**Natural Product Sciences**
16(4) : 223-227 (2010)

# DNA Topoisomerase I Inhibitory Activity of Stilbenes and Oligostilbenes from Leaf and Stem of *Vitis amurensis*

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**Abstract –** The DNA Topoisomerase I (DNA Topo I) inhibitory effect of ten isolated compounds (**1**–**10**) from the leaf and stem of *Vitis amurensis* were examined. Among them, amurensin G (**5**) and *r*-2-viniferin (**7**) showed high potent inhibitory activity against DNA Topo I. DNA Topo I, an important target for anticancer drugs, can cause DNA breaks and play a key role during cell proliferation, transcription and repair. Thus, the results suggest that the selected compounds (**5** and **7**) from *Vitis amurensis* have a possibility as DNA Topo I-targeting anticancer agents.
**Keywords –** *Vitis amurensis*, Stilbenes and Oligostilbenes, DNA Topo I

## Introduction

DNA topoisomerases are enzymes that can alter the topology of DNA and to be implicated in various cellular processes, including replication, recombination, transcription, and repair (D'Arpa and Liu, 1989; Pommier, 1993; Wang, 1996; Redinbo *et al.*, 1998; Stewart *et al.*, 1998). Two types of DNA topoisomerases (DNA Topo I and II) have been isolated from prokaryotes and eukaryotes. DNA Topo I is one of the most important enzymes that can break a single DNA strand, while DNA Topo II can break both strands with the requirement of ATP for full activity. Because of the involvement in many cellular processes, both DNA Topo I and DNA Topo II have been target enzymes for cancer treatment, and inhibitors of topoisomerases have been considered as important targets of anticancer drugs in the clinic (Topcu, 2001; Chowdhury *et al.*, 2002). Many anticancer agents, such as amsacrine, ectomposide, teniposide, and doxorubicin have identified, which are inhibitors of DNA Topo II. Compared with DNA Topo II inhibitors, fewer inhibitors of DNA Topo I have been found and the most widely studied and characterized inhibitors are campotothecin and its derivatives (Hsiang *et al.*, 1985; Hsiang and Liu, 1988).

In the development of new inhibitors, plants have formed the basis for traditional medicine systems (Annon., 1998), natural products from plant sources can be attractive target and may also serve as a suitable lead for the production of semi-synthetic agents. Therefore, there is a lot of interest in discovering novel inhibitors from natural products as potential lead compounds for drug development.

*Vitis amurensis* Rupr. (Vitaceae), a wild-growing grape, is widely distributed in Korea, China, and Japan. Its fruit has been used as the raw materials for juice and wine in Korea, and its root and stem have been used as a traditional medicine for the treatment of cancer and various pains including injury, rheumatalgia, stomachache, neuralgic pain, and abdominal pains (Huang and Lin, 1999; Jang *et al.*, 2007). The roots of *V. amurensis* possess anti-inflammatory (Huang *et al.*, 2001), antioxidant (Jang *et al.*, 2007) and anti-tumor activity (Lee *et al.*, 2004; Lee *et al.*, 2006), and contain diverse stilbenes and oligostilbenes. In addition, the seeds of *V. amurensis* also possess antioxidant activity (Wang *et al.*, 2000) and the fruits have anti-allergic effect (Kim *et al.*, 2008). In recent studies, we isolated various stilbenes and oligostilbenes from the leaf and stem of *V. amurensis*, which possessed cytotoxic activity (Ha do *et al.*, 2009a), antioxidant and lipoxygenase inhibitory activity (Ha do *et al.*, 2009b), and anti-microbial activity (Yim *et al.*, 2010). And other groups reported that stilbene oligomers showed

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significant inhibitory activity against DNA Topo II (Yamada *et al.*, 2006a; Yamada *et al.*, 2006b; Yamada *et al.*, 2006c). Thus, this study is aimed to evaluate for the inhibitory effect of the isolated stilbenes and oligostilbenes from leaf and stem of *V. amurensis* on DNA Topo I.

**Table 1.** Inhibitory effects of the extracts / fractions of *V. amurensis* for DNA topoisomerase I

| Extracts/ fractions | [a)] Inhibition for Topoisomerase I (%) | |
|---|---|---|
| | 50 μg/mL | 100 μg/mL |
| 70% EtOH | 45.86 ± 3.06 | 69.31 ± 12.36 |
| MeOH | 46.51 ± 6.24 | 65.32 ± 15.00 |
| EtOAc | 53.64 ± 11.18 | 94.42 ± 7.30 |
| BuOH | 65.37 ± 12.75 | 93.81 ± 13.63 |

[a)] Inhibition ratio of relaxation. Inhibitory effects were displayed as mean ± S.E. of triplicate experiments.

## Results and Discussion

**Results** – *DNA Topo I inhibitory activity of the extracts/ fractions and the isolated compounds from V. amurensis* – An assay was carried out for the inhibition of DNA Topo I using the 70% EtOH and MeOH extracts and subsequent partitions of the MeOH extract, including EtOAc and BuOH. As showed in Table 1 and Fig. 2, the EtOAc and BuOH fractions presented high potent DNA Topo I inhibitory activity at the concentration of 100 μg/mL (94.42 ± 7.30 and 93.81 ± 13.63%, respectively). Thus, the subsequent isolation of these fractions was performed led to isolate ten compounds (**1 - 10**) (Fig. 1). The identities of these compounds were verified by comparing their physicochemical and spectroscopic data to published values for piacetannol (**1**) (Vastano *et al.*, 2000), (+)-ampelopsin A (**2**) (Vastano *et al.*, 2000), (+)-ampelopsin F (**3**) (Tanaka

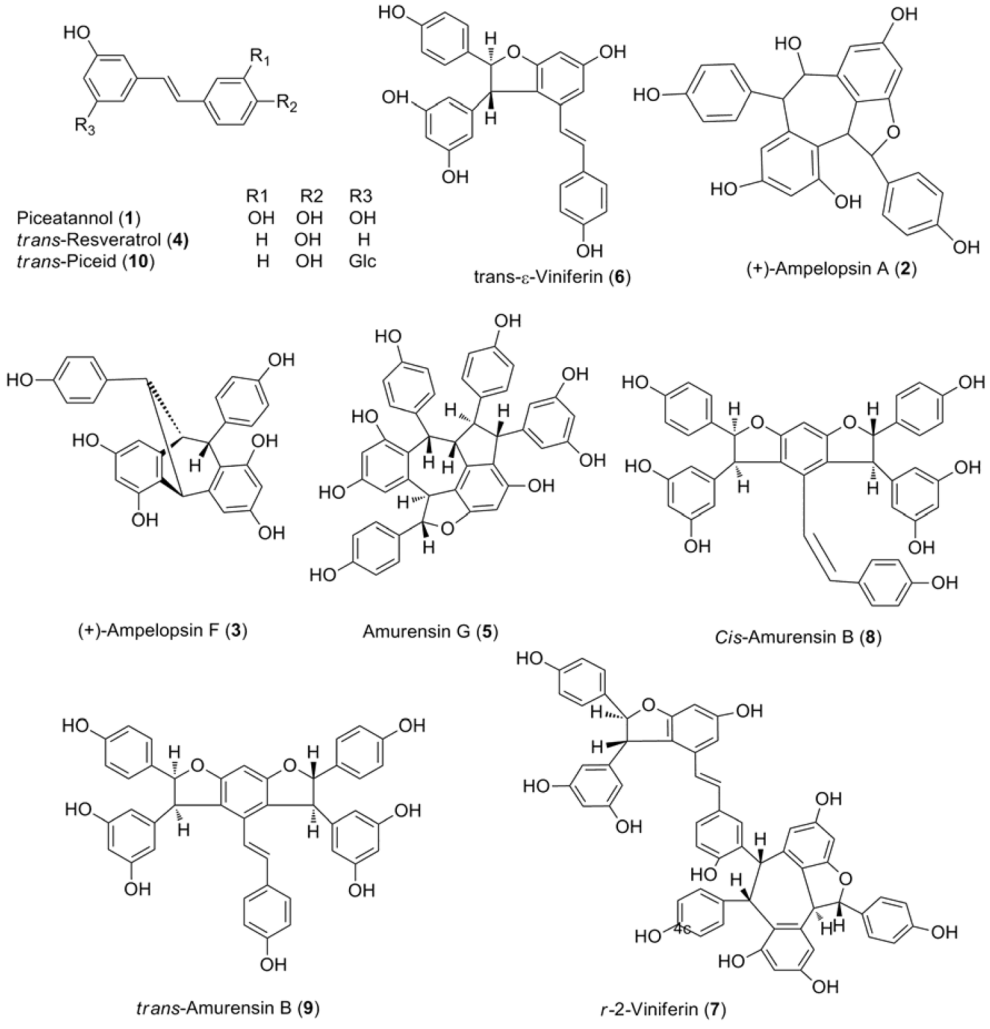


**Fig. 1.** Chemical structures of the isolated compounds **(1 - 10)** from the leaf and stem of *V. amurensisi.*

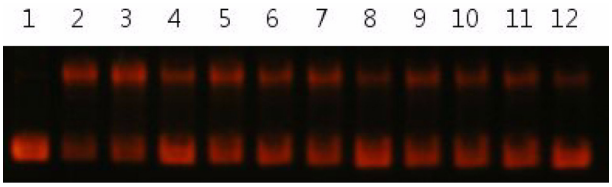


**Fig. 2.** DNA Topoisomerase I inhibitory activity of the extracts and subsequent partitions.

Lane 1: supercoiled DNA only; lane 2: supercoiled DNA + topoisomerase I; lane 3: supercoiled DNA + topoisomerase I + camptothecine (20 μM); lane 4: supercoiled DNA + topoisomerase I + camptothecin (100 μM); lane 5: supercoiled DNA + topoisomerase I + 70% EtOH extract (50 μg/mL); lane 6: supercoiled DNA + topoisomerase I + 70% EtOH extract (100 μg/mL); lane 7: supercoiled DNA + topoisomerase I + EtOAc fraction (50 μg/mL); lane 8: supercoiled DNA + topoisomerase I + EtOAc fraction (100 μg/mL); lane 9: supercoiled DNA + topoisomerse I + MeOH extract (50 μg/mL); lane 10: supercoiled DNA + topoisomerse I + MeOH extract (100 μg/mL); lane 11: supercoiled DNA + topoisomerse I + BuOH extract (50 μg/mL); lane 12: supercoiled DNA + topoisomerse I + BuOH extract (100 μg/mL)

**Table 2.** Inhibitory effects of the compounds (**1 - 10**) of *V. amurensis* for DNA topoisomerase I

| Compounds | [a] Inhibition for Topoisomerase I (%) | |
|---|---|---|
| | 20 μM | 100 μM |
| [b]Camptothecin (**CPT**) | 27.49 ± 5.25 | 59.95 ± 7.18 |
| Pceatannol (**1**) | 58.10 ± 3.63 | 79.62 ± 3.10 |
| (+)-Ampelopsin A (**2**) | 33.83 ± 3.35 | 29.84 ± 5.93 |
| (+)-Ampelopsin F (**3**) | 48.27 ± 12.12 | 37.49 ± 10.79 |
| Resveratrol (**4**) | 33.13 ± 21.66 | 61.33 ± 15.39 |
| Amurensin G (**5**) | 83.12 ± 8.01 | 105.15 ± 8.89 |
| *Trans*-ε-Viniferin (**6**) | 46.32 ± 13.99 | 83.60 ± 13.65 |
| 2-*r*-Viniferin (**7**) | 65.00 ± 13.83 | 96.23 ± 9.71 |
| *Cis*-Amurensin B (**8**) | 35.73 ± 11.95 | 53.53 ± 10.78 |
| *Trans*-Amurensin B (**9**) | 36.26 ± 15.37 | 61.71 ± 12.63 |
| Piceid (**10**) | 52.10 ± 10.94 | 56.99 ± 12.47 |

[a] Inhibition ratio of relaxation. Inhibitory effects were displayed as mean ± S.E. of triplicate experiments. [b] Positive control.

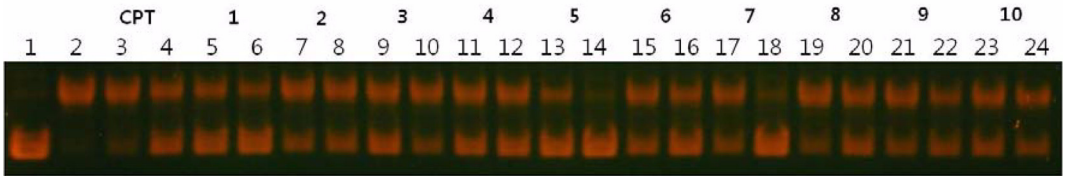


**Fig. 3.** DNA topoisomerase I inhibitory activity of compounds (**1-10**) from *V. amurensis*.

Lane 1: supercoiled DNA alone; lane 2: supercoiled DNA + topoisomerase I; lane 3: supercoiled DNA + topoisomerase I + camptothecine (20 μM); lane 4: supercoiled DNA + topoisomerase I + camptothecin (100 μM); lane 5,7,9,11,13,15,17,19,21,23: supercoiled DNA + topoisomerase I + compounds **1 - 10** (20 μM); lane 6,8,10,12,14,16,18,20,22,24: supercoiled DNA + topoisomerase I + compounds **1 - 10** (100 μM).

*et al.*, 1998; Takaya *et al.*, 2002), resveratrol (**4**) (Jin *et al.*, 2002), amurensin G (**5**) (Huang *et al.*, 1999), *trans*-ε-viniferin (**6**) (Li *et al.*, 1996), *r*-2-viniferin (**7**) (Korhammer *et al.*, 1995), *cis*-amurensin B (**8**) (Ha do *et al.*, 2009b), *trans*-amurensin B (**9**) (Huang and Lin, 1999), and *trans*-piceid (**10**) (Teguo *et al.*, 1996). All the isolated compounds (**1 - 10**) were evaluated for the DNA Topo I inhibitory activity using DNA Topoisomease I Drug screening kit (TopoGEN, Inc.) (Table 2 and Fig. 3). Campothecin, known as a DNA Topo I poison (Hsiang *et al.*, 1985) that results in DNA breaks (Nelson and Kastan, 1994), cell cycle arrests at G1, S, and G2/M cell cycle checkpoint (Kastan *et al.*, 1991), was used as a positive control. The result indicated that the isolated compounds possessed inhibitory effect on the DNA relaxation induced by DNA Topo I enzyme. However, **1**, **4 - 9** displayed considerable inhibitory effect against DNA Topo I at both two test concentrations (20 and 100 μM) as compared to those of camptothecin (Table 2, Fig. 3). Administered 100 μM, **5** and **7** exhibited the DNA Topo I inhibition ratio of relaxation were 105.15% and 96.23%, respectively. Especially, under high concentration of DNA Topo I enzyme, the highly inhibitory activity against DNA Topo I was still observed to **5** and **7** (data not shown). In contrast, camptothecin did not inhibit DNA Topo I activity in this condition, suggesting **5** and **7** have high potent anti-Topo I activity.

## Discussion

In previous reports, we investigated cytotoxic activity (Ha do *et al.*, 2009a) of stilbenes and oiligostilbenes from leaf and stem of *V. amurensis*. In the study, **5** showed significant cytotoxic activity against L1210, K562, and HTC116 cancer cell lines ($IC_{50}$ values ranging from 17.7 ± 0.6 to 23.4 ± 0.5 μM). In addition, compound **2**, **3**, **5**, and **6** demonstrated inhibitory activity against the Gram-positive cariogenic oral streptococci, *S. mutans* and *S. mutans* in a dose-dependent manner. Among them, **6** displayed strongest activity against *S. mutans* and *S.*

*mutans* (Yim *et al.*, 2010). Especially, **6** showed significant inhibitory activity against DPPH radical scavenging activity (antioxidant activity) with the $IC_{50}$ values of 62.5 ± 0.8 μM, compared to a positive control, quercetin (Ha do *et al.*, 2009b). In the anti-lipid peroxidation assay, **5** and **8** displayed significant anti-lipid peroxidation activity with the $IC_{50}$ values of 52.8 ± 0.9 and 44.3 ± 0.8 uM, respectively.

In the present study, **5** and **7** exhibited strong inhibitory activity against DNA Topo I and other compounds **1**, **4**, **6**, **8**, and **9** exhibited moderate inhibitory activity. Especially, **5** has strong cytotoxic activity against three cancer cell lines (L1210, K562, and HCT116) through the MTT assay, significant anti-lipid peroxidation activity, and antimicrobial activity. In summary, the results of present study demonstrate that the leaf and stem of *V. amurensis* are rich sources of stilbenes and oligostilbenes that posses DNA Topo I inhibitory activity. The DNA topoisomerases are now considered to be an important cancer chemotherapeutic target. Although a number of antitumor agent against DNA Topo II, camptothecin and its derivatives are known only as DNA Topo I-targeting anticancer agents. Therefore, the results of present study suggest that the compounds from *V. amurensis* have a possibility as DNA Topo I-targeting anticancer agents like the camptothecin and its derivatives. Further studies need to investigate inhibitory mechanism of the compounds from *V. amurensis* against DNA Topo I.

## Experimental Methods

**Plant materials** – The leaf and stem of *V. amurensis* were collected in Keryong Mountain, Daejeon, Korea, in July 2007. Botanical identification was performed by Prof. K. Bae and the voucher specimen (CNU-1522) was deposited in the Herbarium of the College of Pharmacy, Chungnam National University, Daejeon, Korea.

**Drug and chemicals** – Recombinant Human DNA Toposomerase I and DNA Topoisomerase I Drug Screening Kit were purchased from TopoGEN, Inc.(FL, USA). All other chemicals and solvents were of analytical grade, and used without further purification.

**Extraction and isolation** – Extraction and isolation compounds from leaf and stem of *Vitis amurensis* was reported in detail by Ha et al., 2009a. In this study, we briefly described as following: the dried leaf and stem (4.6 kg) of *V. amurensis* were extracted with MeOH at room temperature and the combined extract was filtered and concentrated to yield a crude extract (658 g). This extract was suspended in $H_2O$ and then successively partitioned with hexane, EtOAc, and BuOH to afford a hexane-soluble fraction (106 g), an EtOAc-soluble fraction (185 g), and a BuOH-soluble fraction (149 g). Separation of this fraction using a silica gel column (15 cm × 80 cm) and eluted with a gradient of hexane-ethyl acetate to provide seven fractions (Fr. 1 - 7). Fractions 4 - 6, found to be most active, were used for further study. Nine known compounds, piacetannol (**1**), (+)-ampelopsin A (**2**), (+)-ampelopsin F (**3**), resveratrol (**4**), amurensin G (**5**), *trans*-ε-viniferin (**6**), *r*-2-viniferin (**7**), *trans*-amurensin B (**9**), were obtained from Fr. 4 - 6, using silica gel, LH-20, and reverse phase column chromatographies. *cis*-Amurensin B (**8**) was yielded from Fr. 6 using HPLC manner [SPD-10A UV-VIS multi-wavelength detector, a reversed-phase Waters Spherisorb# S5 ODS2 column, (USA, 10 mm × 250 mm), ACN 40%. Compound **10** was obtained from the BuOH soluble fraction using a Dianion HP-20 column chromatography, a gel chromatography column, and a RP column, respectively.

**Assay for DNA Topo I inhibition** – A DNA Topo I inhibition was performed using DNA Topoisomerase I Drug Screening kit (TopoGEN). The stock concentrations of the 70% EtOH and MeOH extracts and EtOAc, MeOH, and BuOH fractions of the MeOH extract were used at 25 mg/mL. The activity of DNA Topo I was determined by assessing the relaxation of supercoiled DNA. The reaction mixtures comprised of 10X assay buffer, 200 ng of supercoiled DNA, 1.2 U of human recombinant DNA Topo I and the test compounds at the indicated concentrations in a final volume of 10 μL. The reaction mixtures were incubated for 30 min at 37 °C water bath, and terminated by adding of a 2% SDS. After digestion with proteinase K (50 μg/ml) for 60 min at 37 °C water bath, the samples were extracted once with chloroform : isoamyl alcohol (24 : 1) prior to loading the gel. The samples were loaded onto a 1% agarose gel and electrophoresed for 2 h with running buffer of Tris-acetate EDTA. The gel was stained with ethidium bromide (0.5 μg/mL) and photographed under transillumination with 300 nM UV light using GELMANAGER™ (Prime-Tech Coporation) with Cam2Com software (Sabsik).

**Statistical analysis** – The means and standard errors of means (S.E.M) were calculated for all experiments and all data are presented as means ± SEM.

## Acknowledgement

This research was supported by grant from the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST) (2010-0001356)

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Received November 11, 2010
Revised December 4, 2010
Accepted December 6, 2010