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Extracts of the medicinal herb *Sanguisorba officinalis* inhibit the entry of human immunodeficiency virus-1

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ABSTRACT

Highly active antiretroviral therapy (HAART) has been successful in reducing human immunodeficiency virus (HIV)-1-associated morbidity and mortality since its introduction in 1996. However, it fails to eradicate HIV-1 infection. The high cost of life-long highly active antiretroviral therapy and the emergence of drug resistance among HIV-1-infected individuals have brought renewed pressure for the discovery of novel antivirals and alternative medicines. Traditional Chinese medicine (TCM) is a complementary and alternative medicine, and serves as a rich resource for new drug development. Despite the almost 100 plant-derived compounds that are in clinical trials, few target HIV-1 infection. In this study, we discovered that *Sanguisorba officinalis* extract (SOE) has anti-HIV-1 properties. Using a cell-based assay and single-cycle luciferase reporter viruses pseudotyped with envelopes from HIV-1 or control viruses, we found that SOE exhibited significant inhibitory ability against both CCR5 and CXCR4 tropic HIV-1 (ADA and HXB2), with respective IC_{50} values of 1.91 ± 0.16 μg/mL and 3.70 ± 0.53 μg/mL. SOE also inhibited simian immunodeficiency virus infection but failed to block vesicular stomatitis virus, severe acute respiratory syndrome coronavirus, and influenza H5N1 pseudoviruses. Furthermore, we showed that SOE had no effect on postentry events of HIV-1 replication. Because SOE pretreatment with the virus but not with cell lines expressing viral receptors showed the maximal inhibitory activity, we can state that SOE probably blocks entry by acting on the viral envelope directly. In addition, SOE was able to inhibit reverse transcriptase inhibitor resistant viruses (K103N, Y188L, and K103N/Y188L/G190A) and a protease inhibitor resistant strain (PI-2840). Our findings demonstrate SOE as a novel and specific entry inhibitor, which sheds light on the discovery of anti-HIV-1 drugs from traditional herbal medicines.

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1. Introduction

Traditional Chinese medicine (TCM) includes various forms of herbal medicine, acupuncture, moxibustion, massage, Qi exercise, meditation, and dietary therapy. TCM was developed in China as a personalized medical practice based on a tradition of more than 5000 years. As a result, thousands of plants have been used as herbal medicines for treating different types of diseases. For example, one of the most famous drugs, artemisinin, was originally extracted from the plant *Artemisia annua* and is now a standard treatment worldwide for *Plasmodium falciparum* malaria [1]. During the past decade, the use of TCM has increased globally as one of the mainstreams of complementary and alternative medicine. It also serves as a rich resource for new drug development.

Prior to the availability of highly active antiretroviral therapy (HAART), people with human immunodeficiency virus (HIV)/AIDS often sought herbal therapy in China. This situation continues today because HAART is still not readily accessible or affordable especially in rural areas, where the majority of patients reside. Even in the era of HAART, HIV-infected people who used herbal therapy at a high rate sought more frequent visits to TCM providers and reported helpful improvement with the treatment [2,3]. In most cases, however, it remains unknown whether the herbs used had any anti-HIV activities, and therefore it is unknown if they were regarded as enhancing patients' immune function, as the treatment of HIV-related symptoms, or as the management of HAART-related side effects [4]. In recent years, studies have demonstrated that evidence-based research on compounds extracted from herbal plants can elucidate their biochemical activity, revealing antitumor activity in some cases and anti-HIV activity in others [5–9]. The study of some herbal compounds has been moved forward into clinical trials [6,7,10]. Prior to this study, however, it was unclear if *Sanguisorba officinalis* had any anti-HIV activity.

Sanguisorba officinalis (also called *Great Burnet*) is a plant in the family Rosaceae, subfamily Rosoideae. It is easily found in the northern regions of China and has been used as TCM for thousands of years to treat hemostasis and inflammation [11]. Some other functions that have been discovered in recent years include its antioxidant and antitumor properties [12–14].To the best of our knowledge, we are the first group to study the anti-HIV-1 activities of the extract of *S. officinalis* (SOE). Our findings have implications for exploring TCM for new antiviral discoveries.

2. Materials and methods

2.1. Preparation of SOE

The stem of *S. officinalis* was cut into small pieces and immersed in distilled water. The mixture was treated by ultrasound for 1 hour, followed by boiling twice at 100°C for 30 minutes. After filtration, the supernatant was concentrated

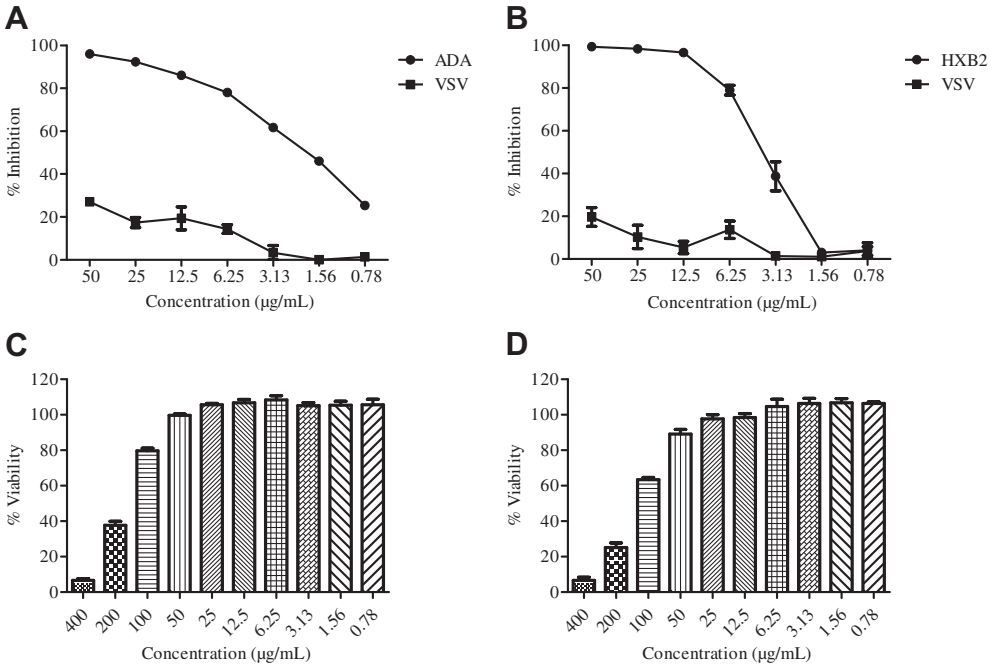

Fig. 1 – Activity of *Sanguisorba officinalis* extract (SOE) against HIV-1_{ADA}, HIV_{HxB2}, and HIV_{VSV}. Serially diluted SOE was added to GHOST-CCR5 and GHOST-CXCR4 infected with (A) HIV-1_{ADA} and (B) HIV_{HxB2}, respectively. HIV_{VSV} was tested as a negative control. The luciferase level was measured 2 days postinfection. All results are means ± standard errors of the means from three independent experiments. To test SOE cytotoxicity, (C) GHOST(3)-CD4-CCR5 and (D) GHOST(3)-CD4-CXCR4 cells were cultured in serially diluted SOE at 37°C for 48 hours in 5% CO_2. Cell viability was then measured using the Promega CellTiter-Glo Luminescent Cell Viability Assay kit. The data represent the mean ± standard deviation of triplicate experiments.