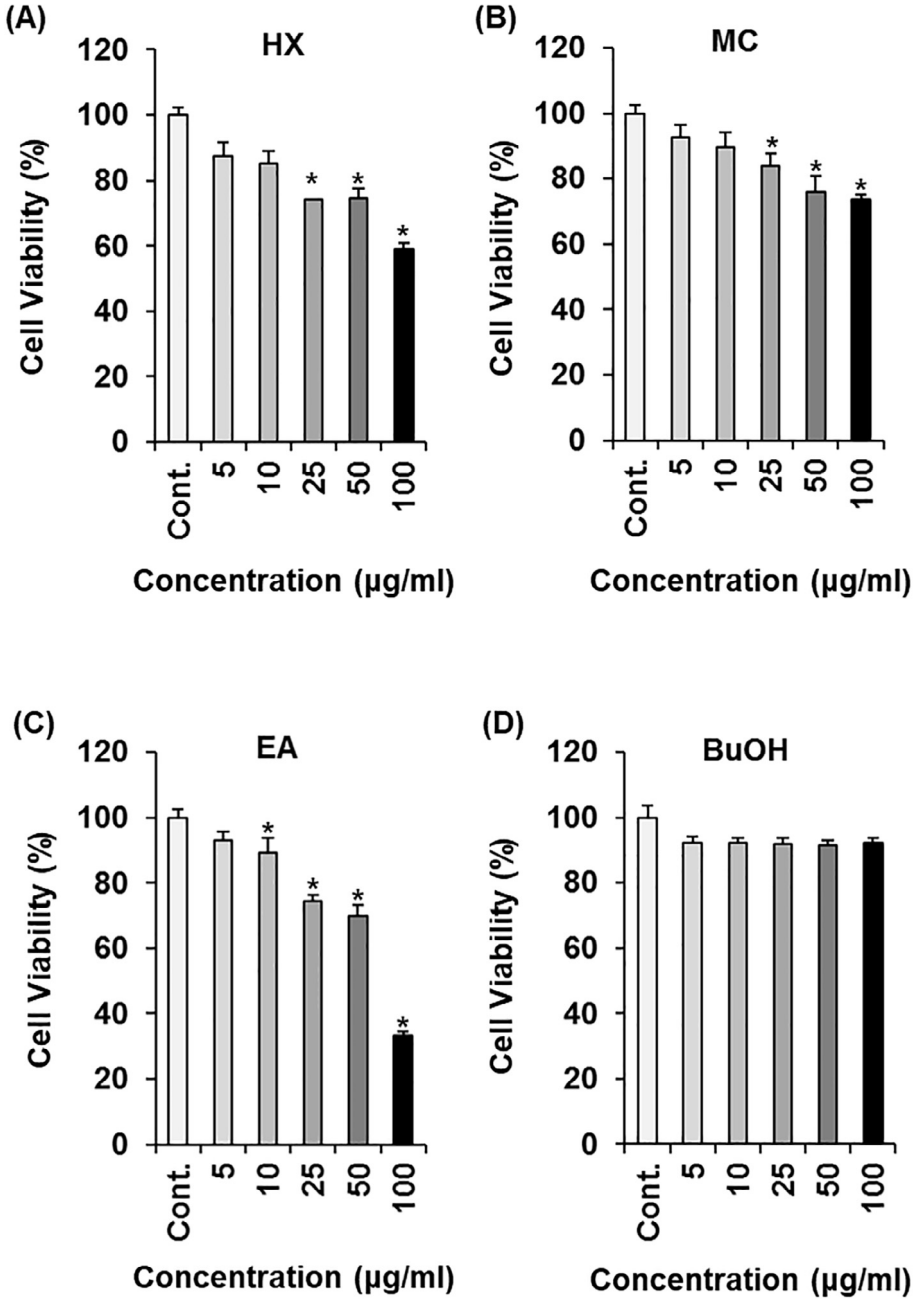

Fig. 1. Effects of fractions from the *L. cuneata* methanolic extract on A2780 cell viability. Cytotoxic effects were shown by the hexane (HX) (A), dichloromethane (MC) (B), ethyl acetate (EA) (C), and *n*-butanol (BuOH) (D) fractions on A2780 human ovarian carcinoma cells. Cell viability assays were done in triplicate for each assay and were repeated at least three times. $^{*}p < .05$ compared to the not-treated value.