Chemical profiling and cytotoxic activity of aqueous extract of Veronica peduncularis M.Bieb.: A chemotaxonomical approach

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ABSTRACT

Background and Aims: Genus Veronica (Plantaginaceae) is represented by 79 species in Turkish flora, 26 of which are endemic. Veronica species have a variety of uses including diuretic, anticancer, and rheumatic pains, wounds, and respiratory problems. According to phytochemical studies, Veronica species contain predominantly iridoid glucosides with some phenyl-ethanoid and flavonoid glycosides.

Methods: The aqueous extract of Veronica peduncularis M.Bieb. was tested for its cytotoxic activity on human rhabdomyosarcoma (RD) and human epidermoid carcinoma (HEp-2) cell lines using the MTT method. Chemical profile of the extract was determined by HPLC-DAD, and isolation studies were conducted.

Results: The extract was found to show concentration-dependent cytotoxicity against tested cell lines. In addition, a comparison of the iridoid fraction of Veronica peduncularis with previously isolated iridoid glucosides on the HPLC-DAD system, showed the presence of aucubin, amphicoside, veratroyl catalpol, and veronicoside in this fraction. On the other hand, isolation and structure elucidation of plantamajoside and 4′-O-methylisoscutellarein-7-O-2′-O-(6‴-O-acetyl-ß-D-allopyranosyl)-ß-D-glucopyranoside from the phenolic fractions were performed by serial chromatographic and spectroscopic methods.

Conclusion: To the best of our knowledge, this is the first cytotoxic activity and phytochemical study on the titled plant. The presence of iridoid glucosides and 8-hydroxyflavone glycosides is important for the chemotaxonomy of the genus Veronica.

Keywords: 4′-O-methylisoscutellarein-7-O-2′-O-(6‴-O-acetyl-ß-D-allopyranosyl)-ß-D-glucopyranoside, HPLC, iridoid glucosides, phenolics, plantamajoside, Veronica

INTRODUCTION

Genus Veronica formerly a member of the Scrophulariaceae family, was moved to Plantaginaceae after phylogenetic and chemotaxonomic studies (Olmstead, 2002). The genus is represented by 79 species in the flora of Turkey, 26 of which are endemic (Fischer, 1978).

Veronica species have been used as a diuretic, expectorant, antiscorbutic, and in the treatment of rheumatic pains, wounds, cough, and influenza in Turkish traditional medicine (Baytop, 1999; Fujita et al., 1995; Harput, Genc, Khan, & Saracoglu, 2011).
According to this study, IC₅₀ values of aqueous fraction were compared to reference compounds; ascorbic acid, quercetin and BHA. It was observed and the results were found to be comparable with superoxide (SO) and nitric oxide (NO) radicals, spectroscopically. Radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), was tested for its radical scavenging activity against different radicals and flavonoid glycosides (Harput et al., 2011; Saracoglu, Ozturunca, Nagatsu, & Harput, 2011; Saracoglu, Varel, Harput, & Nagatsu, 2004). Biological activity studies on Veronica extracts showed their antimicrobial, antioxidant, cytotoxic, anti-tumour, anti-inflammatory activities via in vitro and in vivo experiments (Harput, Saracoglu, Inoue, & Ogihara, 2002; Salehi et al., 2019). Additionally, it is thought that Veronica can be used as a natural food preservative, considering its antimicrobial effects (Salehi et al., 2019).

In our previous studies, water extract from Veronica peduncularis was subjected to vacuum liquid chromatography (45 g using CH₃OH: 40–63% methanol) to get 6 sub-fractions, Frs. B1-B6. Fr. B5 was subjected to polyamide column chromatography eluting with increasing concentrations of MeOH. Fraction A (Fr. A, 9.8 g) eluted with H₂O was determined as iridoid fraction according to TLC characteristics. Fr. A was dissolved in water and partitioned with n-butanol to remove the sugar part of the fraction. The refined iridoid fraction was subjected to analytical HPLC analysis to determine the iridoid composition of the plant using previously isolated iridoid glucosides as reference compounds. Fr. B (0.9 g) eluted with 25% methanol was subjected to vacuum liquid chromatography (45 g using CH₃OH: H₂O, 0%–70%) to get 6 sub-fractions, Frs. B1-B6. Fr. B5 was subjected to Sephadex LH 20 (100% methanol) to get 15 sub-fractions, Frs. D1-D15. For purification of 4’-O-methylisoucectearaline-7-O-β-D-β-acetyl-(6’’-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (7.8 mg), Fr. D12 was chromatographed on Sephadex LH 20 column (100% methanol).

**Preparation of extract and isolation of compounds**

The air-dried aerial parts of Veronica peduncularis (185 g) were extracted with 1 L MeOH for four times at 40°C. The combined extracts were evaporated under vacuum to give 45.8 g of crude MeOH extract. MeOH extract was dissolved in water and partitioned with petroleum ether to remove chlorophylls and other lipophilic compounds. The aqueous fraction (36.2 g) was subjected to polyamide column chromatography eluting with increasing concentrations of MeOH. Fraction A (Fr. A, 9.8 g) eluted with H₂O was determined as iridoid fraction according to TLC characteristics. Fr. A was dissolved in water and partitioned with n-butanol to remove the sugar part of the fraction. The refined iridoid fraction was subjected to analytical HPLC analysis to determine the indoid composition of the plant using previously isolated iridoid glucosides as reference compounds. Fr. B (0.9 g) eluted with 25% methanol was subjected to vacuum liquid chromatography (45 g using CH₃OH: H₂O, 0%–70%) to obtain 15 sub-fractions, Frs. D1-D15. For purification of 4’-O-methylisoucectearaline-7-O-β-D-β-acetyl-(6’’-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (7.8 mg), Fr. D12 was chromatographed on Sephadex LH 20 column (100% methanol).

**Plantamajoside (5):** White amorphous powder. UV λₘₐₓ (MeOH) nm: 291, 330. NMR data are consistent with the literature (Kawada, Yoneda, Asano, Kan-No, & Schmid, 2006; Ravn, Nishibe, Sasahara, & Li, 1990; Zou et al., 2008). Furthermore, iridoid glucosides are characteristic of the genus Veronica and play an important role in the reclassification of the genera in the families of Scrophulariaceae and Plantaginaceae (Jensen, Albach, Ohno, & Grayer, 2005). Therefore, in the current study, the cytotoxic effect of aqueous extract of Veronica peduncularis was evaluated in addition to the determination of the chemical profile of the extract by HPLC-DAD for indoid glucosides and isolation studies for phenolic compounds.

**MATERIALS AND METHODS**

**Plant materials**

 Veronica peduncularis Bieb. (Plantaginaceae) was collected from Macka, Trabzon, Turkey. A voucher specimen (HUEF 09012) was deposited in the Herbarium of the Faculty of Pharmacy. The authentication of plant specimens was made by Serdar Aslan, Duzce University, Duzce, Turkey (previous address: Gazi University, Ankara, Turkey).

**General**

Polyamide (50–160 μm, Fluka, Seelze, Germany), Sephadex LH-20 (GE Healthcare, Chicago, IL, USA), and thin-layer chromatography (TLC) plate (Kieselgel 60 F254, 0.20mm, Merck, Darmstadt, Germany) were used in chromatography system. In vacuum liquid chromatography (VLC), samples were chromatographed on LiChroprep C18 (40–63 μm, Merck, Darmstadt, Germany). Minimum essential medium Eagle with Earl’s salts (MEM) and Dulbecco’s phosphate-buffered saline (DPBS) were obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Antibiotics (penicillin and streptomycin) and fetal bovine serum (FBS) and were purchased from Biochrom AG (Berlin, Germany).

**Determination of cytotoxicity by MTT method**

In the determination of the cytotoxic activity of the extract, MTT [3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyl tetrazolium bromide] method developed by Mossman was used (Moss-
man, 1983). Activity studies were performed on HEp-2 (Human Epidermoid Carcinoma) and RD (Human Rhabdomyosarcoma) series, which are cancer cells of human origin. Cells were incubated in MEM containing 10% fetal bovine serum and 1% penicillin/streptomycin solution. 100 µL cell suspensions at a concentration of 1x10^5 cells/mL for RD and HEp-2 were transferred to 96 well plates. After incubating for 24 hours in an incubator containing 5% CO₂, 95% humidity at 37°C, supernatant in the wells was aspirated and 100 µL of extract solutions (200 and 400 μg/mL) in the medium was added and kept in the incubator for another 48 hours. At the end of the period, the wells were washed with 100 µL of fresh medium and then 100 µL of new medium was added to each well. 10 µL of MTT solution in PBS (phosphate-buffered saline) at a concentration of 5 mg/mL was added to each well and the wells were incubated for another 4-6 hours. During the incubation, the dehydrogenase enzyme in living cells reduced MTT to the purple formazan crystals. After incubation, 100 µL of 10% SDS (Sodium dodecyl sulfate) solution was added to the wells and incubated for 20 hours to dissolve the formazan crystals. The absorbance was measured at 577/655 nm (Harput, Genc, & Saracoglu, 2012; Saracoglu & Harput, 2012).

HPLC analysis
HPLC analyses were carried out on a Dionex HPLC instrument system (Thermo Fisher Scientific, Waltham, MA, USA): P680 HPLC pump, Dionex ASI-100 autosampler, and Dionex Photodiode Array Detector. The column was Hichrom-Nucleosil 100-5 C18 (5 µm, 250 mm X 4.6 mm, Berks, UK) and the column temperature was maintained at 27°C. 20 µL injection volume and 1 mL/min flow rate were used for each experiment. Samples were passed through a 0.45 µm filter and injected into the HPLC system. The mobile phase consisted of phosphoric acid (1%) in water (solution A), and acetonitrile (solution B). The gradient system developed by authors was used for elution of samples as 95% A, 5% B for 0–15 min; 80% A, 20% B at 20th min; 70% A, 30% B at 45th min, and then 67% A, 33% B at 52nd min.

RESULTS AND DISCUSSION
In this study, the cytotoxic activity of V. peduncularis was evaluated on two cancer cell lines; HEp-2 and RD. The aqueous extract was tested at different concentrations, 200 and 400 µg/mL. While the extract showed slight cytotoxicity on HEp-2 cells with the cell viability value of 89.87% ± 3.6 and 36.66% ± 2.7, it showed moderate cytotoxicity with 85.62% ± 3.8 and 8.43% ± 3.2 against RD cells at 200 and 400 µg/mL, respectively (Figure 1). According to Saracoglu et al. (2011), cytotoxic activities of V. cuneifolia subsp. cuneifolia D. Don and V. cymbalaria Bodar aqueous extracts were tested on the same cell line, IC₅₀ values of extracts were found between 250.4-546.5 µg/mL with similar results to our results (IC₅₀: 230 and 390 µg/mL for RD and HEp-2, respectively). According to Harput et al. (2002), five different Veronica species; V. polita Fries, V. persica Poiret, V. hederifolia L., V. pectinata L. var. glandulosa Riek ex M.A., V. cymbalaria were tested for their cytotoxic effects on KB epidermoid carcinoma and B16 melanoma cells. In that study, it was found that chloroform fractions of methanolic extracts were more potent than the main methanolic extracts, although water-soluble portions didn’t exhibit cytotoxic activity on the two tested cell lines.

![Figure 1. Cytotoxic activity of V. peduncularis aqueous extract.](image)

Main iridoid glucosides of the iridoid fraction of the extract were determined with a specific HPLC-DAD method. The previously isolated iridoid glucosides from V. cymbalaria and V. cuneifolia subsp. cuneifolia, whose structures were elucidated by advanced NMR techniques, were used as reference (Saracoglu et al., 2011) (Figure 2). The comparison of the iridoid fraction with the reference compounds showed the presence of aucubin (1), amphicoside (2), veratroyl catalpol (3), and veronicoside (4) in this fraction (Figure 3). Their presences were confirmed by comparing their retention time and UV spectra with those of reference compounds (Figure 4). Iridoid glucosides are the most abundant constituents in Veronica species (Xue et al., 2019).

![Figure 2. HPLC chromatogram of iridoid fractions from V. peduncularis and the mixture of reference iridoid glucosides (aucubin, amphicoside, veratroyl catalpol and veronicoside) at 200 nm.](image)
Veronica species are classified into 4 sections; Chamaedrys, Alsinibe, Beccabunga, and Veronicastrum. *V. peduncularis* belongs to section Chamaedrys (Fischer, 1978). It is known that 4-substituted iridoid glucosides are absent in section Chamaedrys (Saracoglu et al., 2011; Taskova, Albach, & Grayer, 2004). In the present study, the HPLC results also support this knowledge about the lack of such molecules in section Chamaedrys.

Besides the chemotaxonomic importance of iridoid glucosides, they have also various biological effects as antitumor, anti-inflammatory, hepatoprotective, neuroprotective, hypoglycemic, hypolipidemic (Saracoglu & Harput, 2012; Wang et al., 2020). In the current study, the cytotoxic activity of the aqueous extract was studied and the iridoid glucosides profile of the extract was determined. Iridoid glycosides may contribute to the cytotoxic effect of the extract. According to Saracoglu and Harput (2012), while aucubin had no activity on RD and HEP-2 cells, veratroyl catalpol showed cytotastic activity. Veronicoside exhibited a cytotoxic effect on RD and HEP-2 cell lines with IC50 values of 153.3 and 355 µM, respectively. Moreover, amphicoside showed cytotoxic effect only on HEP-2 cell line with IC50 values of 340 µM. In another study, amphicoside had stronger anti-hepatocarcinoma activity on the Hep-G2 cell line than the reference compound, 5-fluorouracil. On the other hand, veronicoside showed strong cytotoxic activity on the proliferation of Hep-G2 cells (Yin et al., 2016).

Phenolics naturally occurring in plants are potential antioxidant compounds and important for the chemotaxonomy of genus Veronica. They may possess cytotoxic activity via their radical scavenging or prooxidant effects (Harput et al., 2012). For that reason, it is important to identify the phenolic profile of *V. peduncularis*. As a result of our isolation studies on phenolic fractions, two compounds; plantamajoside (5) and 4'-O-methylisoscutellarein-7-O-2''-O-(6''''-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (6) were isolated from aqueous extract of *V. peduncularis* (Figure 3). Compound 6 is an acylated 8-hydroxyflavone glycoside. It has been previously reported that allose-containing acylated 8-hydroxyflavone glycosides are important as chemotaxonomic markers, especially for section Alsinibe and section Chamaedrys (Albach et al., 2005; Tomas-Barberan et al., 1988). The presence of these types of compounds in *V. peduncularis* (Section Chamaedrys) was detected chromatographically previously, however, this is the first isolation study of compounds (5 and 6) from *V. peduncularis* (Albach et al., 2005; Tomas-Barberan et al., 1988). Compound 5 was previously isolated from *V. orsifolia* Ten. (Sin: *V. fuhsii*) (Ozipek, Saracoglu, Kojima, Ogihara, & Calis, 1999), and *V. beccabunga* L. (Jensen, Opitz, & Gotfredsen, 2011). Compound 6 was isolated from another Veronica species; *V. pectinata* var. *glandulosa* (Saracoglu, Harput, et al., 2004) and *V. orientalis* (Albach et al., 2003).
CONCLUSIONS

Cytotoxic activity of V. peduncularis was performed on HEp-2 and RD cancer cell lines. Four iridoid glucosides, aucubin (1), amphicoside (2), veronicoside (3), and veratroyl catalpol (4) were determined from iridoid fraction of V. peduncularis by the HPLC-DAD method. Isolation of plantamajoside (5) and 4′-O-methyliscutellarein-7-O-2′″O-(6″-O-acetyl-β-D-allopyranosyl)β-D-glucopyranoside (6) were also performed. To the best of our knowledge, this is the first cytotoxic activity and phytochemical study on the titled plant. The current study contributed to chemotaxonomic studies on Veronica species in terms of iridoid glucosides and 6-hydroxyflavone glycosides.

Figure 4. UV spectra of reference compounds (1A-4A) and iridoid glucosides in iridoid fraction of V. peduncularis (1B-4B).
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