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Short Communication

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Co-administration of Methylophiopogonanone A Might Affect the Safe Utilization of Drugs for Patients with HIV

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***SUMMARY*. Herb-drug interaction related with the drugs used to treat HIV patients was speculated in the present study. Therefore, zidovudine (AZT) was selected as an example, and *in vitro* incubation model was utilized to evaluate the inhibitory effect of herbal component methylophiopogonanone A towards the metabolism of AZT. The results showed the concentration-dependent inhibition of methylophiopogonanone A towards human liver microsomes (HLMs)-catalyzed AZT glucuronidation. Dixon plot and Lineweaver-Burk plot using the reaction velocity *versus* the concentrations of AZT and methylophiopogonanone A were performed to demonstrate the competitive inhibition of methylophiopogonanone A towards the glucuronidation of AZT. The inhibition kinetic parameter (K_i) value was calculated to be 87.8 μM. All these information indicated the necessary monitoring of clinical safety for the co-administration of AZT and methylophiopogonanone A-containing herbs.**

INTRODUCTION

Human immunodeficiency virus (HIV) is a lentivirus able to cause acquired immunodeficiency syndrome (AIDS). Many governments and research institutes have paid much attention and many interests for HIV/AIDS research. Consensus international and national therapy guidelines to treat HIV-infected patients contain non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor-based regimen [1]. HIV treatment drugs can have high potential to induce clinical drug-drug interaction. For example, the drug-drug interaction has been reported between HIV treatment drugs and drugs employed for management of neglected tropical diseases [2]. The involved mechanisms contain the influence of compounds towards drug-metabolism enzymes (DMEs), drug influx and exflux transporters, nuclear receptor activation, and pH-dependent absorption [3,4].

The utilization of herbs has become more and more popular due to the challenge for searching of the drugs with fewer side effects and lower cost. With the wider application of herbs, the possibility of the co-administration between herbs and drugs occurs, and there is more risk of herb-drug interaction. Methylophiopogonanone A is an important herbal ingredient isolated from *Ophiopogon japonicus* (Thunb.) Ker Gawl., known as Hang-maidong (grown in Zhejiang province) and Chuan-maidong (grown in Sichuan province) [5]. The present study aims to evaluate the inhibitory potential of this herbal component towards the metabolic behaviour of HIV treatment drugs.

MATERIALS AND METHODS

Chemicals and reagents

Methylophiopogonanone A was purchased from Beijing Chemical Corporation (Beijing, China). Zidovudine (HPLC purity ≥ 98%), alamethicin from *Trichoderma viride* (HPLC purity ≥ 98%) were obtained from Sigma-Aldrich (A2169-25MG). All other agents were purchased from their respective manufacturers and at least of analytical grade.

KEY WORDS: Herb-drug interaction (HDI), HIV, Metabolic inhibition.

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The inhibition of AZT glucuronidation by Methylophiopogonanone A

As previously described [6,7], the incubation system (200 µL) for AZT glucuronidation contained 500 µM of AZT as substrate, 50 µg of HLMs, 50 mM Tris-HCl buffer (pH 7.4), 4 mM $MgCl_2$, 25 µg/mL alamethicin, and 5 mM UDPGA. After 30 min incubation, the reaction was terminated using 100 µL methanol. Centrifuged at 20000 ×*g* for 10 min at 4 °C, aliquots of supernatants were transferred for UPLC analysis. The Waters Acquity UPLC system (Waters, MA, USA) was used, and the instrument contained binary solvent manager, autosampler manager, and column compartment. An Acquity UPLC BEH C18 column (50 mm × 2.1 mm i.d., 1.7 µm) was utilized. The column temperature was maintained at 40 °C. The mobile phase composition was a mixture of water-acetonitrile (95:5, v/v), the flow rate was set at 0.3 mL/min, and the injection volume was 5 µL. The wavelength was selected at 267 nm to perform ultraviolet detection.

Determination of inhibition kinetic type and parameters (K_i)

The reaction velocity was determined at various concentrations of AZT and methylophiopogonanone A. Data fitting using Dixon plot and Lineweaver-Burk equations was performed to determine the kinetic type. K_i value was calculated through the second plot using the slopes from Lineweaver-Burk plot *versus* methylophiopogonanone A's concentrations.

RESULTS

Dose-dependent inhibition behaviour of methylophiopogonanone A towards AZT glucuronidation was observed, as shown in Fig. 1. The residual activity of AZT glucuronidation was determined to be 97.0%, 90.6%, 84.3%, 77.1%, 64.2%, 51.4%, 34.3%, and 27.0% of control activity at 5, 10, 20, 40, 60, 80, 100, and 200 µM of methylophiopogonanone A.

Dixon plot (Fig. 2A) and Lineweaver-Burk plot (Fig. 2B) indicated the competitive inhibition of methylophiopogonanone A towards AZT glucuronidation reaction, and the K_i value was calculated to be 87.8 µM (Fig. 3).

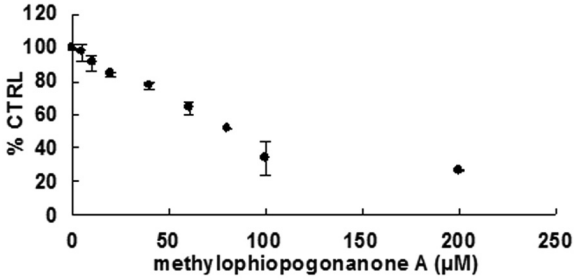

Figure 1. Dose-dependent inhibition of methylophiopogonanone A towards the glucuronidation of AZT. The data point represented the mean ± S.D. of triplicate experiments.

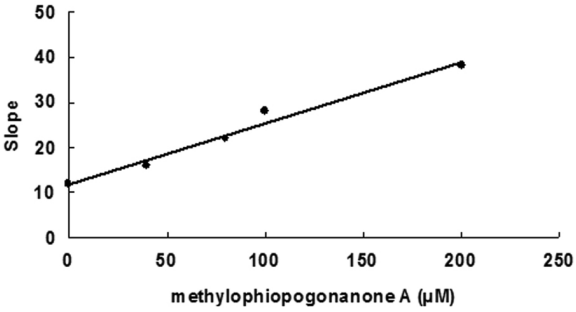

Figure 3. Second plot to calculate the inhibition kinetic parameter (K_i). The plot was drawn using the slopes from the Lineweaver-Burk plot towards the concentrations of methylophiopogonanone A.

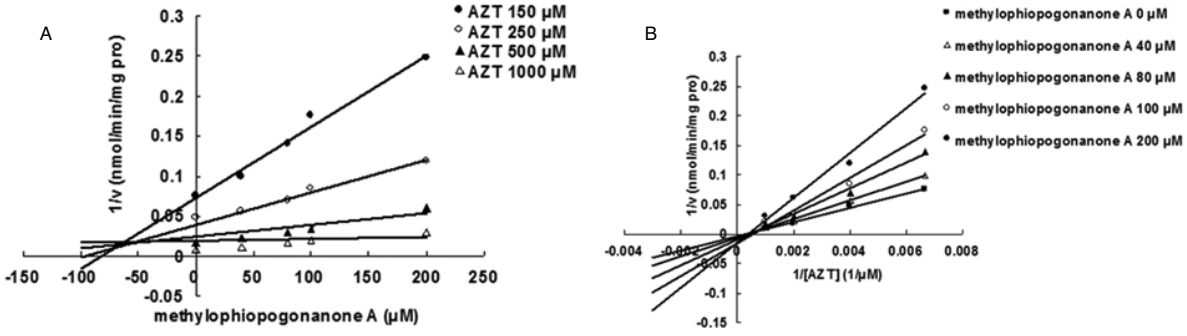

Figure 2. Determination of inhibition kinetic type through drawing Dixon plot (**A**) and Lineweaver-Burk plot (**B**) using multiple reaction velocity at various concentrations of AZT and methylophiopogonanone A. Each data point represent the mean value of two independent experiments.

DISCUSSION

AZT has a narrow therapeutic index and the slight alteration of its glucuronidation activity will strongly influence its efficiency and toxicity. Previous studies have demonstrated that the changed activity of UGT2B7 due to the UGT2B7*1c polymorphism will significantly affect the glucuronidation and clearance of AZT [8]. Many xenobiotic drugs and herbal ingredients have been reported to exhibit inhibition towards this glucuronidation process of AZT. For example, the non-nucleoside reverse transcriptase inhibitor efavirenz (EFV) can be eliminated through UGT2B7-catalyzed conjugation reaction, and showed strong inhibition towards the glucuronidation of AZT [9]. Kampo medicines were demonstrated to strong inhibition potential towards UGT2B7 [10]. The important component of *Tripterygium wilfordii* Hook F. celastrol also exhibited the strong inhibition towards UGT2B7 [11].

In the present study, the competitive inhibition influence of herbal compound methylophiopogonanone A towards the metabolic reaction of AZT was demonstrated, indicating the possibility of the HDI between AZT and methylophiopogonanone A-containing herbs. Additionally, human liver microsomes-catalyzed glucuronidation of AZT has been frequently adopted as the probe reaction for UGT2B7. Therefore, the clinical monitoring of herb-drug interaction is needed when methylophiopogonanone A-containing herbs are co-administered with other drugs mainly undergoing UGT2B7-catalyzed metabolic reaction.

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