1. Introduction

Osteoarthritis (OA) is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and a variable degree of local inflammation. Approximately 10% of the population worldwide aged 60 years or older has symptomatic problems that can be attributed to OA [1]. Many of these patients rely on prescription medications, even though their effects are often minimal and...
can cause severe side effects, such as gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use [2]. Owing to the limitations of prescribed medication, acupuncture has been studied as a novel alternative treatment for OA. The positive effects of acupuncture used as OA treatment have been demonstrated in many systematic reviews [3,4] and meta-analysis studies [5,6].

Pharmacopuncture is a form of acupuncture in which the basic treatment involves stimulation of acupoints [7]. Solutions of herbal medicine extracts are injected into the acupoints. The mechanical stimulation of acupuncture and the chemical effects of an herbal medicine are combined to enhance and prolong the effects of acupoint access [8].

The root bark of *Ulmus davidiana* Planch (UDP) var. japonica Nakai has long been used by practitioners of Oriental medicine for treatment of inflammation. The bark also has analgesic and anti-edema properties, and has been shown to inhibit leukocyte migration [9]. In the present study, the herb was used to manufacture pharmacopuncture injections and was tested for safety and efficacy in OA patients in a double-blind randomized controlled trial.

### 2. Materials and Methods

#### 2.1. Subjects

Patients were recruited by the Department of Acupuncture and Moxibustion of Dongguk University, Ilsan Hospital through advertisements posted within the hospital from August 2008 to December 2008.

Subjects satisfying the following criteria were included:
1. At least 40 years of age, but below 80 years of age;
2. Presence of knee OA diagnosed by an orthopedist based on American College of Rheumatology classification criteria;
3. Knee pain from OA in one or both knees rated >4 cm on a 10 cm Visual Analog Scale (VAS);
4. An understanding of the objectives and methods of the clinical trial, and willingness in completing the consent form.

Subjects meeting any of the following criteria were excluded:
1. A physical or laboratory finding indicating infection, presence of an autoimmune disease, or inflammatory arthritis;
2. Trauma to or surgery on the knee(s) within 6 months prior to enrollment, causing pain or functional problems;
3. A history of prolotherapy, injection of hyaluronic acid or cortisone within the last 3 months;
4. Serious organic disease, including mental disorders;
5. More severe pain in regions other than the knee joint.

After a brief telephone screening, patients were asked to visit the hospital to learn about the clinical trial and to sign an informed consent statement. Blood tests (including a complete blood count, erythrocyte sedimentation rate, and measurement of rheumatoid arthritis factor and uric acid levels), and radiographic and physical examinations were performed. Statisticians were consulted to randomly assign patients into two groups: an UDP pharmacopuncture group (UDP group) and a normal saline injection control group (control group). Allocation concealment was maintained by employment of opaque sealed envelopes. All subjects, practitioners, and the assessor were blind to treatment allocation.

#### 2.2. Procedures

This study was a two-branched parallel double-blind randomized controlled trial. The control intervention was adopted from prior studies [10] using normal saline as the control for pharmacopuncture. All subjects went through 2 weeks of screening, and received 6 weeks of treatment followed by 10 weeks of follow-up. The total follow-up period was 16 weeks. This study abided by the general guidelines of the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Board of Dongguk University, Ilsan Hospital, prior to study commencement.

The treatment intervention was based on traditional meridian theory and an acupuncture method widely used in clinics to treat knee joint pain, known as the ‘Bi’ syndrome. Treatment was administered by two doctors of Oriental medicine with extensive clinical experience of pharmacopuncture and the following qualifications:
1. Certified by the Korean Ministry of Health and Welfare as an Oriental medicine doctor;
2. More than 1 year of postgraduate clinical training in an Oriental medicine hospital;
3. Completion of the first-year residency program of our Department of Acupuncture and Moxibustion;
4. Graduate of a 6-year full-time course in Oriental medicine, taught as a college program.

Each subject was treated by a single practitioner throughout the 6-week period. Both the UDP pharmacopuncture patients and normal saline control patients received treatment twice a week for 6 weeks, to yield a total of 12 treatment sessions. Four local acupoints on the affected side were used. The points used were Dubi (ST35), Xiyan (EX-LE5),
Heding (EX-LE2), and Ashi. A pharmacopuncture needle (29 gauge; 1 mL disposable insulin injection syringe) was employed. The depth of needle insertion was about 5–15 mm for each acupoint. A penetrating, sharp and painful sensation was induced when the skin was broken. A spreading and lumpish sensation around the injection site was also reported. If both knees of a patient were affected, both knees were treated.

The injection of UDP pharmacopuncture was produced using extraction via distillation. Dried root bark of UDP var. japonica Nakai (200 g) was washed and grinded in order to make the active elements extract easily. The prepared material was inserted into a tubular flow reactor together with 1.5 L of water distilled three times. The material was sufficiently soaked before being boiled. The vapor was condensed to liquid using a circulative cooling system. The obtained solution was refrigerated and the top layer was collected. The pH was adjusted to 7.3 by using Na₂PO₄, and the salinity was regulated to be 0.98% by using NaCl. Afterwards the solution was filtered, subdivided, sterilized and injected into the acupoints using a syringe.

As the control intervention, normal saline was used in place of UDP pharmacopuncture to identically stimulate acupoints, minus the chemical effects. The needle used, the acupoints selected, the depth of needle insertion, and the treatment schedule for the control group were identical with those of the UDP group. As normal saline is no different in appearance from that of the UDP pharmacopuncture preparation, blinding of both patient and practitioner was possible. To ensure blinding of the patient, practitioner, and assessor, the UDP pharmacopuncture and normal saline injections were prepared by an independent research assistant.

Patients in both the treatment and control groups already taking medication were allowed to maintain prior medication until the end of the study. Any change of medications in patients of the treatment or control groups due to increased pain was reported immediately to the research assistant. And use of pain killers or patches was monitored and recorded by the research assistant on every visit.

A 100 mm VAS to evaluate the severity of pain was used as the primary outcome measurement in this trial. Secondary outcome measurements were obtained using the Western Ontario and McMaster Universities (WOMAC) instrument (both the total score and the subscores), the KHAQ (Korean Health Assessment Questionnaire), and the SF-36 (36-Item Short Form Health Survey Instrument). The 0–100 mm VAS and WOMAC pain scales were assessed at baseline, before each treatment, and after 16 weeks. The WOMAC, SF-36, and KHAQ scores were assessed at baseline and after 3, 6, and 16 weeks. For bilateral OA patients, the side with more pain at baseline was evaluated throughout the study.

To explore the masking effect of the control intervention, participants in the UDP pharmacopuncture and control groups were asked which treatment they believed they were receiving at each session: “true UDP pharmacopuncture”, “normal saline”, or “uncertain”. Any physical or clinical changes, whether or not considered to be related to acupuncture (excluding progression of disease), were to be reported by the practitioner and patient at each treatment visit.

### 2.3. Statistical analysis

The statistical analysis package SAS version 9.1 (SAS Institute, Cary, NC, USA) was used. All data of patients who complied with the clinical study plan were analyzed by the Per-protocol (PP) method, and not by Intention-to-treat (ITT). Continuous variables were compared using Student’s t test or a paired t test. Discontinuous variables were analyzed with the Chi-squared test. Statistical significance was fixed at $p < 0.05$.

### 3. Results

Of the 107 volunteers, 38 were excluded before randomization. This exclusion was due to insufficient pain ($n=16$), severe pain in other parts of the body or other serious medical conditions ($n=13$), or abnormal blood test results indicating that rheumatoid arthritis or gout might be present (such as elevated rheumatoid arthritis factor or uric acid levels; $n=9$). Also, nine further patients were excluded before randomization for personal reasons. Thus, the 47 subjects mentioned above were excluded from statistical analysis. The remaining 60 subjects were randomly assigned to one of two groups. One patient from each group discontinued the study for personal reasons. Two patients from the normal saline control group were lost to follow-up owing to a traffic accident. Three additional subjects from the control group were excluded from statistical analysis because each failed to attend assessment visits. Data from 29 subjects in the treatment group and 24 in the control group were ultimately analyzed (Figure 1).

Among the 53 subjects, 83% were women, and 55% were aged more than 60 years. There were no significant between-group differences in demographic characteristics or baseline VAS scores, suggesting that randomization procedures were appropriate and had successfully produced similar groups at baseline (Table 1). No cases of increased OA medication dosage were reported. The use of
Painkillers or patches in the two groups showed statistically insignificant differences.

Figure 2 shows changes in mean 100mm pain VAS. Figures 3, 4 and 5 indicate changes in mean WOMAC pain score, total WOMAC score, and KHAQ score in each group. All measurements, except the SF-36 scores, showed significant improvements in both groups. As shown below, VAS was almost the same at baseline and during initial treatment. The UDP group showed better improvement after the third assessment compared with the control group, but this was not significant until the sixth assessment. After the seventh treatment, the UDP pharmacopuncture treatment group (44.1 ± 18.0), compared with the control group (55.2 ± 21.6), showed a significant difference in pain improvement (p = 0.04). However, the between-group difference then decreased and was again insignificant.

The WOMAC pain score, total WOMAC score and KHAQ score of the UDP group showed improvement at the time of the seventh treatment, but between-group differences were not significant throughout the study (Figures 3, 4 and 5).

To evaluate the masking effect of the control intervention, participants in the UDP pharmacopuncture and control groups were asked which treatment they believed they were receiving at each session: “true UDP pharmacopuncture”, “normal saline”, or “uncertain”. The number of patients who responded “uncertain” was greatest at baseline (UDP group 82.8%; control group 70.8%). After the 13th treatment, the number of subjects who believed that they were receiving true UDP pharmacopuncture increased (UDP group 44.8%; control group 45.8%). The difference between the two groups was not significant, indicating that blinding was successful (Tables 2 and 3).

During the 6-week study period, 3 of the 60 subjects who completed the study reported side effects. One subject reported nausea (UDP group),
Figure 2  Mean 100 mm visual analog scale (VAS) change in the *Ulmus davidiana* Planch (UDP) pharmacopuncture group and the normal saline control group. *p* = 0.04.

Figure 3  Mean Western Ontario and McMaster Universities (WOMAC) pain score change in the *Ulmus davidiana* Planch (UDP) pharmacopuncture group and the normal saline control group.

Table 2  Assessment of blinding at first visit

<table>
<thead>
<tr>
<th>Guesses at first visit</th>
<th>UDP pharmacopuncture group (n=29)</th>
<th>Normal saline control group (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDP pharmacopuncture</td>
<td>2 (6.9%)</td>
<td>7 (29.1%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>24 (82.8%)</td>
<td>17 (70.8%)</td>
</tr>
<tr>
<td>Normal saline</td>
<td>3 (10.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

UDP = *Ulmus davidiana* Planch.

Table 3  Assessment of blinding at 13th visit

<table>
<thead>
<tr>
<th>Guesses at 13th visit</th>
<th>UDP pharmacopuncture group (n=29)</th>
<th>Normal saline control group (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDP pharmacopuncture</td>
<td>13 (44.8%)</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>13 (44.8%)</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>Normal saline</td>
<td>3 (10.3%)</td>
<td>3 (12.5%)</td>
</tr>
</tbody>
</table>

UDP = *Ulmus davidiana* Planch.
Pharmacopuncture using root bark of *Ulmus davidiana* Planch

one itching (UDP group), and one slight dizziness (control group). These minor complaints resolved in a short time and did not recur. The incidence of such symptoms was 5%, indicating that side effects were rare. The patients wished to continue treatment, and therefore did not drop out during the study.

4. Discussion

Pharmacopuncture is a recent innovation of traditional acupuncture that aims to enhance and prolong the effects of stimulation of acupoints [8]. Pharmacopuncture is also termed “aquapuncture” [11] or “herbal acupuncture” [12] and is used in Korea, China, and Russia [13−15].

Among the various pharmacopuncture formulae, this clinical study used UDP pharmacopuncture because the dried root bark of UDP var. *japonica* Nakai is known to be effective for treating inflammations in Oriental medicine. In fact, recent *in vitro* and *in vivo* assays have reported UDP to have a positive effect for arthritis treatment [16−21].

We sought to determine whether UDP pharmacopuncture was effective in patients suffering OA of the knee. Our findings indicate that UDP pharmacopuncture was effective in improving VAS-rated pain after the seventh treatment (in the third week), compared with normal saline. It has been reported that traditional acupuncture requires 6−8 weeks of treatment before development of significant effects when used to treat OA of the knee [22]. The studies by Witt et al [23], Williamson et al [24], Berman et al [25], and Miller et al [26] ranging from 7 to 12 weeks all support this idea. However, the pharmacopuncture used in the present study was administered over seven treatment sessions within 3 weeks in an effort to show a significant difference between test and control groups. This is shorter than traditional acupuncture treatments. However, pharmacopuncture may be stronger than traditional acupuncture [8]. The chemical effects of UDP solution have been reported in recent *in vitro* and *in vivo* studies [16−21].

Overall, the results showed that only VAS-rated pain (after the seventh treatment) showed a significant between-group difference and that all other outcomes (WOMAC−, total WOMAC−, SF-36−, and KHAQ-rated pain) were similar in both groups. One possible reason is that the normal saline group may not have been a suitable placebo control. A placebo in a clinical trial should appear to be real, but must be inert [27,28]. UDP pharmacopuncture and normal saline were identical in appearance and the patient-masking effect was successful (Tables 2 and 3). However, the inertness of normal saline is debatable. In a prolotherapy study on musculoskeletal disease, normal saline injection showed the same treatment effects as did prolotherapy [29,30]. Also, in studies of joint lavage [31−33], the control group intervention, a normal saline injection, improved VAS-assessed pain. Normal saline injection into the P6 acupoint was also found to be as effective as droperidol in controlling nausea and vomiting [34]. Many earlier pharmacopuncture studies [10,35−39] used normal saline injection as a control group intervention owing to the identical appearance of test and control solutions. We followed the recognized placebo design; however, just as minimal acupuncture was concluded to be an invalid placebo control for randomized controlled trials of acupuncture in a physiological setting [28], normal saline injection might not be a valid control intervention for pharmacopuncture studies because the injection has a pain-relieving effect.

The effects of pharmacopuncture treatment are a combination of placebo, needle stimulation,
mechanical effects of the solution, and the chemical effects of UDP. However, normal saline injection also has the first three effects, perhaps rendering saline inappropriate as a control placebo intervention.

In summary, UDP pharmacopuncture, compared with normal saline injection, caused pain improvement after the seventh treatment session, but overall, differences were generally insignificant. This may be due to the inappropriateness of the control intervention. For accurate reassessment of pharmacopuncture, an inert control intervention such as dry needling or a waiting list control should be used in future studies. Also, more work on efficient extraction and concentration of useful components in UDP are needed. Furthermore, pharmacopuncture is usually applied together with traditional acupuncture in clinical practice. Therefore, a further study investigating the effects of a combination of acupuncture and pharmacopuncture is required.

Acknowledgments

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References

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