

# Enhancement of extraction efficiency of paclitaxel from biomass using ionic liquid-methanol co-solvents under acidic conditions



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## ABSTRACT

In this study, a new ionic liquid co-solvent is proposed and optimized for the extraction of paclitaxel from plant cell culture. When using an ionic liquid ([Bmim]BF<sub>4</sub>) as co-solvent, most of the paclitaxel (~90%) was recovered from biomass by extracting once for 30 min at a ratio of ionic liquid to methanol of 0.166:1 (w/w) and a ratio of solvent to biomass of 1:1 (v/w) at room temperature. In addition, when the pH of the extracting solution containing an ionic liquid as co-solvent was reduced, the paclitaxel recovery increased. When paclitaxel was extracted from glycoside-containing biomass using an acidic ionic liquid ([Bmim]BF<sub>4</sub>) as co-solvent (pH: 2.2), paclitaxel recovery was high (1.4-fold increase compared to control) due to glycoside hydrolysis arising from a low pH (acidic conditions) of the extracting solution as well as good extractability of ionic liquid itself.

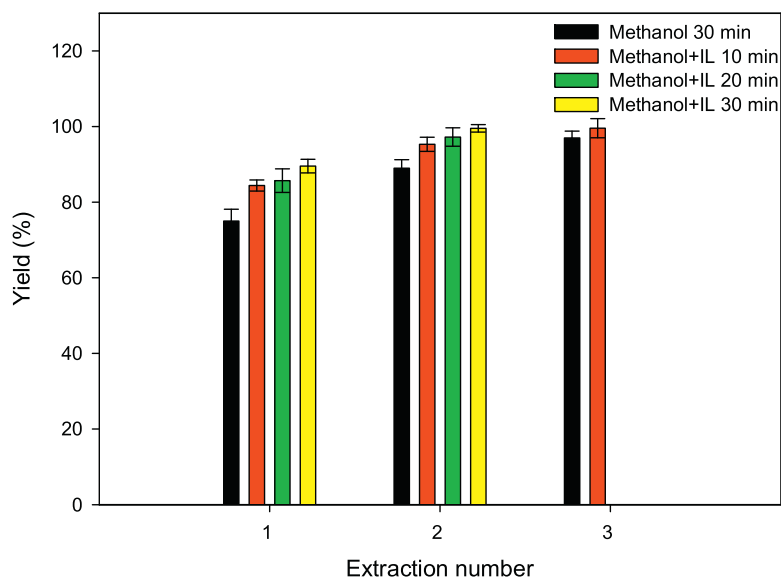
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## 1. Introduction

Paclitaxel is a diterpenoid anticancer agent that was discovered in the bark of the yew tree [1]. It is one of the most effective anti-cancer drugs for treating ovarian cancer, breast cancer, Kaposi's sarcoma, and non-small cell lung cancer. Its application has also been expanded to the treatment of acute rheumatoid arthritis and Alzheimer's disease [1]. Since clinical trials regarding its combined prescription with various other treatments are underway, the demand for paclitaxel is expected to increase [2]. The main paclitaxel production methods are direct extraction from the yew tree, semi-synthesis, and plant cell culture [3–5]. Among these methods, plant cell culture enables stable mass production of paclitaxel of consistent quality in a bioreactor without being affected by such external factors as climate and environment. Most of the paclitaxel produced by plant cell culture is contained in plant cells and debris [6] and it is important to efficiently extract paclitaxel included in cells to increase recovery. In the existing extraction methods, paclitaxel has been primarily recovered from biomass, which is plant cells, using organic solvents [7–9]. However, the existing solvent extraction (conventional solvent extraction, CSE) method has drawbacks such as requiring a long extraction time and a large amount of organic solvents, as well as a low extraction efficiency.

An ionic liquid (IL) is a liquid ionic compound composed of cations and anions at room temperature. It is called a “green solvent” due to its low volatility and high thermochemical stability under atmospheric pressure [10–12]. In addition, it has good miscibility in water and organic solvents, good solubility and extractability for various organic compounds and the remarkable advantage over conventional solvents of being easy to control [13]. Due to their unique properties, ionic liquids were recently used as solvents or co-solvents to extract keratin from poultry feathers [14], bioactive compounds from plants [15], lipid from algal biomass [16,17], and phorbol ester and bio-oil from *Jatropha* biomass [18] to improve the extraction efficiency. When using an ionic liquid as co-solvent for polar covalent molecules, which are the main solvents, the extraction efficiency was remarkably improved; in particular, using methanol as the main solvent led to good mixing with IL to cause high selectivity [17]. Based on this result, it was expected that the extraction efficiency of paclitaxel would increase by adding an ionic liquid as co-solvent to methanol, which is the main solvent used for the CSE process, in order to recover paclitaxel from plant cells. According to the study conducted by Wei et al. [19], the pH of an extracting solution considerably improved the extraction efficiency in heavy metal ion extraction using an ionic liquid. In addition, Zeng et al. [20] reported that the pH of an extracting solution remarkably contributed to improvement of the extraction efficiency in rutin extraction of Chinese medicinal plants using an ionic liquid. In particular, a higher extraction efficiency was achieved in an acidic extracting solution.

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**Fig. 1.** Effect of number of extractions on the extraction yield of paclitaxel using various extraction methods. The type of ionic liquid, extraction solvent ratio of ionic liquid to methanol, ratio of solvent to biomass, and temperature were [Bmim]BF<sub>4</sub>, 0.166:1 (w/w), 1:1 (v/w), and room temperature, respectively.

In our previous study [21], hydrochloric acid (HCl) was added to decrease the pH of an extracting solution for acid hydrolysis of glycoside (sugar-binding paclitaxel, 7-xylosyl paclitaxel), contained in biomass, in order to increase paclitaxel recovery. In other words, when 90% aqueous methanol, was used as the extracting solution for the CSE process under acidic conditions (pH: 2.2), the recovery of paclitaxel was increased at least 1.7-fold compared to the existing methods (no pH control, pH: 8.29). The result was caused by acid hydrolysis of glycoside in biomass to increase the paclitaxel recovery.

Therefore, this study aims at proposing and optimizing a new ionic liquid co-solvent to increase the extraction efficiency of paclitaxel from biomass. In particular, the effect on the pH of an extracting solution in the extraction using an ionic liquid as co-solvent was investigated in detail and paclitaxel recovery was intended to be maximized by glycoside, sugar-binding paclitaxel, hydrolysis in biomass using an acidic ionic liquid. After all, we aimed to maximize the recovery of paclitaxel from biomass using an acidic ionic liquid as co-solvent due to glycoside hydrolysis arising from a low pH (acidic conditions) of the extracting solution as well as good extractability of ionic liquid itself.

## 2. Materials and methods

### 2.1. Plant materials

A suspension of plant cells originating from *Taxus chinensis* was cultured in a bioreactor [22]. Following cultivation, biomass (plant cell and debris) was recovered using a decanter (CA150 Clarifying Decanter; Westfalia, Germany) and a high-speed centrifuge (BTPX 205GD- 35CDEFP; Alfa Laval, Sweden). The biomass was provided by Samyang Genex Company, South Korea.

### 2.2. Paclitaxel and glycoside (7-xylosyl paclitaxel) analysis

An HPLC system (SCL-10AVP, Shimadzu, Japan) and a Capcell Pak C18 column (250 × 4.6 mm, Shiseido) were used to analyze the paclitaxel and glycoside contents. Acetonitrile/water (35:65–65:35, v/v gradient) for paclitaxel and acetonitrile/water (25:75–65:35, v/v gradient) for glycoside were used as the mobile phase. Using a UV detector, paclitaxel and glycoside were analyzed at 227 nm

and 228 nm, respectively [23]. In addition, the flow rate and sample injection volume were 1.0 mL/min and 20 μL, respectively. Authentic paclitaxel and 7-xylosyl paclitaxel were purchased from Sigma–Aldrich (purity: 95%) and Quality Phytochemicals (purity: 99%), respectively, and were used as standards. Each sample was analyzed in triplicate.

### 2.3. Conventional solvent extraction (CSE)

The biomass from plant cell cultures was mixed with methanol and stirred at room temperature for 30 min [9]. The mixture was filtered under vacuum in a Buchner funnel through filter paper (150 mm, Whatman), where the methanol was preferably added to biomass at a ratio of 1:1 (mL/g, v/w). Methanol extract was collected, pooled, concentrated and dried at 40 °C under vacuum (635 mm Hg) for HPLC analysis.

### 2.4. Extraction using an ionic liquid as co-solvent

According to a previous study [9], the optimum ratio of solvent to biomass and extraction temperature in the CSE process was confirmed to be 1:1 (v/w) and room temperature, respectively. First, the effect of extraction time (10, 20, 30 min) and extraction number (1, 2, 3 times) were investigated in the extraction using an ionic liquid under the optimum conditions. In addition, the effect of the ratio of ionic liquid to methanol in an extracting solution (0.080:1, 0.100:1, 0.125:1, 0.166:1, 0.250:1, 0.500:1, w/w), the ratio of extracting solution to biomass (1:1, 2:1, 3:1, 4:1, v/w), and extraction temperature (25, 30, 35, 40 °C) were also investigated. To examine the effect of the type of ionic liquid, the extraction efficiency was determined using the four ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate [Bmim]BF<sub>4</sub> (purity: 97%), 1-methyl-3-octylimidazolium tetrafluoroborate [Omim]BF<sub>4</sub> (purity: 97%), 1-butyl-3-methylimidazolium chloride [Bmim]Cl (purity: 95%), and 1-butyl-3-methylimidazolium hexafluorophosphate [Bmim]PF<sub>6</sub> (purity: 98%) as co-solvent. In addition, the pH of an extracting solution having each ionic liquid as co-solvent was identified to determine the effect of pH. All the ionic liquids used for the test were purchased from Sigma–Aldrich.

To determine the effect of the pH of the extracting solution on the extraction efficiency, HCl was added to an extracting solution

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