

## Original Article

## Evaluation of physical stability and preliminary study on effectiveness of Benjakul cream in the treatment of primary knee osteoarthritis patients

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### Abstract

**Introduction:** Benjakul remedy is a Thai traditional medicine containing 5 herbs, these were *Piper retrofractum* Vahl., *Piper sarmentosum* Roxb. ex Hunter, *Piper interruptum* Opiz, *Plumbago indica* L., and *Zingiber officinale* Roscoe. Benjakul as an oral drug had been used in the treatment of various pain treatment and was effective in treating primary osteoarthritis. It had no skin irritation when applied to the skin.

**Objective:** To evaluate the physical properties of the Benjakul cream and evaluate their effectiveness in the treatment of primary osteoarthritis.

**Method:** Benjakul cream was tested under accelerated conditions. The physical was appearance assessed these were color, phase separation and pH value. Preliminary clinical studies on the effectiveness of Benjakul cream were performed on 15 primary knee osteoarthritis patients. Aged between 40 - 80 years. Patients received 2 g. of Benjakul remedy extract cream 3 times per day for 14 days. The efficacy was evaluated by using visual analogue scales and, Modified Thai WOMAC Index scores, time measurement after 100 metres walking.

**Result:** Benjakul cream was stable under accelerated condition testing. It could reduce volunteer with knee pains after 100 metres walking, reduced time. The volunteers significantly showed better quality of life when evaluated by WOMAC index scores.

**Conclusion:** Benjakul cream was stable under accelerated conditions tested and was effective in the treatment of primary knee osteoarthritis.

**Keywords:** Benjakul, Knee osteoarthritis, Cream, Thai traditional remedy

Received: 10 June 2019

Revised: 5 July 2019

Accepted: 8 July 2019

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## Introduction

Benjakul, a Thai traditional remedy, is in the National List of Essential Medicines.<sup>1</sup> It consists of 5 herbs: fruit of *Piper retrofractum* Vahl., root of *Piper sarmentosum* Roxb. ex Hunter, stem of *Piper interruptum* Opiz, root of *Plumbago indica* L., and rhizome of *Zingiber officinale* Roscoe. Benjakul, a hot taste recipes, is used for adjusting the balance of the four elements in body and relieving indigestion. Folk medicine healers used Benjakul in combination with other medicines to treat diseases related with muscle and bone and also paralysis.<sup>2</sup> Moreover, anti-inflammation of Benjakul has been reported. It was found that the ethanolic extract could to inhibit the secretion of nitric oxide by  $IC_{50}$  as 18.23  $\mu\text{g/ml}$ .<sup>3</sup> It also could reduced the swelling of rat paws induced with carrageenin, and exerted It was reported of antipyretic effects which caused from yeasts inducing fever in animal. These results suggested that Benjakul extract might inhibit prostaglandins synthesis which were responsible for of fever and intermediary substances for inflammation.<sup>4</sup> The study of its chronic toxicity on mice showed that Benjakul extract had no effect on tested animals and their blood chemistry after 6 month feeding.<sup>3</sup> In a clinical study, Benjakul extract was given orally to healthy volunteers for 28 days, there were no unwanted symptoms or toxicity found.<sup>5</sup> Benjakul extract is effective in treating primary osteoarthritis and was not different from diclofenac and it had no toxicity on the liver and the kidney functions.<sup>6</sup> It was also tested for skin irritation, which revealed no irritation on skin.<sup>7</sup> Benjakul cream was developed for applying on skin in the treatment of primary osteoarthritis. Therefore, the aim of this study was to estimate the physical properties and effectiveness of Benjakul cream on 15 primary knee osteoarthritis volunteers.

## Methods

### Preparation of Benjakul extract

The fruits of *P. retrofractum* Vahl., root of *P. sarmentosum* Roxb. ex Hunter, stem of *P. interruptum* Opiz, root of *P. indica*, and rhizome of *Z. officinale* were dried in oven at 50 degrees Celsius incubate overnight, then ground into coarse powder, mixed ratio 1:1:1:1:1 together and macerated with 95% ethanol for 3 days. After that, filtered and the filtrate was evaporated by the rotary evaporator. The residue was consecutively macerated twice. The crude extracts were combined and the percentage yield was calculated Benjakul ethanolic extracts at concentration of 23.13  $\mu\text{g/ml}$  could inhibiting 50% nitric oxide release. The amount of piperine of Benjakul extract was evaluated by High Performance Liquid Chromatography method (HPLC)<sup>8</sup>, the piperine content was found to be 70.7 mg /g and piperine content in Benjakul was not less than 27 mg/g.

### Preparation of Benjakul remedy extract cream

Cream preparation consists of two parts i.e. oil phase and water phase. Preparation of cream was done by melting the oil phase until the temperature reached 70 °C. The water phase was heated to 75 °C. Then add the oil phase into the water phase and mixed well, stirred until getting an emulsion at a temperature not exceeding 45 °C. Then add the flavors and Benjakul extract and stirred well. Kept Benjakul extract cream in well closed container.

### Evaluation of physical characteristics and stability of Benjakul remedy extract (Accelerated Condition)

Assessment of physical characteristics and stability were performed by heating - cooling cycle method. Benjakul cream was kept in the refrigerator at temperature of 4 °C. for 48 hours, then brought into the oven incubator at 45 °C. for 48 hours. These treatments were considered as one cycle.<sup>9</sup> It was repeated 6 times. The physical appearance was evaluated by observing the general characteristics of the creams, such as color, odor, and pH values.

### The preliminary clinical study of Benjakul cream

This research is quasi-experimental research which is one of the experimental group studies by pre test and post test measurement design. Benjakul cream was applied to volunteers and the results obtained were evaluated by comparing with before and after treatment. In this research 15 volunteers were selected by specific inclusion criteria such as

1) Males and females aged 40 - 80 years old who were diagnosed with primary osteoarthritis from the specialist physician. The diagnosis with clinical symptoms and radiographic images in grade levels 1-3.

2) Patients who have knee pain level 3 or higher when measured by Visual Analogue Scale (VAS).

3) There were body mass index number more than 32 kg/m<sup>2</sup>

4) Willing to follow instructions during the study and were not engaged in another research project.

5) There were no serious congenital disease and there was no wound either at the knee or knee crook.

6) There were no herbal medicine allergy.

The exclusion criteria in this project were as follow; 1) There were adverse reactions or serious danger from embrocation such as swelling, severe nausea and vomiting, angina, suffocation, rash etc. 2) Fail to follow the instructions during the study. This project was accepted by ethic committee of

Thammasat University approved by FDA Thai Government standard (registry number MTU-EC-TM-3-206/59)

### Testing the effectiveness of Benjakul cream

Fifteen volunteers who passed the screening criteria, applied 2 grams Benjakul cream on their knees 3 times per day for 14 days. Evaluation and following up of symptoms were done on day 7 and day 14 after receiving medication. This testing was evaluated by measuring the level of knee pain before and after walking on flat ground distance of 100 meters with Visual Analogue Scale (VAS). Evaluation the performance of the joint with WOMAC index score in Thai version<sup>10</sup> and measuring the time duration of the walk on the flat 100 meters.

### statistical tests

Collected and analyzed data were subjected to statistical analysis using Paired T-Test at 95%, confidence level (P - value < 0.05).

## Results

### Physical characteristics of stability testing under accelerated conditions.

Freshly preparation of Benjakul cream had greenish-yellow color. The cream was homogeneous with 5.5 pH value After testing in accelerated conditions (heating - cooling cycle), the results showed that the cream had no change in color and no phase separation. The pH value remained at 5.5. (Table 1).

**Table 1** Physical characteristics of Benjakul cream after storage in accelerated conditions (Heating - cooling cycle)

Physical characteristics	Beginning	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Cream color	Greenish-Yellow	Greenish-Yellow	Greenish-Yellow	Greenish-Yellow	Greenish-Yellow	Greenish-Yellow	Greenish-Yellow
Phase Separation	No	No	No	No	No	No	No
pH value	5.5	5.5	5.5	5.5	5.5	5.5	5.5

### The effectiveness of Benjakul cream with knee osteoarthritis volunteers.

The females volunteers were 93.33 percent, with an average age of 63 years old and an average BMI of 26.19 kg / m<sup>2</sup>. Most volunteers had osteoarthritis in level 3 as diagnosed by radiology images.

The comparison study of the effectiveness in volunteers who received Benjakul cream found that the scores of their knee pain after walking 100

meters were reduced significantly by judgement with VAS. The duration time of walking 100 meters were also reduced significantly at day 7 and day 14. In addition, the score in the test WOMAC index score (Pain index, Stiff index, Physical function index) also reduced significantly in every measure and on day 7 and day 14, in comparison with day 0 ( $P < 0.05$ ). (Table 2 and Figures 1 to 3).

**Table 2** The effectiveness of Benjakul cream with 15 volunteers

Information	Follow up *		
	Day 0	Day 7	Day 14
Visual Analogue Scale (VAS) (cm.)	7.33 (1.95)	4.53 (2.39)	2.80 (2.37)
P - value**		0.001 <sup>† ††</sup>	0.000 <sup>† ††</sup>
100-meter walking time (second)	133.47 (23.80)	113.53 (17.23)	113.33 (18.31)
P - value**		0.000 <sup>† ††</sup>	0.000 <sup>† ††</sup>
<b>WOMAC index score</b>	113.33 (18.31)		
Pain index	9.20 (3.36)	4.53 (2.56)	3.73 (2.74)
P - value**		0.000 <sup>† ††</sup>	0.000 <sup>† ††</sup>
Stiff index	3.67 (1.50)	1.73 (1.22)	1.60 (1.18)
P - value**		0.001 <sup>† ††</sup>	0.000 <sup>† ††</sup>
Physical function index	23.33(11.92)	11.27 (6.83)	8.53 (8.60)
P - value**		0.000 <sup>† ††</sup>	0.000 <sup>† ††</sup>

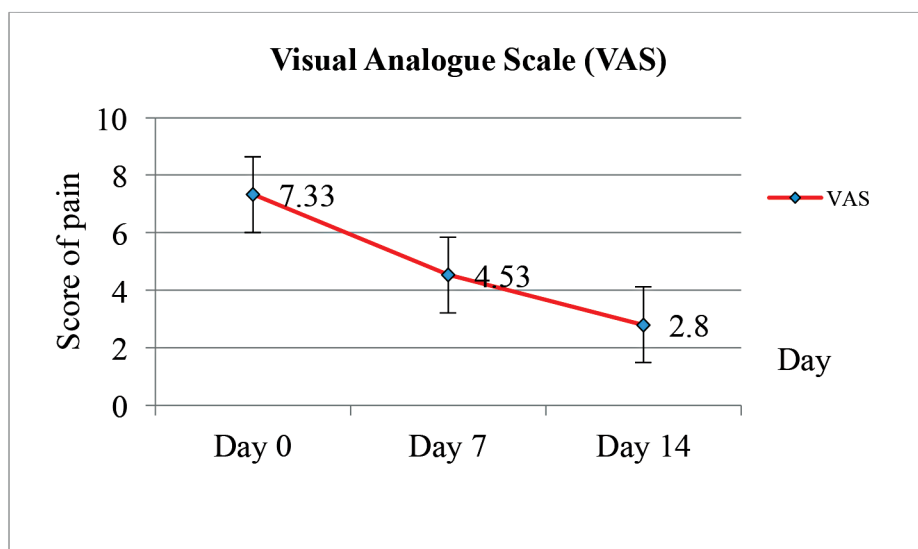
\* Data represent mean (SD)

\*\* Statistic analysis: Paired Sample T-Test

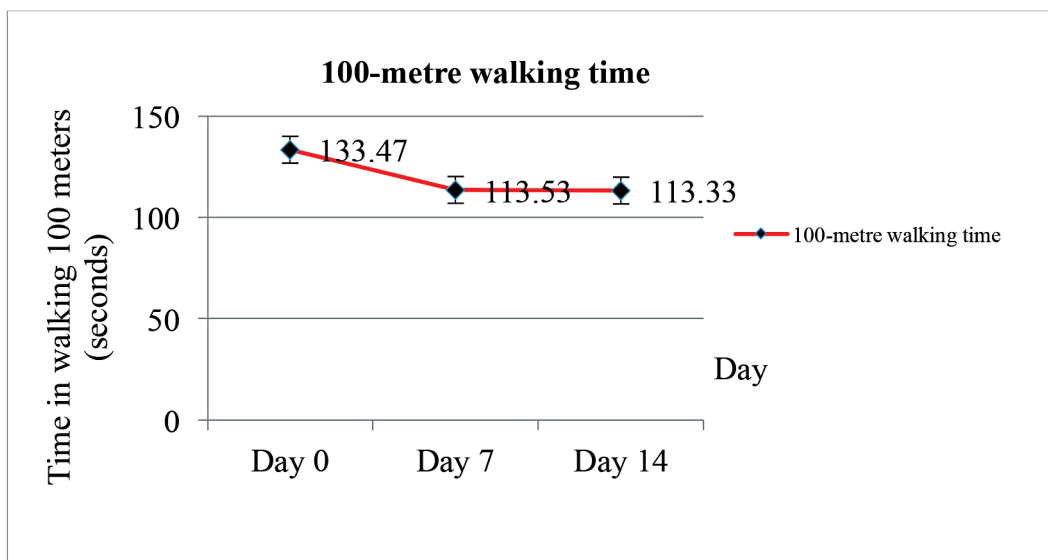
<sup>†</sup> significant difference from day 0 within group ( $P$  - value  $< 0.05$ )

<sup>††</sup> significant difference from day 0 within group ( $P$  - value  $< 0.01$ )

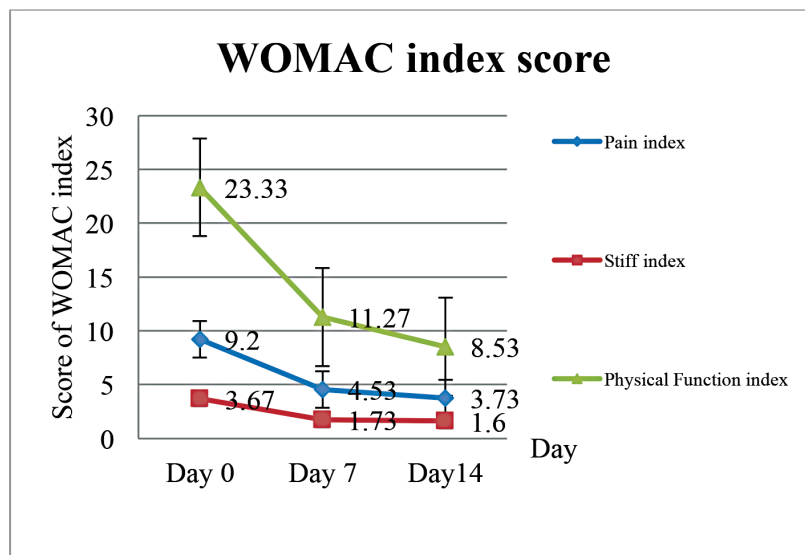
<sup>†††</sup> significant difference from day 0 within group ( $P$  - value  $< 0.001$ )



**Figure 1** The scores of Visual Analogue Scale (VAS) or scores of knee pain after walking distance of 100 metres on day 0, day 7 and day 14.



**Figure 2** The time used in walking 100 metres (seconds) on day 0, day 7 and day 14.



**Figure 3** The scores of WOMAC index score which included scores of Pain index, scores of Stiff index and scores of Physical Function index on day 0, day 7 and day 14.

### Discussion

The study on stability of Benjakul extract cream under accelerated conditions showed that the cream was stable on physical characteristics. Stability testing accelerated conditions indicate that the product has physical stability but this result cannot tell its age. However, there should be further study of cream stability for keeping under accelerated condition at least 6 months in order to get the shelf-life know the age of this product.

The study of effectiveness of Benjakul cream with primary knee osteoarthritis showed that scores of knee pain after walking 100 meters were decreased. On day 0, pain scores were an average of 7.33. On day 7, pain scores were an average of 4.53. At the end of 14 days, average pain score decreased to 2.80. The reduced pain scores indicated that Benjakul cream was effective in reducing the pain of primary knee osteoarthritis. In addition, the time spent to walk 100 meters also decreased. On day 7, the average

time of walk 100 meters was 113.53 seconds. On day 14, it was 113.33 seconds. It showed that Benjakul cream could reduce the duration time in walking 100 meters. As well as evaluating. The quality of life tests with WOMAC index score (Pain index, Stiff index, Physical function index) showed declined scores in all measurands. The Pain index scores on day 0, day 7 and day 14 with a mean score of 9.20, 4.53, and 3.73 respectively. The Stiff index scores on day 0, day 7 and day 14 with a mean score of 3.67, 1.73 and 1.60 respectively. The Physical function index scores on day 0, day 7 and day 14 with a mean score of 23.33, 11.27 and 8.53, respectively. It was obvious that the average score in these three measure and were reduced. These results indicated that Benjakul cream could help volunteers to have a better quality of life. Our results were in accordance with previous research in which 100 mg Benjakul capsule, taking oral administrator 3 times per day after meal for 28 days<sup>6</sup>. The results found that Benjakul extract

capsules was effective in the treatment of primary osteoarthritis.<sup>6</sup> However, the duration of treatment by Benjakul oral capsule as 28 days which its time of application was longer than applying Benjakul cream. Thus, this research of applied this cream had the advantage of reducing the duration of treatment down to 7 days, more comfortable and reduced side effects of hot sensation due to gastric irritation from using oral route in the treatment. The results of all experiments concluded that Benjakul cream was effective in treating primary knee osteoarthritis. However, this was preliminary study in 15 volunteers, further research should be carried out on a only larger number of volunteers and should be compared with modern drug. The examination on blood chemistry should also be conducted for safety purpose. This is the first report on a the medical cream containing ethanolic extracts of Benjakul as the active ingredient and clinically proven its effectiveness on primary knee osteoarthritis.

### Acknowledgment

The project received funding from annual government statement of expenditure budget year 2017 and supported the research by Department of Applied Thai Traditional Medicine, Faculty of Medicine, Thammasat University and Thammasat University Hospital.

### References

1. Thailand development research institute. National List of Essential Medicines. National List of Essential Medicines Website. <http://kpo.moph.go.th/webkpo/tool/Thaimed2555>. Published 2012. Accessed December 20, 2018.
2. Itharat A, Singchangchai P, Ratanasuwan P. Wisdom of Southern Thai traditional doctors. Research Report of Prince Songkla University, Songkla, Thailand 1998; 126.
3. Itharat A, Sireeratawong S, Vannasiri S, Charoenphandhu J, Siyakun K, Tappayutpijarn P. Development of Benjakul extract as health products for cancer patients. Research Report of Applied Thai Traditional Medicine, Faculty of Medicine, Thammasat University; 2010.
4. Chunlaratthanaphorn S. Anti-inflammatory, anti-pyretic, analgesic and antitumor effects of Benjakul extract in animal. Patumthani: Department of Preclinical Science, Faculty of Medicine, Thammasat University; 2000.
5. Amorndoljai P, Kietinunand S, and Somparn N. Study on safety of Benjakul recipies extract tablets in normal volunteers. TMJ 2011;11:195–202.
6. Rachawat P, Pinsornsak P, Kanokkangsadal P, and Itharat A. Clinical efficacy and safety of Benjakul remedy extract for treating primary osteoarthritis of knee compared with diclofenac: double blind, randomized controlled trial. Evid Based Complement Alternat Med 2017;1-8.
7. Triyasut V, Itharat A, Chakkavittumrong P, Kanokkangsadal P. Irritant reaction on skin of long pepper extract in healthy volunteers (clinical trial phase I). TMJ 2016;16:608-615.
8. Itharat A, Sakpudeechoen I. Determination of cytotoxic compounds of Thai traditional medicine called Benjakul using HPLC. J Med Assoc Thai 2010;93:S198-S203.
9. Rattanadechsakul J. Development of *Echinacea purpurea* (L.) Moench extract creams and gels. Master thesis dissertation. Chiang Mai University. Faculty of Pharmaceutical Sciences; 2007.
10. Kuptniratsaikul V, Rattanachaiyanont M. Validation of a modified Thai version of the Western Ontario and McMaster (WOMAC) osteoarthritis index for knee osteoarthritis. JCR 2007;26: 1641-45.

**บทคัดย่อ**

การประเมินความคงตัวทางกายภาพ และประเมินประสิทธิผลเบื้องต้นของครีมสารสกัดเบญจกูล ในการรักษาโรคข้อเข่าเสื่อมปฐมภูมิ

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**ที่มาและความสำคัญ:** เบญจกูล เป็นตำรายาไทย ประกอบด้วยสมุนไพร 5 ชนิด ได้แก่ ดีปลี ข่าพลู สะค้าน เจตมูลเพลิงแดง และเหง้าขิง ใช้รักษาสมดุลงของร่างกาย บรรเทาปวด ต้านการอักเสบ และมีผลที่ดีในการรักษาโรคข้อเข่าเสื่อมปฐมภูมิในรูปแบบของยารับประทาน ไม่พบการระคายเคืองผิวหนังเมื่อใช้ทาผิวหนัง

**วัตถุประสงค์:** เพื่อประเมินสมบัติทางกายภาพของครีม และประเมินประสิทธิผลในการรักษาโรคข้อเข่าเสื่อมปฐมภูมิ

**วิธีการศึกษา:** เตรียมครีมนำไปทดสอบในสภาวะเร่ง แล้วประเมินลักษณะทางกายภาพ นำไปทดสอบประสิทธิผลในอาสาสมัครที่มีโรคข้อเข่าเสื่อมในระดับปฐมภูมิ จำนวน 15 คน อายุระหว่าง 40-80 ปี ได้รับครีมเบญจกูล 2 กรัม ทาวันละ 3 ครั้ง นาน 14 วัน ประเมินด้วยการวัดระดับความปวดของข้อเข่าหลังจากการเดินระยะทาง 100 เมตร ประเมินสมรรถภาพของข้อด้วย WOMAC index scores และวัดระยะเวลาการเดิน 100 เมตร

**ผลการศึกษา:** ครีมเบญจกูลมีความคงตัวหลังจากการทดสอบในสภาวะเร่ง และพบว่าสามารถลดการปวดเข่าหลังเดินระยะทาง 100 เมตร ระยะเวลาในการเดินลดลง มีคุณภาพชีวิตดีขึ้นเมื่อประเมินด้วย WOMAC index scores อย่างมีนัยสำคัญทางสถิติ

**สรุปผลการศึกษา:** ครีมเบญจกูลมีความคงตัวและมีประสิทธิผลในการรักษาโรคข้อเข่าเสื่อมปฐมภูมิได้

**คำสำคัญ:** เบญจกูล, ข้อเข่าเสื่อม, ครีม, ตำรายาสมุนไพรไทย