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Phytotoxicity and cytotoxicity of disesquiterpene and sesquiterpene coumarins from *Ferula pseudalliacea*

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ABSTRACT

Relative toxicity of a new disesquiterpene- and five sesquiterpene coumarins from the roots of *Ferula pseudalliacea* was investigated on tobacco cells, as a plant model cell line. The effects of these compounds on the germination of certain weeds and crop plants (from solanaceae) were evaluated as well. The cytotoxic effects of these compounds were also evaluated on human cancer cell line, HeLa. The highest inhibitory effect on the growth of tobacco cells was observed by sanandajin and farnesiferol B. Sanandajin also remarkably inhibited seed germination of all tested weeds and plants. Sanandajin, farnesiferol B, and kamolonol acetate displayed the highest potency against HeLa cells with IC_{50} of 2.2, 6.7, and 4.9 μM, respectively. The results of the present investigation indicated that disesquiterpene and sesquiterpene coumarins isolated from *F. pseudalliacea* root extract can be considered as potent herbicides and cancer chemopreventive agents.

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1. Introduction

Noxious weeds and non-native invaders are of ever growing factors which limit crop production and are usually controlled by vast application of herbicides. Increased application of herbicides however, is considered a risk to human health and the environment as well. The capability of accurately predicting the herbicidal activity and site of action of a new chemical class without extensive laboratory studies would be worth tens of millions of dollars to the herbicide industry (Duke, 1990). Selective herbicides control specific weeds, protect crops and allow the intensification and spread of key crops such as corn, rice, soybeans and wheat. They provide a highly efficient, cost-effective, flexible and convenient method of in-crop weed control. Several plant materials and their constituents have been reported to have sufficient phytotoxicity to act as natural herbicides or allelochemicals (Duke et al., 2000; Pandey, 1996; Pandey et al., 2005). These compounds may directly or indirectly influence on other plants through leaching from roots, leaves or volatile emissions (Taiz and Zeiger, 2010; Weir et al., 2004). Their phytotoxicity is attributed to their ability to change the normal metabolic processes in other plants, including respiration, cell division, growth and development, and enzyme activity (Zeng et al., 2008). Oxidative phosphorylation uncouplers, mitosis inhibitors, fatty acid, amino acid, and lipid biosynthesis inhibitors are of major categories of herbicides whose their mode of action have been widely tested (Duke, 1990).

Application of natural herbicides has been recently increased as safer and more environmental friendly for weed control. So far some natural products have been used as herbicides (Duke et al., 2000; Macías, 1995). For example, Bialaphos was a commercial natural herbicide produced by fermentation of *Streptomyces hygroscopicus* and *Streptomyces viridochromeogenes* (Murakami et al., 1986). Trans, trans-germacranolide sesquiterpene lactones costunolide, parthenolide, and their 1,10-epoxy and 11,13-dihydro derivatives showed inhibitory effects on the growth and germination of certain mono and dicotyledonous species in a similar manner to that of the commercial herbicide Logran (Macías et al., 2000). Nonetheless, herbicidal potential of a large number of plant constituents has not been studied adequately.

Many phytotoxins produced by plants are secondary metabolites i.e., terpenes, tannins, steroids, quinines, flavonoids and coumarins (Li et al., 2010). Cytostatic activity of coumarins in plant cells in vitro was discovered (Gawron and Glowniak, 1987). Phytotoxic effects of methoxycoumarins from *Myrraya paniculata* was reported by Jiwajinda et al. (2000). Inhibition of ATPases and acid phosphatases activities accompanied by ultrastructural damages

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were induced in meristematic cells of *Allium cepa* root tips by 4-hydroxycoumarin, 7-hydroxycoumarin, psoralen, and xanthotoxin (Podbielkowska et al., 1996). Inhibitory effects of some synthetic phosphorus-containing coumarin derivatives on the growth of the shoots of pea, wheat, and cucumbers have been also reported by Aleksieva et al. (1995).

Secondary metabolites of the plants have also been regarded as potential chemotherapeutic agents for combating cancers. Podophyllotoxin, Taxol, and Topotecan are major instances of such compounds (Cragg and Newman, 2009). There are some studies about the cytotoxic activity of sesquiterpene coumarins from genus *Ferula*, such as umbelliprenin from *F. szowitsiana*, farnesiferol C from *F. assa-foetida*, umbelliprenin, farnesiferol A, gummosin and badrakemone from *F. persica var. persica* (Barthomeuf et al., 2008; Lee et al., 2010; Shahverdi et al., 2006).

The genus *Ferula* (Apiaceae) comprises about 180 species which grow mainly in central Asia, the Middle East, and central Europe (Pimenov and Leonov, 2004). This genus is well documented as a good source of biologically active compounds such as monosaccharides, sulfur-containing derivatives, coumarins, sesquiterpenes, sesquiterpene coumarins, sesquiterpene lactones and daucane esters (Abd El-Razek et al., 2001; Iranshahi et al., 2007; Kajimoto et al., 1998; Kapoor, 1990). Sesequiterpene coumarins are built up of a common coumarin group and a sesquiterpene moiety, therefore more extensive and promising biological properties can be expected from this class of natural compounds. The sesquiterpene coumarins isolated from genus *Ferula* have wide range of biological activities such as anticoagulant, antibacterial, antiviral (anti HIV), spasmolytic, anti-inflammatory, P-glycoprotein (P-gp) inhibitory and cytotoxic properties (Abd El-Razek et al., 2003; Nazari and Iranshahi, 2011). Therefore, further investigations on biological activities of coumarin derivatives of *F. pseudalliacea* seem to be necessary for completion of the knowledge about the potentials of this valuable class of natural products.

The aim of the present study was to evaluate the effects of disesquiterpene and sesquiterpene coumarins from *F. pseudalliacea* on the growth of tobacco cells and germination of certain weeds and crop plants seeds. The cytotoxic effects of these compounds were also evaluated on human cancer cell line, HeLa. We have previously reported the extraction and identification of a new disesquiterpene- and five sesquiterpene coumarins from *F. pseudalliacea* roots (Dastan et al., 2012). It opens new approaches on possible use of these compounds as herbicide in management of the weed and to our knowledge; this is the first report on the phytotoxicity and cytotoxicity of disesquiterpene and sesquiterpene coumarins.

2. Materials and methods

2.1. Plant material

Different parts of *F. pseudalliacea* plants were collected from Sanandaj, Kurdistan province, Iran, in September 2012. They were identified and a voucher specimen (MPH-1197) was deposited at the Herbarium of the Institute of Forests and Rangelands Researches, Sanadaj, Iran. Plant specimen was identified by Hossein Maroufi from the same institute.

2.2. Extraction and isolation of natural compounds

The roots of *F. pseudalliacea* were separated and their constituents were extracted, purified, and identified following the previously described method with a few modifications (Dastan et al., 2012). In brief, root samples (1 kg) were crushed and extracted with 3 L of *n*-hexane during 24 h, and the extraction procedure was repeated three times. Evaporation of solvent under reduced pressure afforded 30 g of a light brown gum. Aliquots of this gum (25 g) was fractionated on a silica gel column (5 cm × 70 cm) eluted with *n*-hexane/$CHCl_3$/EtOAc mixtures of increasing polarity (100/0/0, 8/2/0, 5/5/0, 0/100/0, 0/9/1, 0/3/7, respectively) to give fractions 1–11. A preliminary thin layer chromatography test for coumarins was conducted using anisaldehyde reagent as well as observation under UV 254 and 366 nm. Based on the results of this experiment, fraction 4 (5 g) was selected and purified on a silica gel column (3 cm × 50 cm) [*n*-hexane/EtOAc (19/1) to EtOAc], to afford nine fractions (4.1–4.9). Silica gel chromatography (2 cm × 120 cm) [*n*-hexane/$CHCl_3$/EtOAc (12/7/1–2/9/9)] of fraction 4.5 afforded five fractions (4.5.1–4.5.5). Gel permeation chromatography (GPC) of fraction 4.5.1 gave sanandajin (**1**) (10 mg). Column chromatography on silica gel (1.5 cm × 120 cm) [*n*-hexane/$CHCl_3$/EtOAc (8/11/1–4/8/8)] of fraction 4.5.3 gave four fractions (4.5.3.1–4.5.3.4). Methyl galbanate (**2**) (18 mg) was isolated from fraction 4.5.3.1 on a reversed-phase (C18) column (1 cm × 170 cm) [C_3H_6O/H_2O (8/2)].

Fraction 4.8 was more purified on a silica gel column (2 cm × 100 cm) [$CHCl_3$/EtOAc (9/1–4/6)], to afford ethyl galbanate (**3**) (15 mg) and four other fractions (4.8.1–4.8.4). Fekrynol acetate (**4**) (10 mg) was obtained from fraction 4.8.3 on a semi-preparative RP-HPLC using MeOH in H_2O (75–100% MeOH) as mobile phase. Silica gel column chromatography (3 cm × 70 cm) [*n*-hexane/EtOAc (7/3–4/6)] of fraction 8 (2.0 g) afforded five fractions (8.1–8.5). Farnesiferol B (**5**) (12 mg) was obtained from fraction 8.1 on a silica gel column (2 cm × 150 cm) [*n*-hexane/EtOAc (19/1–1/1)] followed by semi-preparative RP-HPLC using MeOH in H_2O (80–100% MeOH) as mobile phase. Kamonolol acetate (**6**) (20 mg) was purified from fraction 8.4 on a silica gel column (1.5 cm × 120 cm) [*n*-hexane/$CHCl_3$ (8/2–1/9)].

2.3. Phytotoxicity bioassay

Phytotoxicity of the purified compounds extracted from the roots of *F. pseudalliacea* was assessed on suspension-cultured tobacco (*Nicotiana tabacum* L. cv. Burley 21) cells as a plant model cell line. Suspension cultures established from calli of tobacco cells (*N. tabacum* L. cv. Burley 21) that had been maintained in our laboratory for 252 subcultures. Both calli and subsequent suspensions were grown in a modified MS (Murashige and Skoog, 1962) medium without glycine and containing 3% sucrose. The medium was contained: NH_4NO_3, 20.61 mM; KH_2PO_4, 1.25 mM; $CaCl_2$, 2.99 mM; $MgSO_4$, 1.50 mM; $MnSO_4$, 0.1 mM; Fe-EDTA, 0.1 mM; H_3BO_3, 0.1 mM; $CoCl_2$, 0.11 mM; $CuSO_4$, 0.1 mM; Na_2MoO_4, 1.03 mM; $ZnSO_4$, 29.91 mM, KI, 5 mM, at pH 5.8. All chemicals were purchased from Sigma (Tokyo, Japan). Suspension-cultured cells were grown at 25 °C in darkness on an orbital shaker at 120 rpm and were sub-cultured every 7 days, when they were still in their logarithmic growth phase (Ghanati et al., 2001). Frequent subcultures provided us homogenous and undifferentiated batches of tobacco cells. Seven day old tobacco cells were treated with 0.83 ppm of each compound for 1 h. After these periods, the cells were harvested on Bukner funnel using nylon mesh (42 μm) under reduced pressure, washed 3 times with fresh media and returned to the new control MS media. The same procedure of filtration and washing was conducted on control cells. The cells were allowed to grow in control media for further 1 week in order to determine the inhibitory effect of tested compounds on their growth (Yamamoto et al., 1994). The cells were then harvested and weighed. Phytotoxicity of the tested compounds was determined regarding to the change of fresh weight of tobacco cells in the control media.

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