Clinical trial of osteoarthritis jamu formula compare to piroxicam

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Abstract

Background: Indonesian herbs have several formulas which have been used traditionally to reduce pain of osteoarthritis (OA). However, there is a lack of evidence of its efficacy and safety. The objectives of study were to investigate the efficacy and safety of a traditional formula for OA.

Methods: Design of the study was a randomized clinical trial (RCT) involved 123 patients (subjects) for 28 days intervention. This study was conducted between March - December 2014 with 30 physicians were participated at 20 regencies in Indonesia. The variables measured were VAS score, PGAP functional status assessment (FSA), and Short Form (SF-36) to assess jamu formula using values of SGOT, SGPT, BUN, and creatinine.

Result: The jamu formula administration effects can reduce VAS significantly (p<0.05) if it was compared to baseline. FSA score of jamu formula group was decreased significantly (p<0.000) when compared to the start of intervention. Short Form (SF)-36 of jamu formula group were significantly improved when compared with baseline value. The result of the three parameters between jamu group and piroxicam group should not significantly different. There was no difference in those parameters between both groups (p>0.05). In biological parameters, SGPT, SGOT, BUN, and creatinine level, showed normal range in both groups.

Conclusion: This study showed that the efficacy and safety of jamu formula was clinically comparable to piroxicam after 28 days of treatment. (Health Science Journal of Indonesia 2016;7(2):84-92)

Keywords: efficacy, safety, RCT, jamu formula
Steoarthritis (OA) results from an imbalance between breakdown, repair of the tissues in the synovial joint organ and occurs as a result of multiple risk factors including trauma, overuse, and genetic predisposition. It was estimated that 9.9 million adults had symptomatic osteoarthritis of the knee in 2010. Risk factors of the condition increase with age, especially in women. Genetics, large body mass, certain occupations, repetitive knee bending or heavy lifting, and hereditary vulnerability are other factors that increase one’s risk of developing the disease.¹

Some alternative therapy can be used to reduce OA. Neuromuscular electrical stimulation (NMES) is presented as a technique used by physical therapists,² and moderate pressure massage therapy can reduce pain and increase motion.³ Yoga and tai chi showed significant reductions in pain caused by OA[⁴]. Hundreds of herbal remedies are used for treating OA and the research literature, it reflect only a small percentage of them. It seems that herbal remedies could effective to lower or stop the consumption of Nonsteroidal Antiinflammatory Drugs (NSAIDs) and to reduce the incidence of adverse effect of NSAIDs.⁵

Randomized controlled trial (RCT) of traditional herbal formulation administrated by topical from chamomile oil, can decrease pain and consumption of analgesic.⁶ A lot of studies about oral herbal administrated are increasing and also interesting because it is compare with NSAIDs such as Chinese herbal recipes versus diclofenac. It shows that herbal recipes are as effective than conventional drug to reduce OA.⁷ Previous study of jamu formula has been done before with pre post design and it shows jamu formula can decrease the joint pain.⁸

Indonesia has several herbs formulas which have been used traditionally to reduce pain of OA. The present study was conducted to investigate the efficacy and safety of traditional herbs formula that consist of Curcuma xanthorrhiza rhizome, Centella asiatica herbs, Curcuma domestica rhizome, Foeniculum vulgare seeds, Orthosiphon stamineus leaves, Phyllantus niruri herbs, Equisetum debile herbs. The efficacy of formula would be compared to piroxicam. The safety of formula would investigated by examined the kidney and heart function through evaluate the values of SGOT, SGPT, BUN, and creatinine.

**METHODS**

Plants and piroxicam materials

The formula were prepared by Post Harvest Section, Department of Research and Development Medicinal Plant and Traditional Medicine Center (B2P2TOOT) Tawangmangu Indonesia. The jamu was consisted of 15g Curcuma xanthorrhiza dried rhizome, 3g Centella asiatica dried herbs, 15g Curcuma domestica dried rhizome, 3g Foeniculum vulgare seeds, 5g Orthosiphon stamineus dried leaves, 7g Phyllantus niruri dried herbs, and 5g Equisetum debile dried herbs respectively.

Ten mg capsule of commercially marketed generic piroxicam were provided by PT. Indofarma (Indonesia). Subjects were selected randomly which use piroxicam, are prescribed once daily 1 capsule, after meal.

Inclusion and exclusion criteria

Inclusion criteria of subject for this study were as follow: age within 50 – 70 years old, Visual Analogue Scale (VAS) that classified as medium or light cathegory with V AS 70 ≤ VAS > 30 score, no history of allergic to herbal drugs, and did not take any other medication (analgesic, NSAIDs, etc) at least 2 weeks before intervention (washed out period). Exclusion criteria of subject included having complication diseases (subject’s medical record), gastritic disorder, ulcus pepticus or ulcus duodenum, allergic of bitter herbs, hypersentitive of curcumin, and taking medication during the study.

Study design

This study was conducted at Medicinal Plant and Traditional Medicine Research and Development Center, Tawangmangu, Indonesia. The study designed was a prospective, randomize, open label, and multicenter to evaluate efficacy and safety of jamu formula that claims reduce pain of OA. The study was carried out between March - December 2014. Ethical clearance was approved by The Ethic Commission of Health Research and Development Department, Health Ministry Republic of Indonesia (LB.02.02/5.2/KE.148/2014).

Among 30 physicians and 123 patients were participated in this study. The physicians were from 20 regencies in Indonesia, who involved in Saintifikasi Jamu (SJ) program held by Ministry of Health Republic of Indonesia (Fig. 1). Prior to receive
treatment, all patients were checked on VAS score, PGAP functional status assessment (FSA), Short Form (SF-36), SGOT, SGPT, BUN, and creatinine. Every subject who had inclusion criteria, received a form of compliance, and they should sign the form after they took the jamu formula or piroxicam as well as when they forgot to take it.

**Efficacy and safety measures**

The efficacy of jamu formula was assessed as baseline, at days 7, 14, 21, and 28. These assessments consist of VAS that evaluated pain, PGAP functional status assessment (FSA), and SF-36. The safety was performed by examining the values of SGOT, SGPT, BUN, and creatinine, to assess kidney and liver function at baseline, days 14, and 28.

Besides VAS, this study used PGAP functional status assessment (FSA) to demonstrate its reliability in the dimension of degree of dependence in performing basic activities of daily living. There are three dimensions of this measurement namely dependency, difficulty, and pain for 44 different activities of daily living (Table 1). Dependence score was assigned as follows: 0 = independent, 1 = uses mechanical assistance, 2 = uses human assistance, 3 = uses both mechanical and human assistance, and 4 = cannot perform the activity even with maximum assistance. Score for degree of difficulty and pain were assigned on a 4-point scale which range from 1 = no pain/difficulty, 2 = mild pain/difficulty, 3 = moderate pain/difficulty, and 4 = severe pain/difficulty respectively.

![Flowchart of recruitment and enrollment process](image-url)

**Table 1. PGAP Functional Status Assessment (FSA) Instrument Items**

| Mobility                        | Personal Care                       | Work                                      |
|---------------------------------|-------------------------------------|-------------------------------------------|
| Driving/Other transportation    | Using a Telephone                   | Empouement/Occupation                     |
| Shopping                        | Writing                             | Using Stove/Oven/Refrigerator             |
| Walking Inside                  | Cutting Food                        | Using sink/faucets                        |
| Walking Outside                 | Drinking                            | Reaching Cupboards (High/Low)            |
| Stairs in/to Home               | Ability to wash all areas           | Lifting Pots/Pans                         |
| Other Stairs                    | Turning Faucets                     | Peeling/Cutting                           |
| Curbs                           | Care of Teeth                       | Opening containers                        |
| Transferring to/from bed        | Shaving                             | Doing Laundry                             |
| Transferring to/from chair      | Combing Hair                        | Sweeping/ Mopping                        |
| Transferring to/from toilet     | Setting Hair                        | Cleaning Bathroom                         |
| Transferring to/from bath       | Putting on and tying shoes          | Washing Windows                           |
|                                 | Putting on hose/pants               | Doing home repairs                        |
|                                 | Putting on shirt/blouse             | Doing Yardwork                            |
|                                 | Buttoning/ Zipping                  | Making beds                               |
|                                 | Putting on sweater/coat             | Washing dishes                            |
**Jamu formula**

All subjects were instructed to boil 1L of water, and put jamu formula into boiling water, wait 15 minutes and stop the boiling process. Let the water cooling down, filtered and take it each a glass three times a day after breakfast, lunch, and dinner.

**Statistical analysis**

Data were analyzed statistically using a software program for statistical analysis version 18.0. Descriptive data were calculated and presented as table to assess demographic characteristic, VAS, FSA, SF-36, and level of SGOT, SGPT, BUN, and creatinine between two groups.

**RESULTS**

A total of 123 subjects (patients) were randomly selected and administrated by jamu formula and piroxicam (17 male and 46 female in formula group, 19 male and 41 female in piroxicam group). The majority of patients are women, it shows that women have higher prevalence of OA than man at age of 50 years or more [7]. The result shows that jamu formula and piroxicam group were not significantly different (p<0.05) in demographic data e.g., sex, age, occupation, body mass index (BMI), and duration of OA (Table 2).

| Characteristic            | Formula group (n) | Piroxicam group (n) | Total (n) | P     |
|---------------------------|-------------------|---------------------|-----------|-------|
| Age 50 – 60 y.o           | 17                | 25                  | 42        | 0.237a|
| 61 -70 y.o                | 46                | 35                  | 81        |       |
| Sex                       |                    |                     |           |       |
| Men                       | 17                | 19                  | 36        | 0.043a|
| Women                     | 46                | 41                  | 87        |       |
| Occupation                |                    |                     |           |       |
| Retired                   | 19                | 23                  | 42        | 0.579a|
| Military/Police/Officer   | 9                 | 11                  | 20        |       |
| Employee                  | 6                 | 5                   | 11        |       |
| Entrepreneur              | 16                | 11                  | 27        |       |
| Labor/farmer/fisherman    | 4                 | 5                   | 9         |       |
| Other jobs                | 7                 | 5                   | 12        |       |
| BMT                       |                    |                     |           |       |
| Underweight               | 2                 | 2                   | 4         |       |
| Normoweight               | 10                | 12                  | 22        | 0.493a|
| Overweight                | 14                | 15                  | 29        |       |
| Obes 1                    | 32                | 25                  | 57        |       |
| Obes 2                    | 7                 | 4                   | 11        |       |
| Duration of OA            | 41.25 months      | 40.36 months        | 0.356b    |

(1) Chi-square test; (2) paired t test

![Figure 2. Comparison VAS score between formula and piroxicam group](image-url)
This study was demonstrated the efficacy of the formula based on improvement of clinical parameters that were showed by VAS score, PGAP functional status assessment (FSA), and SF-36. VAS score that evaluated pain and stiffness, was assessed on the end of days 7, 14, 21, and 28. They were significantly different (p<0.001) if it was compared to their own VAS score on base-line. VAS score were decrease in both groups every time they were measured. To assess significantly VAS score between formula group and piroxicam group, was used independent t-test at the similar period. Mean baseline of both groups were not statistically significant (p=0.952) and the effect of formula and piroxicam on the end of days 7, 14, 21, and 28, were not statistically significant either (p>0.05) (Table 3).

FSA score were measured on the end of day 7, 14, 21, and 28. The values of FSA were decreased gradually on formula and piroxicam group every measured. FSA score on the end of day 7, 14, 21, and 28, were significantly different (p<0.05) if it was compared to their own FSA score at baseline. To assess significantly FSA score between two groups, was used independent t-test at the similar period. Mean baseline of both groups were not statistically significant between them (p= 0.982). The jamu formula and piroxicam administration effects on FSA score statistically were not different (p>0.05) on the end of day 7, 14, 21, and 28 (Table 4).

| VAS score | Formula group (Mean±SD) | Piroxicam group (Mean±SD) | p value |
|-----------|-------------------------|---------------------------|---------|
| Baseline  | 59.44 ± 10.9            | 59.33 ± 9.67              | 0.952; NS |
| Day 7     | 52.06 ± 9.98            | 52.58 ± 10.4              | 0.778; NS |
| Day 14    | 48.57 ± 13.24           | 50.17 ± 12.34             | 0.491; NS |
| Day 21    | 41.90 ± 15.46           | 43.00 ± 14.53             | 0.686; NS |
| Day 28    | 36.75 ± 19.40           | 37.50 ± 17.55             | 0.821; NS |

Note: Statistical analysis was carried out using independent 't' test , p value p<0.05 (significant), NS = not significant

| FSA score | Formula group (Mean±SD) | Piroxicam group (Mean±SD) | p value |
|-----------|-------------------------|---------------------------|---------|
| Baseline  | 9.82 ± 1.57             | 9.35 ± 1.53               | 0.982; NS |
| Day 7     | 8.62 ± 1.91             | 8.25 ± 6.9                | 0.892; NS |
| Day 14    | 8.38 ± 1.83             | 7.77 ± 1.67               | 0.461; NS |
| Day 21    | 7.14 ± 1.76             | 6.83 ± 1.68               | 0.911; NS |
| Day 28    | 5.72 ± 1.40             | 5.51 ± 1.22               | 0.780; NS |

Figure 3. Comparison FSA score between formula and piroxicam group
The Short Form (SF)-36 is a generic measure which generated a profile of eight dimensions and for which there is some evidence for validity in OA patients [10]. Eight dimension of the SF-36 are physical functioning, social functioning, physical limitations, emotional limitation, pain, mental health, vitality, and general health perception. In this parameter, patients were measured only at baseline, day 14 and 28 (every two weeks) for generic and condition-specific outcomes. The statistical significantly of formula and piroxicam group in SF scores were assessed using paired T test, and it was significantly improved when compared to their baseline (Table 5). They were not statistically significant when compared between both of them on the similar period (p>0.05) except social functioning dimension on baseline (p=0.047) (Table 6).

To assess safety of the formula on liver and renal functions, the levels of the biological profiles were measured on baseline (pre-treatment) and day 28 (post-treatment). In biological parameters, SGPT, SGOT, BUN, and Creatinine level, showed normal range in both groups. There was no significant alteration in the levels of SGPT, SGOT, BUN, and Creatinine when compared with their own baseline (p>0.05) (Table 7). The statistical significantly of formula versus piroxicam group were assessed using independent T test, there was no significant differences (p>0.05) of the biological parameters when compared between them (Table 8).

**DISCUSSION**

A challenge osteoarthritis treatment is deciding which medications will provide the greatest symptom relief with lowest serious adverse effects[11]. Meanwhile, people who use of complementary and alternative medicine (CAM) belief that using“natural” treatments are safer than conventional medical treatments[12]. This study indicates the excellent efficacy and safety of the jamu formula and these promising OA symptoms relief result when compared with piroxicam as standart drug. Pain of the OA patient was significantly reduced after one week of formula intervention and much better after the end of intervention (day 28). The formula was found to be safe based on SGPT, SGOT, BUN, and creatinine level, showed in normal range.

| Dimensions of SF-36                  | Formula group | Piroxicam group |
|-------------------------------------|---------------|-----------------|
|                                     | Baseline Day 14 Day 28 | Baseline Day 14 Day 28 |
| Physical functioning                | 85.87±20.51 90.40±11.61* | 83.58±15.57 89.75±13.35* |
| Social functioning                  | 76.19±19.67 80.75±17.22* | 74.38±22.95 76.88±19.50* |
| Role Limitations (physical)         | 74.60±39.01 88.89±23.67* | 74.58±37.53 91.04±24.26* |
| Role Limitations (emotional)        | 82.01±35.83 93.65±21.67* | 84.44±32.16 92.22±23.26* |
| Pain                                | 66.19±23.40 76.63±20.59* | 63.83±20.64 72.88±18.80* |
| Mental health                       | 74.60±15.29 76.83±14.32* | 70.53±14.34 74.33±14.06* |
| Vitality                            | 71.47±18.20 75.95±15.13* | 71.33±15.15 75.42±13.06* |
| General health perceptions           | 61.35±19.01 63.73±15.59* | 64.67±16.18 66.83±12.85* |

Note: Statistical analysis was carryout using paired t test, p value <0.05 (significant), (*) significant compared with their own baseline.

| Dimensions of SF-36                  | p values | p values |
|-------------------------------------|----------|----------|
|                                     | Baseline | Day 14   |
| Physical functioning                | 0.318    | 0.835    |
| Social functioning                  | 0.047(*) | 0.141    |
| Role limitations (physical)         | 0.646    | 0.459    |
| Role limitations (emotional)        | 0.352    | 0.498    |
| Pain                                | 0.354    | 0.431    |
| Mental health                       | 0.228    | 0.461    |
| Vitality                            | 0.163    | 0.178    |
| General health perceptions           | 0.279    | 0.574    |

Note: Statistical analysis was carryout using independent t test, p<0.05 (significant), (*)significant.
The primary compound of jamu formula is curcuma (Zingiberaceae), the most frequently used in Indonesian herbs formula. Zingiberaceae are generally safe for human consumption \( [13] \). Curcumin is the major compound of \( \textit{Curcuma} \) and \( \textit{Zingiber} \) which are associated with their potency to inhibit ET-1 and to a lesser extent, PAF-mediated inflammatory responses \([20]\). In other compound, stem of \( \textit{Equisetum debile} \) can act centrally (such as narcotics) and peripherally (such as NSAIDs) but the exact mechanism remain in question \([21]\). Lignans are the important compounds in the \( \textit{Phyllanthus niruri} \) which have anti-inflammatory actions. Lignans seem to be directly or indirectly associated with their potency to inhibit ET-1 and to a lesser extent, PAF-mediated inflammatory responses \([20]\).

Mechanism of herbal medicine for OA have not been clearly revealed, but interactions with inflammation mediators and reduce cartilage degradation maybe a rational approach to using herbal medicine\([1]\). This study used piroxicam for standard drug, because it is cheaper than other NSAIDs such as diclofenac and meloxicam. It widely used for OA pain in Indonesia. Piroxicam was used by patient just once a day, it increases compliance of patients. In other group, piroxicam group was an increased biological parameters but it still showed in normal range.

The primary compound of jamu formula is curcuma (Zingiberaceae), the most frequently used in Indonesian herbs formula. Zingiberaceae are generally safe for human consumption \( [13] \). Curcumin is the major compound of \( \textit{Curcuma domestica} \) and \( \textit{Curcuma xanthorrhiza} \). Curcumin showed a significant improvement in morning stiffness, walking time and reduction in joint swelling \([14]\). Other compound of jamu formula is \( \textit{Centella asiatica} \), it contains flavonoid (quercetin, kaempferol, catechin, rutin, etc), triterpene (Asiatic acid, madecassic acid, asiaticoside, madecassoside), and essential oil (sesquiterpene,\( \alpha \)-humulene, trans \( \beta \)-farnesene, farnesene, gemicrene-D, bicyclogermacrene, \( \beta \)-caryophelene, and p-cymol\([15]\). The bioactive compound of \( \textit{Centella asiatica} \) showed antioxidiant activity that could have potential in preventing or slowing the progress of inflammation \([16]\) such as osteoarthritis.

Previous study indicated that an aerial part of \( \textit{Orthosipon stamineus} \) from Indonesia, showed potent inhibitory activity against the NO production in lipopolysaccharide (LPS)-activated macrophages-like \( J774 \) cells \([17]\). Increased concentration of nitrate, indicating elevated NO production in synovial fluid and serum of the inflamed joints in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis\([18]\). Various nonselective NO synthase inhibitors were used, such as orthosiphols A, B, D, X, H, K, M, and N, 7-O-deacetyllorosiphol B, 6- hydroxytornosiphol B, 3-O-deacetyllorosiphol I, 2,0- deacetyllorosiphol J, neoortosiphols A and B, norstaminol A, siphonols A-E, staminols A-D, orthosipholone C and D, 14-deoxy-14-O-acetyllorosiphol Y, 2-O- deacetyllorosipholone A, and neoortosipholone A\([19]\).

Lignans are the important compounds in the \( \textit{Phyllanthus niruri} \) which have anti-inflammatory actions. Lignans seem to be directly or indirectly associated with their potency to inhibit ET-1 and to a lesser extent, PAF-mediated inflammatory responses \([20]\). In other compound, stem of \( \textit{Equisetum debile} \) contains flavonoid, sterol, sapinon and tannin. They are responsible to anti-inflammatory activities. The anti-inflammatory actions of \( \textit{Equisetum debile} \), can act centrally (such as narcotics) and peripherally (such as NSAIDs) but the exact mechanism remain in question \([21]\).

Mechanism of herbal medicine for OA have not been clearly revealed, but interactions with inflammation mediators and reduce cartilage degradation maybe a rational approach to using herbal medicine\([1]\). This study used piroxicam for standard drug, because it is cheaper than other NSAIDs such as diclofenac and meloxicam. It widely used for OA pain in Indonesia. Piroxicam was used by patient just once a day, it increases compliance of patients. In other group, \( \textit{Foeniculum vulgare} \) can increase compliances of the patients because of the fragrant. The fragrant can cover the bitter taste of formula. Study result showed there was a decrease of SGPT, SGOT, BUN, and creatinine level in jamu formula group, it shows nephro-protective \([22,23,24]\) and hepato-protective \([24,25]\) activities. Although, piroxicam group was an increased biological parameters but it still showed in normal range.

The knowledge of Jamu is part of the public health sector within the Indonesian health system. Jamu or herbal medicine in Indonesia has a important role in achieving a better equity of primary health care. Jamu

| Parameters | Formula (Mean±SD) | Piroxicam (Mean±SD) |
|------------|------------------|---------------------|
|            | Baseline Day 28   | p value*            |
|            | Baseline Day 28   | p value*            |
| SGOT       | 20.40±4.74 19.38±3.44 0.335; NS | 20.77±4.61 20.88±4.70 0.344; NS |
| SGPT       | 20.75±4.71 19.94±4.23 0.267; NS | 20.69±4.16 20.95±2.11 0.267; NS |
| BUN        | 24.06±5.79 23.96±5.86 0.145; NS | 24.59±8.09 24.62±7.41 0.767; NS |
| Creatinine | 0.876±0.27 0.817±0.27 0.328; NS | 0.847±0.26 0.949±0.70 0.114; NS |

Table 7. Comparison of formula and piroxicam groups in term of biological parameters

| Parameter | p value |
|-----------|---------|
| SGOT      | 0.828; NS |
| SGPT      | 0.404; NS |
| BUN       | 0.145; NS |
| Creatinine| 0.691; NS |

Table 8. P value of formula versus piroxicam group in term of biological parameters

Note: Statistical analysis was carried out using independent ‘t’ test, p value p<0.05 (significant), (*) = significant
in the daily life of many Indonesians have been used mainly for self-medication. Traditional/herbal medicine has its own market, providing medication to some of the need of Indonesian people. Diversity, flexibility, easy accessibility, broad continuing acceptance, relative low cost, low levels of technological input, relative low side effects and growing economic importance are some of the positive features of Jamu.

In conclusion, the study found that osteoarthritis herb formula is effective and safe alternative for pain relief of OA and clinically comparable efficacy and safety to piroxicam after 28 days intervention.

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