

# Effectivity and safety of mahkota dewa fruit extract compared to meloxicam (*phaleria macrocarpa fructus*) on osteoarthritis

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## ABSTRACT

**Background:** Osteoarthritis (OA) is the most common musculoskeletal disease. World Health Organization (WHO) estimates that 10% of the aged over 60 year population have this disease. The aim of OA treatment is to reduce pain, which is the most OA patients chief complaint. People in Indonesia are very interested in use of herbal therapies from original traditional plant to treat pain now, one of the traditional plants that are known have a benefit is *Phaleria macrocarpa* or Mahkota Dewa fruit. *Phaleria macrocarpa* has been shown to decrease the degree of inflammation of OA animal model experiments. In order to know what is the effect of this fruit extract to reduce degrees of pain and change the levels of IL-1, IL-6, TNF- $\alpha$  in the blood as the marker of inflammation of patients with knee OA, and what is the effects to liver, kidney and haematology in the Indonesian population has not been investigated.

**Methods:** The research method is an experimental study and the research design is PROBE (Prospective Randomized Open End Blinded Evaluation), to evaluate the efficacy of the extract Mahkota Dewa fruit (*Phaleria macrocarpa fructus*) 330 mg (Super Mahkota POM TR 053 345 491) compared to meloxicam 7.5 mg in patients with knee osteoarthritis. The study population was outpatients with knee OA at Rheumatology Clinic Dr Hasan Sadikin Hospital Bandung. Patients are given *Phaleria macrocarpa* 330 mg or meloxicam 7.5 mg once a day for 14 days. Observations were made to evaluate the degree of pain as measured by VAS and Lequesne index at day 0, day 14 and measured again at day 28, after they are not taking the extract anymore.

**Results:** *Phaleria macrocarpa* 330 mg is equal to meloxicam 7.5 mg in reducing the degree of pain as measured by VAS ( $p=0.78$ ) and the Lequesne index ( $p=0.51$ ). Our finding, there is no effect of decreasing the proinflammatory cytokine IL-1 ( $p=0.72$ ), IL-6 ( $p=0.53$ ) and TNF- $\alpha$  ( $p=0.07$ ) in the blood of both groups. Safety analysis shown that this extract is safe for consumption.

**Conclusions:** *Phaleria macrocarpa* 330 mg equal to meloxicam 7.5 mg in reducing the degree of pain however there is no effect on reducing proinflammatory cytokines in the blood of OA patients who had received therapy for 14 days in both groups. There is no adverse effects found on hematological, liver function and kidney

function after consumption this plant's fruit extract.

**Keywords:** osteoarthritis, mahkota dewa, *phaleria macrocarpa*.

Osteoarthritis (OA) is the most common musculoskeletal disease, where the pathogenesis is still not known well, but it is currently developing several hypotheses and theories are still debatable.<sup>1,2</sup> OA formerly regarded as a non-inflammatory diseases caused by degenerative disease due to increasing age, but along with the development of research, it is known that OA is fairly complex disease, multifactorial causes, although the etiology is not well known, and the disease also occurs as a result of not severe acute inflammation.<sup>2</sup> World Health Organization (WHO) estimates that 10% of the entire population over the age of 60 years suffer from this disease. OA and other rheumatic diseases affecting more than 43 million people in the United States in 2020 and is expected to reach to 60 million patients.<sup>3,4</sup> The study in UK shows the OA incidence is 25% per year, with the prevalence of disability due to knee OA is 10% and the severe disability as much as 5%.<sup>5</sup>

OA is also causing high socio-economic impact, both in developed countries as well as in developing countries, including Indonesia.<sup>6,7,8</sup> It is estimated that one to two million elderly people in Indonesia suffer from disability due to OA. In the next century, the challenge of the OA impact will be even greater in elderly population.<sup>9,10</sup> Currently, OA is characterized by the damage to the joint cartilage gradually accompanied by the presence of joint inflammation. OA can affect any joint, but is more common in the knees, hips, spine and hands.<sup>2,11-13</sup> Pain is the main complaint of patients with osteoarthritis. Therefore, in general, the aims to the treatment of OA are to reduce pain, to prevent deformity, to improve quality of life, and to provide knowledge to the people about the disease.

The pathogenesis of OA is not only a degenerative process, but also inflammation. Joint pain, tenderness, limited range of motion, crepitus and swollen, increase intra-articular pressure,

changes in the structure of the joints and tissue debris cause inflammation of the synovial membrane, capsule, tendon, and bursa. Proinflammatory cytokines such as IL-1, IL-6 and TNF- $\alpha$  are found to be high in the synovial fluid of the knee OA patients.<sup>11,12,17,18</sup>

Pharmacologic therapy in knee OA is divided into two main outcomes. The first, to reduce pain by analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections, steroids, hyaluronan acid. The second, drugs used to inhibit the progression of OA are Modifying Osteoarthritis Drugs (DMOADs). DMOADs work by maintaining structural balance and stimulate the growth of cartilage cells of cartilage. Several studies have found that these drugs also have anti-inflammatory effects.<sup>11,12,14,16</sup>

Nowadays people are very interested in the use of herbal therapies derived from traditional plant. One of the traditional plants that are known to have benefits is *Phaleria macrocarpa* or mahkota dewa.<sup>19,20</sup>

Mahkota Dewa fruit extract (*Phaleria macrocarpa fructus*) has been shown to reduce the degree of OA in animals, because the structure of the active substance similar to ketoprofen. Mahkota Dewa fruit ethanol extract with the doses of 15; 22.5; and 30 mg/kg bw mice can reduce levels of interleukin-1 $\beta$  and TNF- $\alpha$  serum -induced arthritis in mice kolagen.<sup>21,22</sup> Study in human clinical trials have not been conducted, but as a process of standardization we get a dose of Mahkota Dewa fruit extract 330 mg per day according to animal study doses.

## Methods

The study design was an experimental research, the research design is Prospective Randomized Open-label Blinded at End Experimental (PROBE) to evaluate the efficacy of the mahkota dewa fruit extract 330mg (Super Mahkota, POM: TR 053 345 491) compared to 7.5 mg meloxicam as control group in patients with osteoarthritis.

The study population was patients with OA at the Rheumatology Outpatient Clinic in Dr. Hasan Sadikin General Hospital who live around Bandung city. Then sample was taken by simple random sampling methods to establish a research subject.

Inclusion criteria are patients with knee OA based on the consensus of the Indonesian Rheumatology Association (IRA), based on clinical (joint pain) and radiological (osteophytes), with at least 1 of the following 3 criteria: stiffness less than 30 minutes, age more than 50 years, crepitus on active joint motion; patients with OA pain intensity scores 2–7 according to Visual Analogue Scale (VAS). Exclusion criteria are there are other comorbidities: COPD, cardiac decompensation, walking disability was not caused by knee OA; undergoing medical rehabilitation; history of allergy to meloxicam or mahkota dewa; AST and ALT exceed twice the upper limit, normal creatinine > 1.1 mg/dl; using NSAIDs and oral or steroid injection 2 weeks or 3 months before the study.

Visual Analogue Scale (VAS) questionnaire is the most easy tool to be used by interviewer to determine the degree of pain that experienced by OA patients in numbers. Lequesne

index for knee OA, also known as (Index of severity for knee OA), was originally developed in French and also in other languages such as German, Korea and Singapore. This index has been studied can be used in Asia and has been proven valid in Southeast Asian populations. This index consists of 11 questions divided into three sections, five questions relating to pain, two questions about distance running, and four questions about the ability of daily activity or quality of life.<sup>47</sup>

Radiological examination is sufficient to support the diagnosis, and also the degree of OA can be classified based on the radiological features. Semi-quantitative assessment done by Kellgren-Lawrence radiographic criteria and Osteoarthritis Research Society International (OARSI).<sup>44</sup>

Test material in this study is the mahkota dewa fruit extracts that have been carried out which one of them is the standardization of assay in accordance with the applicable regulations in Indonesia. This herbal remedy has been registered, with the trademark “Super Mahkota”, which is registered under number : POM TR 053 345 491, in the form of capsules containing 330 mg of extract *Phaleria macrocarpa* each capsule.<sup>23,24</sup>

Patients treated by Mahkota Dewa fruit extract capsules 330 mg once a day for 14 days, in the treatment group and 7.5 mg meloxicam once a day in the control group. Observations were made of the pain degree as measured by VAS and Lequesne index, which was performed before and after administration of Mahkota Dewa fruit extract. If the patients experienced pain during administration of the test material (VAS > 7), then they can be given an additional 500 mg paracetamol orally at the beginning to 4000 mg per day orally (rescue medication).

On day 1 and 14, blood samples were taken to measure the levels of IL-1, IL-6 and TNF- $\alpha$ . VAS and Lequesne index measured on day 14 and 28. Liver function measured with AST and ALT examination, renal function examination with ureum and creatinine, hematology examination with hemoglobin, leukocyte count, platelet count.

Kolmogorov-Smirnov test of Goodness of Fit performed to determine the normality of the distribution of the data. Statistical analysis done by t test for data ratio or interval scale who normally distributed. To compare the data pairs in the experimental group used the Wilcoxon Z test. Level of significance is determined by the value of  $p < 0.05$ .

## Results

This study subjects were 42 patients. Six subjects were excluded from this study, because one person has other diseases like gout arthritis, one person does not follow the rules of taking the medication and four patients had dropped out.

Of the 36 patients who completed the study 19 patients had Mahkota Dewa fruit extract 330 mg in each capsules and 17 patients had Meloxicam 7.5 mg. Average age of knee OA patients was 59.1 years old. Most of the study subjects were women (85.7%), aged between 45 to 69 years old. The severity of radiological OA mostly located in the first degree (45.2%) and second degree (42.9%).

**Table 1 Characteristics of OA patient according to group of treatment**

Variable	Treatment Group Mean (SD)/N(%)		P value
	<i>Phaleria Macrocarpa</i> 330 mg	Control Meloxicam 7.5 mg	
Age (year)	60.24 (5.69)	58.10 (6.32)	0.26
Median	59.00	60.00	
Gender :			
Women	19 (90.5%)	17 (81.0%)	0.38
OA degree			
I	9 (42.9%)	10 (47.6%)	0.88
II	9 (42.9%)	9 (42.9%)	
III	3 (14.3%)	2 (9.5%)	
IL-1 (pg/ml)	4.01 (0.46)	4.03 (0.45)	0.82
IL-6 (pg/ml)	5.17 (5.97)	4.25 (4.53)	0.58
TNF- $\alpha$ (pg/ml)	27.06 (5.66)	25.92 (6.79)	0.56
Hb (gr/dl)	13.13 (1.01)	13.40 (0.96)	0.43
Leukocyt (/mm <sup>3</sup> )	6936.84 (1816.35)	6662.50 (1209.34)	0.61
Trombocyt (x1000/mm <sup>3</sup> )	279.26 (50.96)	271.38 (49.72)	0.65
AST (U/L)	24.79 (12.20)	20.81 (4.28)	0.22
ALT (U/L)	24.05 (14.40)	18.00 (6.30)	0.13
Urem (mg/dl)	29.50 (9.65)	22.81 (6.00)	0.02
Creatinine (mg/dl)	0.87 (0.39)	0.77 (0.17)	0.35
BMI	24.70 (3.72)	24.44 (3.20)	0.81

Inflammatory markers in patients who participated in the study were on average above normal limits levels, IL-1 with a mean of 4.05 pg/ml (SD 0.45), IL-6 with a mean of 4.72 pg/ml (SD 5.28) and TNF- $\alpha$  with a mean of 26.50 pg/ml (SD 6.19). Other laboratory test like haematological liver and kidney function are also within normal limits. Average of BMI were slightly higher with a mean 24.57 (SD 3.43) showed excessive load on the joints, which that is one of risk factor for OA. Table 1 shows there is no statistically significant difference between the groups of patients who get Mahkota Dewa fruit extract 330 mg compared with a control group who received 7.5 mg meloxicam, so the research results obtained to avoid bias due to sample selection are not the same set of characteristics. However ureum level is significantly different, where the group Mahkota Dewa fruit extract 330 mg had higher level with mean 29.50 mg/dl (SD 9.65) compared to meloxicam 7.5 mg, 22.81 mg/dl (SD 6.00) ( $p = 0.02$ ), although the levels are still within normal limits.

The data distribution was normally distributed on VAS and Lequesne index group analyzed by using parametric statistics. Reduction in VAS data ( $p = 0.009$ ) were not normally distributed, and the data is non-parametric, analyzed by the Wilcoxon test.

**Table 2 Efficacy test after Mahkota Dewa fruit extract****(*Phaleria macrocarpa fructus*) 330mg treatment compared to meloxicam 7.5mg at day 14**

Variable	Day 14		P value
	<i>Phaleria macrocarpa</i> 330 mg N = 19 Mean (SD)	Meloxicam 7.5 mg N = 17 Mean (SD)	
VAS			
Before	40.48 (15.65)	36.75 (13.21)	0.42
After	24.47 (10.66)	19.71 (10.07)	0.18
Decrease	15.52 (10.39)	16.47 (10.42)	0.78
Lequesne			
Before	7.45 (2.87)	6.85 (2.32)	0.47
After	4.71 (2.58)	3.77 (1.73)	0.21
Decrease	2.55 (1.94)	3.03 (2.31)	0.51
IL-1 (pg/ml)			
Before	4.07 (0.46)	4.04 (0.45)	0.82
After	4.13 (0.63)	3.98 (0.41)	0.39
Decrease	-0.06 (0.54)	-0.01 (0.25)	0.72
IL-6 (pg/ml)			
Before	5.17 (5.97)	4.25 (4.53)	0.58
After	6.26 (9.47)	4.42 (5.26)	0.48
Decrease	-1.31 (8.16)	0.19 (5.88)	0.53
TNF- $\alpha$ (pg/ml)			
Before	27.02 (5.66)	25.91 (6.79)	0.56
After	27.32 (3.99)	27.88 (7.01)	0.77
Decrease	-0.26 (4.72)	-2.99 (3.86)	0.07

Table 2 shows that the mean VAS decrease after 14 days of Mahkota Dewa fruit extract 330 mg treatment was 15.52 (SD 10.39) did not differ significantly with meloxicam 7.5 mg 16.47 (SD 10.42) ( $p = 0.78$ ). The VAS mean decrease  $> 20\%$  so that it can be considered a significant reduction in the degree of pain. The mean decrease in Lequesne index after 14 days Mahkota Dewa fruit extract 330 mg was 2.55 (SD 1.94) did not differ significantly with meloxicam 7.5 mg, 3.03 (SD 2.31) ( $p = 0.51$ ). Mahkota Dewa fruit extract 330 mg equivalent to 7.5 mg of meloxicam in reducing the degree of pain as measured by VAS and Lequesne Index. The effect of decreasing the proinflammatory cytokine in the blood are IL-1 -0.06 pg/ml (SD 0.54) compared to -0.01 pg/ml (SD 0.25) ( $p = 0.72$ ), IL-6 -1.31 pg/ml (SD 8.16) compared to 0.19 pg/ml (SD 5.88) ( $p = 0.53$ ) and TNF- $\alpha$  -0.26 pg/ml (SD 4.72) compared to -2.99 pg/ml (SD 3.86) ( $p = 0.07$ ).

**Table 3 Efficacy test after Mahkota Dewa fruit extract (*Phaleria macrocarpa fructus*) 330mg treatment compared to meloxicam 7.5mg at day 28**

Variable	Day 28		P value
	<i>Phaleria macrocarpa</i> 330 mg N = 19 Mean (SD)	Meloxicam 7.5 mg N = 17 Mean (SD)	
VAS			
Day 28	22.37 (11.35)	18.35 (9.51)	0.26
Decrease	17.63 (10.05)	17.82 (7.97)	0.95
Lequesne			
Day 28	3.97 (2.07)	3.41 (2.35)	0.45
Decrease	3.29 (2.45)	3.38 (1.68)	0.89

The mean reduction in VAS still continues since day one

to 28 days in the group of Mahkota Dewa fruit extract 330 mg amounted to 17.63 (SD 10.05) did not differ significantly with meloxicam 7.5 mg 17.82 (SD 7.97) ( $p = 0.95$ ), it also in the Lequesne index to 28 days in the group Mahkota Dewa fruit extract 330 mg mean decrease of 3.29 (SD 2.45) did not differ significantly with meloxicam 7.5 mg of 3.38 (SD 1.68) ( $p = 0.89$ ). Mahkota Dewa fruit extract 330 mg is still giving the effect of lowering the degree of pain on day 28 of observation, despite being dismissed for 14 days.

Side effect of NSAIDs are gastrointestinal symptoms such as nausea 5.9% ( $p = 0.28$ ) and heartburn 23.5% ( $p = 0.03$ ), and cause some subjects were excluded from the analysis, while Mahkota Dewa the fruit extract have no any complaint. In a safety testing show that Mahkota Dewa fruit extract 330 mg is safe for consumption, because it does not interfere with liver function, renal function and hematology, and also blood pressure after taking the test material for 14 days.

After Mahkota Dewa fruit extract 330 mg treatment suspended for 14 days or at day 28 observation, when compared to meloxicam 7.5 mg, there is side effect on liver function, kidney function, and haematology. After day 28 observations, Hb of the subjects received 7.5 mg of meloxicam was decrease 0.47 g/dl (SD 0.51) compared to the group Mahkota Dewa fruit extract 330 mg 0.07 g/dl (SD 0.52) ( $p = 0.03$ )

## Discussion

The long term pain in osteoarthritis need medications to reduce pain, but with lower side effects. Some pain medications such as NSAIDs have side effects on the gastrointestinal and cardiovascular systems.<sup>45-48</sup> The use of herbs that have analgesic effect, is an option because of its low side effects. Some of the herbs have been studied to treat OA and is currently developed.<sup>49-55</sup>

Mahkota dewa is a plant that is widely used by people as a traditional medicine to treat various conditions as antimicrobial, anti-hypertension, anti-diabetes, anti-inflammatory and anti-cancer. These herbal drugs have other effects as an anti-oxidant that also may reduce pain in OA.<sup>23,24</sup>

In OA progression chondro process will be disrupted due to several components such as proinflammatory cytokines IL-1, IL-6, TNF- $\alpha$ , metalloproteinase enzymes, and also the role of oxidative stress due to Reactive Oxygen Species (ROS).<sup>56,57</sup>

Inflammation and cartilage degradation is one of the hypotheses of the pathogenesis of OA. Inflammation is caused by arachidonic acid metabolism and the role of various enzyme. While cartilage degradation is caused by an imbalance of proteases and protease inhibitors that leads to excessive degradation of cartilage matrix.<sup>2</sup> Oxidative stress causes damage to mitochondria that plays a role in the aging process, apoptosis, impaired function and tissue degeneration. Oxygen free radicals can penetrate into the cartilage and chondrocyte cells in vitro, although the actual chondrocyte cells can remain alive in a state without oxygen under normal circumstances, because it does not contain blood vessels. Chondrocyte metabolism itself is done anaerobically. Mitochondrial function in chondrocyte cells thought to

prevent free radicals into the chondrocyte cells. Free radicals are already entered into the chondrocyte itself will result in a decrease in the synthesis of extracellular matrix resulting in thinning of the joints and improve joint calcification resulting in the formation of osteophytes. It also will play a role in cell apoptosis of chondrocytes. Mitochondria have their own chromosome is a genetic component in cell metabolism. The presence of genetic mutations will lead to a more rapid degenerative diseases, which will accelerate the occurrence of OA at a younger age.<sup>56,57</sup>

Pain that occurs in OA caused by three things: the inflammatory, ischemic and oxidative stress. Super oxide (SO) as free radicals also have an influence on tissue damage joints and cause pain. Phaleria macrocarpa also known to have antioxidant effects, therefore, anti-pain mechanisms presumably through suppression of this free radical oxidation pathway.<sup>56,57</sup>

The degradation of matrix molecules is actually a part of the remodelling process in the growth, development and joint matrix turnover. The process is actually a physiological process, which is regulated by various cytokines, growth factors, and hormones that regulate the synthesis of proteinase inhibitors and thus are in a balanced state. Excessive proteolysis is a pathological process resulting from an imbalance between proteinases (MMPs) and inhibitors (TIMPs). If there is more matrix destruction, it will be a lot of fragments that have been unraveled as collagen, proteoglycans and calcium crystals, regardless of the synovium space, and cause inflammatory responses, the production of prostaglandins as the end result will be more and more so that the effect of pain will increase. Effects of prostaglandins alone which can lead to vasodilation of blood vessels, increase vascular permeability, cause pain with bradykinin potentiating effect, activating lymphocytes, platelet aggregation, bone resorption, and T-cell suppression. Bone resorption that occurs will cause fragments of calcium such as calcium pyrophosphate crystals, hidroxiapatit, and calcium phosphates went into the synovium. The degree of inflammatory response as a result of this study is usually mild. Pain occurs not only from the experience of OA joints, because the actual joint cartilage does not contain nerves and vessels, but pain can also come from tissue around the joints, such as tendinitis, bursitis, ischemic subchondral bone, muscle spasm, osteophytes, psychic, ligament disruption, and others. Therefore, the degree of pain reduction at Mahkota Dewa fruit extract 330 mg apart due to anti-inflammatory effects may be caused by the effects of antioxidants, the effects of other active substances are not known and may also have the effect of plasebo.<sup>58-60</sup>

This study showed no difference in inflammatory markers found in the serum of patients with OA who have given good treatment with Mahkota Dewa fruit extract 330 mg and Meloxicam 7.5 mg, although the degree of pain was reduced. The cause is probably due to the lack of high-dose or measurement of inflammatory markers IL-1, IL-6, TNF- $\alpha$  in OA should not be taken from the serum but directly from synovial fluid because there is no significant relationship between systemic inflammatory OA with local inflammation.

In the Framingham cohort study, years between 1998-2005 in 1235 obtained subject there was no significant relationship between markers of inflammation in OA.<sup>17</sup> Placebo only actually has the effect to reduce levels of pain that is quite effective in OA.<sup>30</sup> In the other study found that the mean TNF- $\alpha$  and IL-1 $\beta$  levels were lower in chronic OA compared with acute OA.<sup>40</sup> This differs from the type of inflammatory rheumatic diseases such as rheumatoid arthritis else (RA) which can be found higher levels of TNF- $\alpha$ , IL-6 and IL-1 in the serum. EULAR recommendations also provide non-pharmacological therapy in patients with a diagnosis of OA in addition to therapy with multiple drugs.<sup>61</sup>

Experimental research of traditional medicinal native plants in Indonesia, Mahkota Dewa fruit extract 330 mg given for 14 days in patients with a diagnosis of osteoarthritis showed effects can reduce pain by measurement of pain by VAS and Lequesne index. Patients with OA more than 60 years of age who may have renal impairment and cardiovascular disorders when NSAIDs treatment would be very dangerous can be given this treatment. Mahkota Dewa fruit extract is an therapeutic option for OA to reduce the degree of pain yet safe for the elderly.

The incidence of side effects of Mahkota Dewa fruit extract 330 mg against haematological, liver function, kidney function, or the blood pressure in the observation of the day 14 and 28 are not found. This shows that the mahkota of dewa fruit extract is quite safe. LD50 Mahkota dewa extract in mice is greater than 1500 mg/kg bw. There were no significant differences between the groups in toxicity in experimental animals given the extract preparations Mahkota Dewa than the control group.<sup>19</sup>

On day 28 observations obtained significant reduction in Hb subjects who received 7.5 mg of meloxicam for 14 days was 0.47 g/dl (SD 0.51), this shows the long-term administration of NSAIDs for more than 14 days can lead to a decrease Hb due to hidden gastrointestinal bleeding in a person over the age of 60 years as the average age of the study subjects.

Limitation of this study are time of this study was conducted with only a two-week observation period where as in studies using herbs, the new effect can be seen in a longer time around more than three weeks. Measurement of proinflammatory markers IL-1, IL-6 and TNF- $\alpha$  in two weeks has not been able to show a decrease in the blood levels, because the clinical symptoms will disappear earlier than the marker. In OA difficult to find increased inflammatory markers in the blood, but in the synovial fluid it can be higher than in the blood so that the examination in this study did not show significant results.

## Conclusion

The conclusion of this study is Mahkota Dewa fruit extract (*Phaleria macrocarpa fructus*) 330 mg reduces the degree of pain in OA patients as same as meloxicam 7.5 mg. Mahkota Dewa fruit extract 330 mg does not reduce levels of IL-1, IL-6, TNF- $\alpha$  in patients with OA as well as the administration of meloxicam 7.5 mg. Mahkota Dewa fruit extract 330 mg does not impair kidney function, liver function and haematologic

parameters in patients with OA. Further research needs to be done about the content of some active substances *Phaleria macrocarpa* which acts as both an anti-inflammatory, and other effects that may influence the degree of pain decrease. Further research need to do to find the effects of *Phaleria macrocarpa* on levels of IL-1, IL-6 and TNF- $\alpha$  in the synovial tissue or joint fluid in different doses.

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