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Pharmacokinetic synergy from the taxane extract of *Taxus chinensis* improves the bioavailability of paclitaxel

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ABSTRACT

Background: *Taxus chinensis* (Pilger) Rehd is widely distributed in China and the northern hemisphere, and the most popular medicinal component isolated from *Taxus chinensis* is paclitaxel (PTX), which has now become the first-line chemotherapeutic drug for breast cancer and ovarian cancer. Oral administration of pure PTX as a potential anti-cancer agent is compromised by low bioavailability.
Hypothesis/purpose: In the clinical practice of traditional Chinese medicine, drug co-administration in the form of mixtures or formula could achieve pharmacokinetic/pharmacodynamic synergies. In this study, we aimed to investigate whether there exist any 'inherent' phytochemical synergy from *Taxus chinensis* extract that could improve PTX bioavailability.
Study design: Pharmacokinetic study of PTX after oral administration of *Taxus chinensis* extracts or single PTX was performed. In addition, comparative cytotoxic studies were carried out on the MCF-7 breast cancer cell lines.
Methods: The plasma concentrations of PTX were determined using a validated high performance chromatography tandem mass spectrometry method. The cytotoxicity was compared using the MTT assay.
Results: Oral administration of taxane fractions isolated from *Taxus chinensis* (containing 17.2% PTX) could achieve remarkably higher blood concentration and systemic exposure of PTX in rats, while the retention of PTX was significantly improved. Further tissue distribution analysis revealed that the penetration of PTX into major tissues was drastically increased compared with that of single PTX. In addition, in MCF-7 cells, the co-existing components in taxane mixtures could strengthen the inhibitory effects of PTX on tumor cell proliferation.
Conclusion: Together, these results support that administration of PTX in the form of taxane mixtures may become a novel approach to improve the poor bioavailability of PTX. Moreover, the inherent synergy from *Taxus chinensis* taxane extracts promises a novel strategy to strengthen PTX efficacy.

Introduction

Taxus chinensis (Pilger) Rehd, also known as the Chinese yew, is a protected species in China and the extracts of many parts of the plant (e.g., roots, bark and leaves) have been commonly used in traditional Chinese medicine to treat cancer (Shi and Kiyota 2005; Tezuka et al. 2011; Qu and Chen 2014; Zheng et al. 2014). Modern pharmacology has led to the discovery of paclitaxel (PTX, Fig. 1A), a taxane-type diterpenoid, from the barks of *Taxus chinensis*, which is now applied intravenously (i.v.) as a broad-spectrum chemotherapeutic drug for breast cancer, ovarian cancer and non-small cell lung cancer (Dumontet and Jordan 2010). Ample studies have proven that PTX can induce cell cycle arrest and apoptosis via promoting microtubule polymerization and inhibiting microtubule depolymerization (Altmann and Gertsch 2007), and the unique structure and anticancer efficacy of PTX has drawn huge research interests worldwide (Watchueng et al. 2011).

Abbreviations: PTX, paclitaxel; P-gp, P-glycoprotein; CYP, cytochrome P450; MRP2, multidrug resistance protein 2; C_{max}, peak plasma concentration; T_{max}, time to C_{max}; MRT, mean retention time; AUC_{0-t}, area under the curve from 0 to time; $AUC_{0-\infty}$, area under the curve from 0 to infinity; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide; LC–MS/MS, liquid chromatography tandem mass spectrometry; ESI, electrospray ionization; CE, collision energy.

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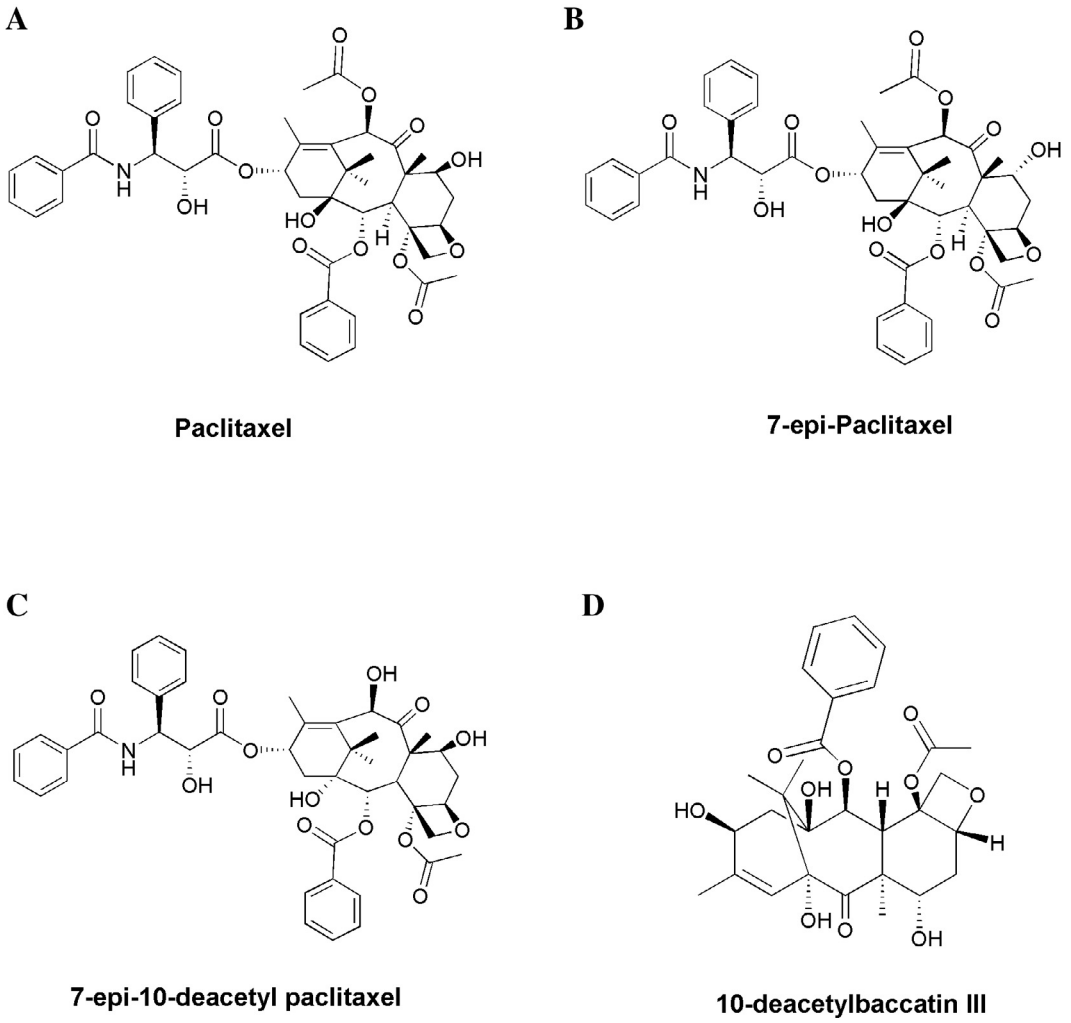

Fig. 1. Chemical structures of paclitaxel (A), 7-epi paclitaxel (B), 7-epi-10-deacetyl paclitaxel (C), and 10-deacetylbaccatin III (D).

The clinical application of commercial paclitaxel injection (Taxol®) is, however, hampered in part by anaphylactic reactions related to Cremophor EL, a surfactant used to improve the solubility of PTX (Nehate et al. 2014). Actually, the very poor solubility has become a major hurdle to the druggability of PTX. Against this disadvantage, oral administration of PTX has emerged as an attractive route (Jibodh et al. 2013), and, to this end, several novel drug delivery systems have been attempted for optimizing the anti-cancer benefit of PTX (Jain et al. 2012; Li et al. 2013; Lian et al. 2013; Hendrikx et al. 2014). However, it has been shown that the oral absorption and tissue distribution of PTX were largely restricted by active efflux and metabolic transformation (Hendrikx et al. 2013). To circumvent this major limitation, concomitant administration of transporter inhibitors (e.g., cyclosporine A, verapamil) with PTX has been proposed (Woo et al. 2003; Jibodh et al. 2013; Hendrikx et al. 2014), and it is noteworthy that several natural compounds (e.g., schizandrol B, ginsenoside Rg3) were found to effectively enhance the systemic exposure and even anti-tumor strength of PTX in animal models when orally co-administered (Jin et al. 2010; Yang et al. 2012). These findings indicated that exploiting potential phytochemical combinations may become an invaluable approach for enhancing PTX exposure.

To explore a potential strategy to improve the production of PTX, we have previously prepared the taxane fractions from *Taxus chinensis* twigs and leaves leading to a 17.2% production of PTX, which was much higher than those traditionally produced from the barks of *Taxus chinensis* (Lv et al. 2014). We noted that, in the clinical practice of traditional Chinese medicine, drug co-administration in the form of mixtures or formula could achieve pharmacokinetic/pharmacodynamic synergies, a phenomenon also known as 'herbal compatibility' (Hao et al. 2014). Based on this rationale, we were particularly interested in whether the co-existing taxane components may influence the pharmacokinetics of PTX when they were administered *per oral* in the form of taxane mixtures. Herein, we report the interesting findings that, compared to giving PTX alone, oral administration of taxane combinations (containing 17.2% PTX) could lead to remarkably higher C_{max} and AUC in rats. Moreover, the tissue distributions of PTX were also significantly increased. In MCF-7 breast cancer cell lines, we also observed that taxane mixtures could elicit more potent inhibitory effects on tumor cell proliferation *in vitro* than pure PTX. Together, our work suggested that administration of *Taxus chinensis* taxane extracts could become a promising avenue to improve the bioavailability of PTX, which might also contribute to better anti-tumor effects.

Materials and methods

Reagents and chemicals

Paclitaxel (HPLC purity > 98%; Lot # 100382–201102), 7-epi-paclitaxel (HPLC purity > 98%; Lot # 100927–201102), 7-epi-10-deacetyl paclitaxel (HPLC purity > 98%; Lot # 100925–200701), and diazepam (HPLC purity > 98%; Lot # 171225–200903) were supplied by the National Institute for the Control of Pharmaceutical and