Effects of Jitai Tablet, A Traditional Chinese Medicine, on Spontaneous Withdrawal Symptoms and Modulation of Dopaminergic Functions in Morphone-Dependent Rats

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Chronic opioid abuse can cause damage to dopamine neurons. However, there are currently no effective pharmacotherapies to reverse this damage, even though progress has been made in the development of therapeutic strategies for opioid dependence. The Jitai tablet (JTT) is a traditional Chinese medicine formulation most commonly used for opioid addiction treatment in China. In a morphine spontaneous withdrawal rat model we investigated the effects of JTT, either given before (pre-treatment) or after (post-treatment) morphine administration, on the dopamine system. Our study has shown the following: (1) pre- and post-treatment with JTT were effective at alleviating the wet dog shakes and episodes of writhing; (2) pre-treatment with JTT inhibited the morphine-induced decreases in dopamine transporter (DAT), dopamine D2 receptor (D2R) and tyrosine hydroxylase (TH) levels in the striatum (p < 0.01, compared with morphine group) and maintained them at normal levels; and (3) post-treatment with JTT restored the densities of DAT, D2R and TH in the striatum to normal levels (p < 0.01, compared with morphine group). These results support the notion that modulation of the dopamine system in the striatum may play a role for JTT’s therapeutic effect on the alleviation of opioid withdrawal symptoms. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: Jitai tablet; morphine dependence; dopamine transporter; dopamine D2 receptor; tyrosine hydroxylase.

INTRODUCTION

Opioid abuse and dependence have imposed a significant medical and economic burden to individuals and society. The United Nations Office on Drug and Crime estimates that 12 to 21 million people abuse opiates worldwide (UNODC, 2011). Current first line medicines for the treatment of opioid addiction, including methadone, buprenorphine, naloxone, naltrexone, lofexidine and clonidine, are effective in alleviating withdrawal symptoms. However, most of them are also associated with certain disadvantages, such as high abuse potential and relapse rate. Therefore, there is still an urgent need for more effective and safer approaches for the treatment of opioid addiction.

Traditional Chinese medicine (TCM) has long been used in the treatment of opioid addiction and shown to present the advantages of negligible side effects, low abuse potential and simultaneous action on multiple targets (Shi and Lu, 2006). The Jitai tablet (JTT), approved by the China Food and Drug Administration (CFDA) in 2004, is one of the most commonly used TCMs for opioid addiction treatment in China. Several animal and clinical studies have shown that JTT is able to alleviate both acute and protracted withdrawal symptoms (Li et al., 2007; Lu et al., 1998; Wang et al., 2012a), and that the combined therapy of JTT with lofexidine or tramadol can even alleviate withdrawal symptoms within 72 h (Dong, 2002; Xiong et al., 2001). In preclinical toxicological studies, JTT was proved to be safe and well-tolerated with low abuse potential even at high doses and during long-term use (180 days) (Chen et al., 2010). In clinical trials, JTT presented only mild side effects (Hao et al., 2013; Li et al., 2007).

Recently, many components in JTT have been identified (Wang et al., 2012a, 2012b; Wang et al., 2010). Pharmacological effects for some of these components have been investigated in preclinical and clinical studies. For example, one of the active components, l-tetrahydropalmatine (l-THP), has been shown to be a dopamine (DA) antagonist, and its antagonistic effect on DA receptors may play an important role in reducing drug cravings (Yang et al., 2008). l-THP was also found to increase the synthesis and release of endogenous opioids in the central nervous system (CNS), an effect that may contribute to its anti-dependence potential (Chu et al., 2008). Scopolamine, another active ingredient in JTT, was effective at enhancing dopamine synthesis and dopamine transporter (DAT) availability (Tsukada et al., 2008).
Animals. Male Wistar rats, initially weighing 180–220 g, were used. They were housed in groups of five in a room with a 12-h light/12-h dark cycle and with ad libitum access to food and water. Animals were maintained according to the international guidelines for the care and use of laboratory animals (NIH publication #85-23, revised in 1985), and all experimental procedures involving animals were approved by the Ethics Committee of Beijing Normal University (BNU/EC/01/2011).

Drugs and reagents. JTT consists of 15 herbs with the following weight percentages: *Rhizoma Corydalis* (10.2%), *Salvia Miltiorrhiza* (16.9%), *Angelic Sinensis* (10.2%), *Rhizoma Chuanxiong* (5.6%), *Persicae Semen* (10.2%), *Carthamunitctorius* (10.2%), *Margarita* (13.5%), *Aconitum Carmichaelii* (2.2%), *Cinnamomum Cassia* (2.2%), *Panax Ginseng* (2.2%), *RhizomaZingiberis* (13.5%), *Carthamunitctorius* (10.2%), *Margarita* (13.5%), *Aconitum Carmichaelii* (2.2%), *Cinnamomum Cassia* (2.2%), *Panax Ginseng* (2.2%), and *Aquilaria Sinensis* (4.4%). In this study, JTT samples (batch number: 050602) were kindly provided by the National Engineering Research Center for TCM, Shanghai, China. The chemical fingerprint of JTT samples was present in the supplement material (as shown in Supplementary Fig. 1). Deionized water was used to dissolve the JTT for administration to animals.

Morphine hydrochloride was purchased from Qinghai Pharmaceutical Co., China and dissolved in 0.9% saline. (S)-(-)-N-((1-ethyl-2-pyridinylidinyl)methyl)-2-hydroxy-6-methoxy-3-(trimethylstannyl)benzamide (TBZM) and (1R,2S,3S,5S)-methyl-8-methyl-3-(4-(trimethylstannyl)phenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (TMS-β-CT) were purchased from Huaiy Isotope Co., Toronto, Ontario, Canada. Na[125I](-2200 Ci/mmol) was purchased from PerkinElmer Inc., Waltham, MA, USA. [125I]-IBZM and [125I]-β-CT were prepared as described in the literature (Kung et al., 1991; Toyama et al., 1993).

Morphine dependence model, JTT treatment and behavior observation. The rats were divided into 6 groups: the control group, the morphine group, the JTT pre-treatment group and the JTT post-treatment groups (0.029, 0.087 and 0.290 g/kg). The rats in the morphine, JTT pre-treatment and JTT post-treatment groups were given morphine via intraperitoneal injections twice daily (9:00 am and 15:00 pm) for 8 days at a volume of 1 mL/kg body weight with a gradually increasing dose (10, 10, 15, 15, 20, 20 and 20 mg/kg per injection each day, respectively) (Buckman et al., 2009; Schulteis et al., 1998). Control animals received 0.9% NaCl solution in the same volume. JTT was dissolved in deionized water and given through oral gavage to the rats in the JTT pre-treatment group at a dose of 0.087 g/kg before each injection of morphine. For rats in the JTT post-treatment groups JTT was given, after the last morphine injection, at a dose of 0.029, 0.087 or 0.290 g/kg, respectively, once daily for ten days, while control rats received the same amount of vehicle. The high JTT dose of 0.290 g/kg was directly converted from the clinical dose, while the other two doses (0.029 and 0.087 g/kg) were added to investigate potential

dose–effect relationship of JTT (Li et al., 2007; Xiong et al., 2001; Zharkovsky et al., 1993).

At 10:00 a.m. on days one, five and ten after the withdrawal of morphine, the animals were placed individually into Plexiglas cages and observed for signs of acclimatization spontaneous withdrawal. Following a 5-min acclimation in the cages, the number of wet dog shakes and writhing episodes were monitored during a period of 30 min (Zharkovsky et al., 1993). Three observers blind to the groups completed the observation and scored independently. Scores were averaged for each behavior test.

**Tissue preparation.** After the last behavioral observation, the rats were sacrificed by decapitation. Brains were rapidly removed and stored at −80 °C until further use. Brains were cut in a cryostat (CM1900, Leica, Germany) at −20 °C into 18-μm coronal sections.

**Immunohistochemical staining.** The immunohistochemical staining of striatal slices was conducted and analyzed for DAT, D2R and TH densities. The striatal slices were prewashed in PBS (0.01 M, pH = 7.4) and then treated with PBS containing 0.2% Triton X-100 for 5 min. After that, the slices were treated with 0.3% H2O2 in PBS for 10 min and then washed in PBS. Finally, the slices were treated with 10% normal goat serum for 10 min and then incubated with the primary antibody (1:200 dilution of D2R antibody AB5084P and 1:100 dilution of DAT antibody MAB369 from EMD Millipore Corporation, Billerica, MA, USA) and then treated for 3 min in 100 μL of 3,3′-diaminobenzidine tetrahydrochloride (DAB) for visualization. The slices for TH staining were incubated with the ABC reagent (VECTASTAIN ABC kit, ZSGB-BIO, Beijing, China) for 30 min at 37 °C before visualization. The slices were then washed in distilled water.

**Autoradiography experiments.** Autoradiography was conducted to confirm the results of the immunohistochemical staining. Brain slices were prewashed at room temperature for 20 min in 50 mM Tris buffer (pH 7.4, containing 120 mM NaCl, 5 mM KCl, 2 mM CaCl2, 1 mM MgCl2) for D2R autoradiography, or in 50 mM Tris buffer (pH 7.4, containing 120 mM NaCl, 5 mM KCl) for DAT autoradiography. The slices were then incubated for 60 min in the same buffer with 50-pM [3H]-IBZM for D2R total binding or 50-pM [3H]-β-CIT in the presence of 1 μM fluoxetine (serotonin transporter inhibitor, Sigma-Aldrich Co., St. Louis, MO, USA) for DAT total binding. Nonspecific binding was determined in adjacent slices in the presence of 10-μM sulpiride (D2R antagonist, Sigma-Aldrich Co., St. Louis, MO, USA) for D2R, or 100 mM nomifensine (DAT inhibitor, Sigma-Aldrich Co., St. Louis, MO, USA) and 100 mM fluoxetine for DAT. After incubation, the slices were washed (5 × 1 min) in ice-cold 50 mM Tris buffer (pH 7.4) and then rapidly dipped in deionized water and dried under a stream of cold, dry air.

The labeled slices were mounted and exposed to super sensitive phosphor screen (PerkinElmer, USA) for 8 h. The densitometry determinations were carried out with a Cyclone-Plus phosphor storage system (PerkinElmer, USA) and analyzed with the Opti-Quant software (PerkinElmer, USA). Specific binding measured in each structure was determined by subtracting the non-specific binding image from that of the total binding. Results were shown as the ratio relative to the control group.

**Statistical methods.** All statistical analyses were conducted using SPSS (version 20.0) with a type I error rate of α = 0.05 (two-tailed). Data were expressed as mean ± SD. The significance of the changes in the behavioral tests was assessed using a Kruskal–Wallis test. If this test was significant, a Mann–Whitney U-test was used to compare the control and test groups. To compare the values obtained from 2 groups, Student’s t-test was performed.

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**RESULTS**

**Effect of JTT on spontaneous withdrawal symptoms**

**Effect of JTT pre-treatment on spontaneous withdrawal symptoms.** As shown in Fig. 1, one day after withdrawal, the number of wet dog shakes decreased to 2.0 ± 0.7 (p < 0.01, significance vs. morphine group) in the JTT pre-treatment group (Fig. 1A). Ten days later, although the symptoms in the morphine group had alleviated over time, they remained notably worse than those in the control group and the number of wet dog shakes remained significantly decreased in the JTT pre-treatment group (Table 1). In this model, the difference in the number of episodes of writhing between the morphine and control groups was only observed one day after withdrawal (Fig. 1B). In the morphine group, the number was 1.1 ± 0.6 (p < 0.01, significance vs. control group). Ten days after withdrawal, no writhing behavior was observed in any group (Table 2). These results show that JTT pre-treatment can effectively alleviate the acute withdrawal symptoms.

The effects of JTT post-treatment on spontaneous withdrawal symptoms. As shown in Fig. 2A, in the acute withdrawal period (day 1), JTT at all three dosages markedly decreased the number of wet dog shakes (JTT 0.029 g/kg, 3.4 ± 0.8, n = 10, p < 0.01; JTT 0.290 g/kg, 2.6 ± 1.2, n = 10, p < 0.01; significance: compared with morphine group, 5.6 ± 1.3) in a trend of dose dependence, that lasted till five days after withdrawal. At the end of the experiment (day 10), although wet dog shakes in the morphine group declined over time, the number was still significantly lower in the JTT post-treatment groups (Table 1). These results indicate that JTT...
post-treatment is able to alleviate wet dog shake behaviors effectively in a time-dependent manner. The difference in the number of episodes of writhing between the morphine and control groups was observed only one day after withdrawal (Fig. 2B). Number of writhing episodes in the JTT groups showed no significant differences from the morphine group afterwards (Table 2).

### Effects of JTT pre-treatment on DAT, D2R and TH densities in the striatum of morphine-dependent rats

**Effect of JTT pre-treatment on DAT.** DAT plays a key role in the reuptake of dopamine, and current research has shown that opioid addiction decreases the level of DAT in the striatum. The effect of JTT pre-treatment on DAT was determined by immunohistochemical staining (Fig. 3A) and autoradiography (Fig. 3B). In the morphine-dependent group, DAT was significantly decreased to 84.4 ± 4.4% of the control group (Fig. 3A). By pretreating the animals with JTT, this decrease was totally inhibited, and DAT was maintained at normal levels. The autoradiography results (Fig. 3B) were consistent with results of immunohistochemical staining (DAT availability: morphine group, 88.7 ± 5.4% of the control; JTT pre-treatment group, 103.7 ± 4.3% of control). The results indicate that JTT pre-treatment is able to completely inhibit the morphine-induced DAT decrease in the striatum.

**Effect of JTT pre-treatment on D2R.** The D2R is greatly affected in opioid addiction and decreased by chronic opioid use. The effect of JTT pre-treatment on D2R was also determined by immunohistochemical staining (Fig. 3C) and autoradiography (Fig. 3D). In the morphine group, the density of D2R decreased to 84.8 ± 2.8% of the control (Fig. 3C). Pre-treatment with JTT inhibited this decrease and maintained the D2R at levels comparable to those of the control group. The results from autoradiography (Fig. 3D) were consistent with those from immunohistochemical staining (D2R availability: morphine group, 78.5 ± 5.97% of the control; JTT pre-treatment group, 100.2 ± 7.7% of the control). These results show that JTT pre-treatment can inhibit the morphine-induced D2R decrease in the striatum.

**Effect of JTT pre-treatment on TH.** It is known that morphine changes DA concentrations in the synapse. Therefore, we examined the levels of TH, which is the key enzyme in DA synthesis. As shown in Fig. 3E, in the morphine-dependent group, the level of TH was decreased to 77.7 ± 4.1% of the control group, while pre-treatment with JTT inhibited this decrease and maintained a normal TH level (101.0 ± 5.9% of the control). These results indicate that JTT pre-treatment is able to inhibit the decrease in TH caused by morphine in the striatum.

### Table 1. Effects of JTT on wet dog shakes

<table>
<thead>
<tr>
<th>Day</th>
<th>NS + NS</th>
<th>NS + Mor</th>
<th>JTT + Mor</th>
<th>Mor + JTT 0.029 g/kg</th>
<th>Mor + JTT 0.087 g/kg</th>
<th>Mor + JTT 0.290 g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.8±0.6</td>
<td>5.6±1.2</td>
<td>2.0±0.6 **</td>
<td>3.4±0.8 **</td>
<td>3.4±0.5 **</td>
<td>2.6±1.2 **</td>
</tr>
<tr>
<td>Day 5</td>
<td>1.0±0.8</td>
<td>4.2±1.1</td>
<td>2.7±0.9 **</td>
<td>2.6±0.5 **</td>
<td>2.4±1.1 **</td>
<td>1.7±0.8 **</td>
</tr>
<tr>
<td>Day 10</td>
<td>0.7±0.7</td>
<td>2.4±0.5</td>
<td>1.7±0.9</td>
<td>1.4±0.5 **</td>
<td>0.9±0.7 **</td>
<td>1.0±0.9 **</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01, compared with morphine group;  
# p < 0.05; ## p < 0.01, compared with control group.

### Table 2. Effects of JTT on episodes of writhing

<table>
<thead>
<tr>
<th>Day</th>
<th>NS + NS</th>
<th>NS + Mor</th>
<th>JTT + Mor</th>
<th>Mor + JTT 0.029 g/kg</th>
<th>Mor + JTT 0.087 g/kg</th>
<th>Mor + JTT 0.290 g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.0±0.0</td>
<td>1.1±0.6</td>
<td>0.0±0.0 **</td>
<td>0.5±0.5</td>
<td>0.7±0.6</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>Day 5</td>
<td>0.0±0.0</td>
<td>0.5±0.7</td>
<td>0.3±0.4</td>
<td>0.5±0.5</td>
<td>0.0±0.0</td>
<td>0.5±0.5</td>
</tr>
<tr>
<td>Day 10</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.1±0.3</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01, compared with morphine group;  
# p < 0.05; ## p < 0.01, compared with control group.
Effects of JTT post-treatment on the densities of DAT, D2R and TH in the striatum

Effect of JTT post-treatment on DAT. As shown in Fig. 4A, in the group treated with a low JTT dose (0.029 g/kg), DAT level (81.6 ± 7.9% of control) was similar to that of the morphine group (84.4 ± 4.4% of control). Meanwhile, JTT restored DAT to normal levels at a dose of 0.087 g/kg (98.0 ± 3.3% of control) or 0.290 g/kg (101.3 ± 3.5% of control). The autoradiography results (Fig. 4B) were consistent with those from immunohistochemical staining (DAT availability: morphine group, 88.7 ± 5.4% of the control; JTT 0.029 g/kg, 89.2 ± 6.3% of the control; JTT 0.087 g/kg, 100.7 ± 3.4% of the control; JTT 0.290 g/kg, 101.1 ± 3.3% of the control). These results show that midle and high dose JTT post-treatment effectively reverses the morphine-induced DAT decrease in the striatum.

Effect of JTT post-treatment on D2R. Immunohistochemical staining showed that in the group of rats treated with low dose JTT (0.029 g/kg), D2R level was 89.6 ± 3.4% of control, significantly higher than that of the morphine group (84.9 ± 2.8% of control) (Fig. 4C). At the middle (0.087 g/kg) and high (0.290 g/kg) JTT doses, D2R was restored to normal levels (JTT 0.087 g/kg, 98.8 ± 3.1% of control; JTT 0.290 g/kg, 99.9 ± 2.1% of control; Fig. 4C). The results from autoradiography (Fig. 4D) were similar (D2R availability: morphine group, 78.5 ± 6.0% of the control; JTT 0.029 g/kg, 85.5 ± 4.0% of the control; JTT 0.087 g/kg, 97.3 ± 7.0% of the control; JTT 0.290 g/kg, 98.2 ± 6.4% of the control). These results indicate that JTT post-treatment effectively halts the decrease of D2R caused by morphine in the striatum.

Effect of JTT post-treatment on TH. Morphine induced a decrease in striatal TH to a level 77.6 ± 4.1% of the control group (Fig. 4E). At the dose of 0.0290 g/kg JTT, TH levels were increased to 89.2 ± 5.4% of the control. Additionally, post-treatment with JTT doses of 0.087 and 0.290 g/kg reversed this decrease and restored TH to nearly normal levels (JTT 0.087 g/kg, 94.0 ± 5.2% of the control; JTT 0.290 g/kg, 98.8 ± 7.8% of the control) (Fig. 4E). Therefore, JTT post-treatment appeared to normalize TH decreases induced by morphine in the striatum.

DISCUSSION

In this study, we designed the experiments to evaluate the effects of both pre- and post-treatment with JTT on the morphine withdrawal symptoms in a spontaneous withdrawal model, in which the withdrawal process is much closer to that of clinical patients. Spontaneous withdrawal from chronic morphine treatment induced only mild signs, and abstinence is commonly evidenced by wet dog shakes and episodes of writhing. Therefore, we chose wet dog shakes and episodes of writhing as the
indices to evaluate the effects of JTT on the withdrawal symptoms. Our results showed that both pre- and post-treatment with JTT effectively inhibited wet dog shakes and episodes of writhing. These findings provide pre-clinical evidence for the effects of JTT on alleviating withdrawal symptoms in clinical practice.
The present study is the first to investigate the effects of JTT on the dopaminergic system in a spontaneous withdrawal rat model, and represents the first attempt to understand the mechanism of action by JTT. Both pre- and post-treatment with JTT were found to effectively alleviate the withdrawal symptoms in morphine dependent rats. And JTT pre-treatment completely inhibited morphine-induced decreases in DAT, D2R and TH in the striatum, suggesting that JTT’s mechanism of action may involve modulation of the dopamine system. In addition, JTT post-treatment appeared to normalize morphine withdrawal-induced decreases in DAT, D2R and TH, confirming that JTT is able to act on the dopamine system effectively and countered the neurobiological injuries caused by morphine. Together, these results support the notion that modulation of the dopamine system may play an important role in JTT’s ability to alleviate withdrawal symptoms and treat opioid dependence.

Restoration of dopamine function is believed to be helpful for the treatment of opioid addiction and relapse. Chronic administration of morphine or heroin to rodents causes decreased concentrations of TH, DAT and D2R in the striatum (Acquas et al., 1991; Crippens and Robinson, 1994; Self et al., 1995; Simantov, 1993; Wang et al., 1997). Decreases in DAT and D2R have also been shown in patients addicted to heroin (Martinez et al., 2012; Shi et al., 2008). Collectively, these findings are consistent with the hypothesis that, if the damaged brain tissue is regenerated and dopaminergic function is restored, an effective treatment of opioid addiction may be achieved (Leshner, 1997). In a previous brain imaging study in heroin-dependent subjects, we have shown that JTT can effectively restore DAT in the striatum (Liu et al., 2013). Results from the present study provide further evidence that modulation of the dopaminergic system plays an important role in the therapeutic mechanism of JTT and offer further insights on new strategies for opioid dependence treatment.

Usually, TCMs act by targeting multiple biological systems and through multiple pharmacological mechanisms. The mechanism underlying the ability of JTT to up-regulate DAT, D2R and TH levels is likely due to the combined effects of its active ingredients. Some components of JTT, such as l-THP, scopolamine and ginsenosides, have been reported to be effective in regulating the DA system in heroin-dependent patients and animals (Chu et al., 2008; Kim et al., 1995; Tsukada et al., 2000; Yang et al., 2008). Taken together, JTT appears to be effective at reversing the morphine-induced decreases in DAT, D2R and TH levels and actions at the dopaminergic system likely contribute to the clinical efficacy of JTT in the treatment of opioid dependence. However, further research is required to determine whether these modulatory actions at the DA system play a role in preventing relapse.

Clear mechanism(s) of action can hardly be attributed to a prescription constituted of a complex herbal mixture (with 15 different herbs with 101 compounds tentatively identified in a previous study) (Wang et al., 2012a, 2012b). Since it is truly difficult to identify how and which of these compounds modulate the dopaminergic activity in the striatum though the normalization of the activity had been seen in this study. Moreover, plant extracts may exhibit synergetic and antagonistic effects, and the quantity of chemical compounds present in extracts depends on the time and area of collection. On the other hand, traditional Chinese medicines (TCMs) are more likely to exert mild and multi-target action with few side-effects based on the practice of evidence-based medicine. Hence, TCMs may stand a chance as an alternative for the treatment of opioid addiction, considering that present medicine for opioid addiction cannot reverse the impaired neuronal system in addicts and possess adverse side-effects and abuse potential.

In summary, results from the present study demonstrate that JTT alleviates spontaneous morphine withdrawal symptoms. JTT treatment is associated with prevention or normalization of the decreases in striatal DAT, D2R and TH levels induced by subchronic morphine administration. This is the first report to demonstrate the modulatory effects of JTT on the dopaminergic system, and our study provides an insight into the clinical advantages of JTT treatment for opioid addiction. However, the use of JTT as a therapeutic agent to produce recovery-promoting effects on the dopamine system still needs to be investigated clinically.

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### Conflict of Interest

The authors declare that there is no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of this article at the publisher’s web site:

**Figure S1.** High-performance liquid chromatography fingerprint profile of JTT samples registered at 280 nm.