Decursin from *Angelica gigas* Nakai Blocks hKv1.5 Channel

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**Abstract**

Decursin was purified from *Angelica gigas* Nakai, and its effects on the human Kv1.5 (hKv1.5) currents were recorded in mouse fibroblasts (Ltk\(^-\) cells) by whole-cell patch-clamp technique. Decursin inhibited hKv1.5 current in a concentration-dependent manner, with an IC\(_{50}\) value of 2.7 \(\mu\)M at +60 mV. Decursin accelerated the inactivation kinetics of the hKv1.5 channel, and slowed the deactivation kinetics of the hKv1.5 current, resulting in a tail crossover phenomenon. Also, decursin inhibited the hKv1.5 current in a use-dependent manner. These results strongly suggest that decursin is a kind of open-channel blocker of the hKv1.5 channel.

**Key Words:** hKv1.5 channel blocker, Decursin, *Angelica gigas* Nakai

**INTRODUCTION**

Atrial fibrillation is the most frequent cardiac arrhythmia that can result in serious morbidity (Chung et al., 2001). It is well known that various K\(^+\) channels regulate the action potential duration and K\(^+\) channel genes are differentially expressed depending on the regions of the heart. The main Kv channel genes expressed in the human heart are the hKv1.4, hKv1.5, hKv4.3 and HERG genes. All these genes are highly expressed in both the atrium and ventricle, whereas the hKv1.5 gene is preferentially expressed in the human atrium. Furthermore, the electrophysiological and pharmacological characteristics of the current generated by hKv1.5 channels is similar to the ultra-rapid delayed rectifier K\(^+\) current (I\(_{UR}\)) recorded in human atrial myocytes (Fedida et al., 1998). Thus, the hKv1.5 channel is thought to be an unique target for atrial fibrillation.

In the present study, we tested decursin from the roots of *Angelica gigas* Nakai (Umbelliferae) on K\(^+\) currents expressed in Ltk\(^-\) cells. *Angelica gigas* Nakai has been used as a traditional medicine for treatment of anemia, a sedative and tonic agent (Yook, 1990). Earlier investigations on the chemical constituents of *A. gigas* mainly dealt with the isolation of coumarins (Ryu et al., 1990; Jung et al., 1991; Pachaly et al., 1996; Lee et al., 2002). The literature survey revealed that several pharmacological works, anti-tumor, inhibition of hepatic microsomal drug metabolizing enzyme, and inhibition of acetylcholinesterase activities, have been carried out on *A. gigas* (Shin et al., 1996; Kang et al., 2001; Lee et al., 2003; Lee et al., 2009; Kim et al., 2010). Our studies have focused on the development of antiarrhythmic drug, and we previously reported that papaverine (Choe et al., 2003), oxypeucedanin (Eun et al., 2005b), psoralen and their derivatives (Eun et al., 2005a; Eun et al., 2007) and torilin (Kwak et al., 2006) inhibited the hKv1.5 current. The present study was examined to investigate the effect of decursin from *A. gigas* on hKv1.5 channels using the whole-cell patch-clamp technique.

**MATERIALS AND METHODS**

**General procedure**

All the 1H- and 13C-NMR spectra were determined on a JEOL JMN-EX 400 spectrometer. The EI/MS (70eV) spectrum was determined on a VG-VSEQ mass spectrometer (VG Analytical, UK). The TLC was carried out on precoated silica gel F\(_{254}\) plates (Merck, Darmstadt, Germany), and the silica gel for column chromatography was Kiesel gel 60 (230-400 mesh, Merck). The column used for LPLC was the Lobar A (Merck Lichroprep Si 60, 240-10 mm). All the other chemicals and solvents were of analytical grade and they were used without further purification.

**Plant materials**

The roots of *A. gigas* were purchased from Namchang-dang, Jeonju, Korea. A voucher specimen is deposited in the herbarium of college of pharmacy, Woosuk University (WSU-
Extraction and isolation

The air-dried plant materials (300 g) were ground and extracted with MeOH under 50°C. The resultant MeOH extract (52 g) followed by the successive solvent partition to give methylene chloride (20 g), n-BuOH (18 g) and H₂O soluble fractions. Methylene chloride soluble fraction showed the most significant hKv1.5 current inhibitory activity. This fraction was chromatographed over silica gel column using a solvent system n-hexane-CH₂Cl₂-EtOAc (3:2:1) as an eluent to give three subfractions. Subfraction 2 was purified by JAI-ODS column (MeOH) to give compound 1 (150 mg).

Compound 1 (Decursin, Fig. 1)

Colorless needles (MeOH); 95°C, the 1H-NMR and 13C-NMR data we obtained were in good agreement with the literature values (Lee et al., 2003).

Fig. 1. Chemical structure of Decursin.

Fig. 2. Effects of decursin on the hKv1.5 current expressed in Ltk− cell line. hKv1.5 current traces were recorded before (A) and 20 min after exposure to 1 μM decursin (B). (C) The resultant I-V relationship of the steady-state current taken at the end of the depolarizing pulses. (D) Concentration-response relationship of hKv1.5 block by decursin. Each point with a vertical bar denotes the mean ± S.E.M.