Microbial Metabolism of Artemisinin by *Penicillium janthinellum*

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**ABSTRACT**

The microbial transformation of artemisinin by *Penicillium janthinellum* was investigated. During 6 days at 28°C and 180 rpm, artemisinin was transformed to a product by *Penicillium janthinellum*. The product was identified as 4α-hydroxy-1-deoxyartemisinin. This is the first report of biotransformation of artemisinin by *Penicillium janthinellum*.

**Keywords:** Microbial metabolism; Artemisinin; *Penicillium janthinellum*

**INTRODUCTION**

Artemisinin (qinghaosu) is a sesquiterpene lactone endoperoxide, isolated from the Chinese herb *Artemisia annua* L., and the endoperoxide bridge is responsible for its activities. Today, artemisinin and its derivatives, dihydroartemisinin and artesunate, are used in the first-line treatment for multidrug-resistant malaria [1,2]. Besides the antimalarial activity, artemisinin and its derivatives also exhibited antifungal [3], antiangiogenic [4,5], anti-inflammatory [6], and antitumor activities [7-10]. There has been much interest in the structural modification of artemisinin and its derivatives in the search for analogues which might serve as clinical alternatives. In this study, we report the biotransformation of 1 by *Penicillium janthinellum*, and one product was obtained.

**MATERIALS AND METHODS**

**General**

1H NMR (nuclear magnetic resonance) and 13C NMR spectra were recorded in CDC13 (chloroform-d) on a Bruker Avance III HD 600 MHz spectrometer. Chemical shifts were reported in ppm (δ), and J-values were reported in Hz.

**Microorganism**

The strain *Penicillium janthinellum* CGMCC 3,5951 was obtained from China General Microbiological Culture Collection Centre.

**Medium**

All culture and biotransformation experiments were carried out in the following medium: Potato infusion is made by boiling 200 grams of sliced potatoes in 1 litre of deionized water for 30 minutes and then filtering the broth through cheesecloth. Deionized water is added such that the total volume of the suspension is 1 litre. 20 grams dextrose is then added and the medium is sterilized by autoclaving at 121°C for 30 minutes.

**DISCUSSION AND CONCLUSION**

The biotransformation of artemisinin (1) by *Penicillium janthinellum*

The mycelia were transferred into 250 mL Erlenmeyer flasks containing 60 mL of medium from the surface of agar slants. Cultures were cultivated for 48 h on a rotary shaker at 28°C and 180 rpm, and used to inoculate 37, 250 mL shake flasks that contained 60 mL of medium. The cultures were then incubated for 48 h using the same conditions as before. Artemisinin (Mediplantex, Vietnam) was dissolved in acetone (25 mg/mL), and 0.4 mL of this solution was added to each flask. A total of 370 mg of artemisinin was transformed. The cultures were incubated for additional 6 days at 28°C and 180 rpm. The mycelia were separated by filtration and discarded. The filtrate was extracted three times with an equal volume of ethyl acetate (EtOAc). The extract was evaporated to dryness under vacuum to afford a residue.

**Chromatographic conditions**

A total of 1.70 g of residue was obtained from the broth. The residue was purified by silica gel column chromatography, using a petroleum ether (60-90°C)-acetone mobile phase in a gradient mode, eluting with 10 to 30% acetone.

The structure of the product was identified on the basis of its spectroscopic data. Data of 1H and 13C NMR spectra of the product was in agreement with the reported literatures’ data [11,12]. So the product was identified as 4α-hydroxy-1-deoxyartemisinin (Figure 1).

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α-hydroxy-1-deoxyartemisinin (2): Colourless needles (from acetone); 1H-NMR (CDCl₃, 600 MHz) δ 5.63 (1H, s, H-12), 3.62 (1H, brs, H-4β), 3.19 (1H, m, H-9), 2.06 (1H, m, H-8α), 1.98 (1H, m, H-5α), 1.92 (1H, m, H-8α), 1.82 (1H, m, H-7α), 1.57 (3H, s, Me-13), 1.55-1.47 (2H, m, H-5α, H-5β), 1.28 (1H, m, H-7β), 1.00 (1H, m, H-8β), 0.93 (3H, d, J=7.1 Hz, Me-15), 0.92 (1H, m, H-7β), 0.90 (3H, s, C-10), 109.1 (s, C-3), 99.2 (d, C-12), 83.1 (s, C-12a), 69.3 (d, C-4), 42.3 (d, C-8α), 40.8 (d, C-5a), 35.3 (d, C-6), 33.6 (t, C-7), 32.9 (d, C-9), 30.5 (t, C-5), 23.7 (t, C-8), 20.7 (q, C-13), 18.6 (q, C-14), 12.8 (q, C-15).

The effectiveness of artemisinin is impaired by its toxicities [13] and low solubility [14]. Chemical and biological modifications of artemisinin have been studied [15-19]. Microbial transformation is an effective route to obtain artemisinin derivatives. The microorganisms, such as Aspergillus niger, Aspergillus terreus, Rhizopus stolonifer, Cunninghamella elegans, Eurotium amstelodami, Mucor polymorphosporus, Penicillium simplicissimum, Streptomyces griseus [20-22] were used in the biotransformation of artemisinin. Here we first report the biotransformation of artemisinin by Penicillium janthinellum.

In conclusion, we investigated the biotransformation of artemisinin by Penicillium janthinellum, and obtained a product, 4α-hydroxy-1-deoxyartemisinin. This is the first report of biotransformation of artemisinin by Penicillium janthinellum.

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REFERENCES


