

Ability of Curcuminoid Compared to Diclofenac Sodium in Reducing the Secretion of Cyclooxygenase-2 Enzyme by Synovial Fluid's Monocytes of Patients with Osteoarthritis

Nyoman Kertia¹, Ahmad H. Asdie¹, Wasilah Rochmah¹, Marsetyawan²

¹Department of Internal Medicine, Faculty of Medicine, Gadjah Mada University-Dr. Sardjito Hospital, Jl. Kesehatan No. 1, Yogyakarta, Indonesia. Correspondence mail: kertianyoman@yahoo.com.

²Department of Histology and Cell Biology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia.

ABSTRAK

Tujuan: untuk mengetahui kemampuan kurkuminoid ekstrak rimpang kunyit (*Curcuma domestica Val.*) dalam mengurangi sekresi enzim sikloksigenase-2 oleh monosit cairan sinovia dibandingkan dengan natrium diklofenak pada penderita osteoarthritis. **Metode:** penelitian ini menggunakan desain prospective randomized open end blinded evaluation (PROBE). Subjek adalah pasien dengan osteoarthritis lutut yang dibagi secara acak menjadi kelompok yang mendapat terapi kurkuminoid ekstrak rimpang kunyit 3 x 30 mg sehari (kelompok kurkuminoid) dan kelompok yang mendapat terapi natrium diklofenak 3 x 25 mg sehari (kelompok diklofenak). Aspirasi cairan sinovia untuk menilai skor sekresi enzim sikloksigenase-2 oleh monosit cairan sinovia dilakukan sebelum terapi dan setelah 4 minggu terapi. **Hasil:** sebanyak 80 pasien osteoarthritis lutut mengikuti penelitian ini. Pada kelompok kurkuminoid rerata skor sekresi enzim sikloksigenase-2 oleh monosit cairan sinovia sebelum dan sesudah terapi adalah $1,84 \pm 0,37$ dan $1,15 \pm 0,28$ ($p < 0,001$). Pada kelompok diklofenak rerata skor sekresi enzim sikloksigenase-2 oleh monosit cairan sinovia sebelum dan sesudah terapi adalah $1,79 \pm 0,38$ dan $1,12 \pm 0,27$ ($p < 0,001$). Pada kelompok kurkuminoid penurunan skor sekresi enzim sikloksigenase-2 adalah $0,70 \pm 0,51$ sedangkan pada kelompok diklofenak adalah $0,67 \pm 0,45$. Tidak ada perbedaan yang bermakna dalam penurunan skor sekresi enzim sikloksigenase-2 antara kedua kelompok terapi ($p = 0,89$). **Kesimpulan:** kemampuan kurkuminoid ekstrak rimpang kunyit tidak berbeda bermakna dibandingkan dengan natrium diklofenak dalam mengurangi sekresi enzim sikloksigenase-2 oleh monosit cairan sinovia sendi lutut yang terserang osteoarthritis.

Kata kunci: kurkuminoid, natrium diklofenak, sikloksigenase-2, osteoarthritis.

ABSTRACT

Aim: to assess the ability of curcuminoid from *Curcuma domestica Val* in reducing the cyclooxygenase-2 secretion by synovial fluid's monocytes compared to diclofenac sodium in patients with osteoarthritis. **Methods:** this was a prospective randomized open end blinded evaluation (PROBE) study. The subjects were patients with knee osteoarthritis who were divided randomly into two groups, the first group received 30 mg 3 times daily of curcuminoid and the second group received 25 mg 3 times daily of diclofenac sodium. The joints aspiration was done and the secretion of cyclooxygenase-2 enzyme by synovial fluid's monocytes was evaluated by scoring method before and after 4 weeks of treatments. **Results:** a total of 80 patients with knee osteoarthritis were enrolled. In curcuminoid group the average scores were 1.84 ± 0.37 and 1.15 ± 0.28 respectively ($p < 0.001$). In diclofenac group the average scores were 1.79 ± 0.38 and 1.12 ± 0.27 respectively ($p < 0.001$). In curcuminoid group the decreasing score of cyclooxygenase-2 secretion was 0.70 ± 0.51 while in diclofenac group was 0.67 ± 0.45 . There was no significant difference in decreasing the score of cyclooxygenase enzyme secretion between both treatment groups ($p = 0.89$). **Conclusion:** the ability of curcuminoid from *Curcuma domestica Val*. rhizome extract

was not significantly different compared to diclofenac sodium in suppressing the secretion of cyclooxygenase-2 enzyme by synovial fluid's monocytes.

Key words: curcuminoid, diclofenac sodium, cyclooxygenase-2, osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a rheumatic disease with the highest prevalence among all types of rheumatic diseases, the second largest cause of physical disability in the world after ischemic heart disease. In the United States in the year 2005 one third of the population aged 65 years and older suffer from knee OA as evidenced by radiological examination.¹

Knee OA is the most prevalent musculoskeletal disorder in the community, affecting 30-40% of the population by the age of 65 years. One of four patients over 55 years old has complained of knee pain, and at the age of 65 years, 30% men and 40% women have abnormalities of knee radiograph.²

the World Health Organization (WHO) in 2004 estimated 400 per thousand of the world population over the age of 70 years suffer from OA and 800 per thousand patients with OA have mild to severe limitation degrees of motion that reduces the quality of their lives.³

There are four important phases in the course of osteoarthritis: the initial phase, the inflammatory phase, pain and degradation phase. The inflammatory phase is characterized by increasing of pro-inflammatory cytokines and leukocyte numbers in the affected joints.⁴ Interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) activates the degradation enzymes such as metalloproteinase, collagenase, gelatinase and agrekanase which can exacerbate the inflammation in the joints affected by OA. Inflammatory products have a negative impact to the joint tissues, especially the joint cartilage and due to destruction of the joints.⁵

There are 2 COX iso-enzymes, i.e. the constitutive COX-1, which has a role in physiological function and the inducible COX-2, which has a role in inflammatory reaction.⁶

Cyclooxygenase-2 (COX-2) enzyme is an important mediator in enhancing the inflammatory responses. In the tissue and synovial fluid of the joints affected by OA, the presence of COX-2 enzyme can be detected.⁷

Curcumin is an extract of turmeric (*Curcuma longa*/*Curcuma domestica*) and temulawak (*Curcuma xanthorrhizae*), which are native Indonesian plants. Such plants are members of the ginger family (*Zingiberaceae*) and have been widely used as raw materials for traditional medicines.⁸

Curcuma domestica Val. is an Asian native plant that is primarily used to reduce the inflammation. Turmeric contains curcumin and other chemical constituents known as the "curcuminoids". The major curcuminoids present in turmeric are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently identified cyclocurcumin.⁹ Curcumin has anti-inflammatory activity¹⁰ and has been shown to inhibit a number of different molecules involved in inflammation including phospholipase, lipooxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12.¹¹

Non-steroidal anti-inflammatory drugs (NSAIDs) do not only inhibit COX-2 enzyme activity, but also inhibit the synthesis of COX-2 enzyme by synovial fluid macrophages of affected OA joints.¹² Monocytes play a very important role in the inflammatory joint reaction. Monocytes are capable of producing cyclooxygenase-2 enzyme and reactive oxygen intermediates (ROI) in the early stages of inflammatory joint reaction. In osteoarthritis, one of the methods to observe the ability of NSAIDs in suppressing the secretion of COX-2 by monocytes is a staining by immunocytochemistry technique. Cyclooxygenase-2 enzyme in the cytoplasm of monocytes will react to the antiserum anti COX-2 monoclonal antibodies. The result of this reaction can be stained by immunocytochemistry technique. The monocytes without secreting the COX-2 their cytoplasm will be pale in color. More and more COX-2 enzyme that is secreted by these cells, the cytoplasm will appear more brown.¹³

The purpose of this study is to assess the ability of *Curcuma domestica* Val. rhizome extract in inhibiting the secretion of COX-2 enzyme by synovial fluid's monocytes of the joint affected by osteoarthritis. That ability was compared to diclofenac sodium as an ordinary NSADs.

METHODS

Study Subjects

A total of 80 patients with knee OA were eligible and willing to participate in this study. Subjects were divided randomly into two groups: the group who received 30 mg 3 times daily of curcuminoid from *Curcuma domestica* Val. rhizome extract (curcuminoid group) and the group who received 25 mg 3 times daily of diclofenac sodium (diclofenac group). The study protocol was approved by the ethics committee Faculty of Medicine Gadjah Mada University, with a permission from the Director of Sardjito Hospital and informed consent was obtained from all patients.

Plant Material

Curcuma domestica Val. rhizome sorted, washed and then cut into pieces with a thickness of 1-2 mm and dried with drying cupboard for 24 hours at 40°C to obtain maximum water content of 10% v/w.

Extraction and Quantitative Analysis of Curcuminoid from *Curcuma Domestica* Val. Rhizome

After drying, the turmeric rhizome is made into powder from with a pollinator machine. The powder obtained is mixed with ethanol and then macerated for 24 hours, then filtered with a Buchner funnel (with vacuum pressure). Filtrate collected was evaporated at 45°C in a vacuum condition to find the curcuminoid. For determination of curcuminoid, the curcumin standard solution was used with varying degrees of concentration. Extract obtained was diluted to 100 mg/ml and spotted on silica gel GF 254 plates, and then eluted with a mobile phase system chloroform-methanol (97-3) v/v. Detection of spots was done by ultraviolet light 254 nm and 365 nm and then scanned by thin layer chromatography scanner. Then the calculation was done to the levels of curcumin, demethoxycurcumin, bis-demethoxycurcumin

which are the components of curcuminoid with linear regression method.

Subjects

The study subjects were patients with OA in Rheumatology Clinic Dr. Sardjito Hospital, Yogyakarta.

Inclusion criteria: patients with mild to moderate knee OA and agreed to follow this study procedure. The diagnosis of OA was depended on the American College of Rheumatology (ACR) criteria for OA. Exclusion criteria: have arthritis other than OA, hypersensitive history to diclofenac sodium or curcuminoid, history of dyspepsia and gastro-intestinal ulceration, liver, kidney or bone marrow function disturbances, using anti co-agulant or other NSIADs.

Study Procedure

After a random assignment, the one week washed-out period was done. In this period the subjects were asked to have enough rest and not walk too much in the hope that the subject with mild or moderate OA did not feel knee pain. Paracetamol was a rescue medication when needed. After washed-out period, knee joint aspiration and evaluation of COX-2 secretion by synovial fluid monocytes was done. The subjects were randomly given 30 mg of curcuminoid or 25 mg of diclofenac sodium three times daily by blinding method. Subjects were again asked to have enough rest and not walk too much in order to make their knee symptom stable with no fluctuation. After four weeks treatment the evaluation as above was repeated and the data found were analyzed.

Assessment of COX-2 Secretion by Synovial Fluid Monocytes

The observation of COX-2 secretion by synovial fluid monocytes was conducted at the Biomolecular Laboratory of Medical Faculty, University of Gadjah Mada. Through painting of COX-2 enzyme produced by monocytes in synovial fluid using the antiserum anti-COX-2 monoclonal then under the light microscope the cytoplasm of monocytes that did not secrete COX-2 was pale, while that secreted COX-2 was brown. Based on the amount of COX-2 enzyme produced, the monocytes were differentiated into 4 groups (**Figure 1**).

The monocyte which did not secrete COX-2 (cytoplasm looked pale, given the score 0), which secreted only a little amount of COX-2

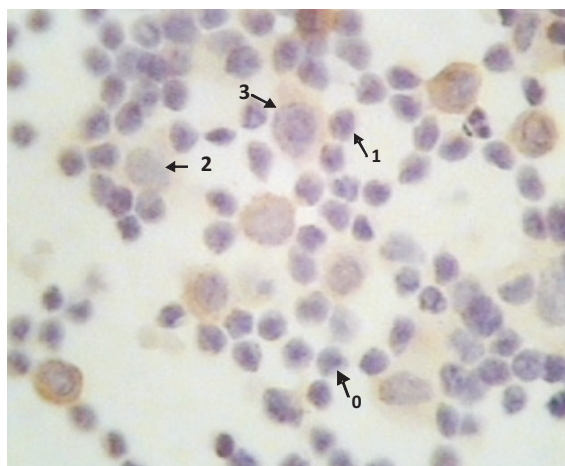


Figure 1. Secretion of COX-2 enzyme by synovial fluid's monocytes

(light brown cytoplasm, given the score 1), which secreted middle amount of COX-2 (brown cytoplasm, given the score 2), and which secreted large amount of COX-2 (dark brown cytoplasm, given the score 3).

Monocytes observations were appraised by two assessors. Before starting the study the kappa test was conducted. Each assessor observed 40 monocytes. Intraobserver consistency of the first researcher was 0.88; intraobserver consistency of the second researcher was 0.86 and interobserver consistency was 0.84. To assess the efficacy of the drugs each assessor observed 100 synovial fluid's monocytes in each preparation before starting and after 4 weeks of treatment.

Statistical Analysis

Statistical analysis was carried out by the SPSS 16.0 for Windows software package. Results are expressed as the mean \pm SD. Student's t-test was used for statistical analyses; p values of less than 0.05 were considered to be significant.

RESULTS

In the curcuminoid group the number of subjects who participated in the study was 39 consisting of 15 men and 24 women. The average of age was 64.05 ± 8.83 year.

Five subjects were excluded from curcuminoid group with the reasons: 1 subject taking piroxicam, 1 subject experienced ureteric colic due to urinary tract stones, 1 subject had hematuria due to urinary vesicles tumors, 1 subject stopped the curcuminoid therapy at the request of his family and 1 subject having chronic obstructive pulmonary disease acute exacerbation. The number of subjects in the curcuminoid group who followed the study through to completion was 34 people, consisting of 11 men and 23 women.

A total of 2 subjects were excluded from diclofenac group because of one subject experiencing dyspepsia on the seventh day of treatment without improvement with the provision of omeprazole 10 mg 1 tablet daily and the other with the synovial fluid was not able to be found in the second aspiration. So the number of subjects in the diclofenac group who followed the

Table 1. Baseline data of subject

Variables	Total (%)		Mean \pm SD	
	Curcuminoid (n=39)	Diclofenac (n=41)	Curcuminoid (n=39)	Diclofenac (n=41)
Gender (%)			-	-
- Man	15 (38.5)	12 (29.3)		
- Woman	24 (61.5)	29 (70.7)		
Age (year)	-	-	64.05 \pm 8.83	64.56 \pm 8.86
OA Duration (month)	-	-	41.23 \pm 32.60	40.37 \pm 30.87
Joint Aspiration (%)			-	-
- Right	21 (53.8)	22 (53.7)		
- Left	18 (46.2)	19 (46.3)		
BMI (kg/m ²)	-	-	26.28 \pm 3.62	26.44 \pm 4.79
Hypertension (%)	17 (43.6)	14 (34.1)	-	-
DM (%)	7 (17.9)	6 (14.6)	-	-
Dislipidemia (%)	1 (2.6)	1 (2.4)	-	-
COX-2 Secretion	-	-	1.84 \pm 0.37	1.79 \pm 0.38

study through to completion was 39, consisting of 11 men and 28 women.

Table 2 shows that COX-2 enzyme secretion by synovial fluid monocytes was significantly decreased in both groups who received curcuminoid as well as diclofenac sodium ($p < 0.001$).

The results of this study indicate that there was no significant difference in the decreasing of COX-2 secretion by synovial fluid monocytes during treatment between both groups **Table 3** shows the ability of both drugs did not differ significantly in reducing the secretion of COX-2 by synovial fluid monocytes in knee OA.

DISCUSSION

Most subjects were women, in accord with osteoarthritis epidemiology data showing that the prevalence of osteoarthritis is higher in women than in men.¹⁴ When the comparison between both groups was done, it was not statistically significant different in frequency of sex in both groups. The average age of subjects was 64.05 ± 8.83 years in the curcuminoid group and 64.56 ± 8.86 years in the diclofenac group. These data indicate that osteoarthritis is common in the elderly. This is consistent with epidemiological data that osteoarthritis is a degenerative disease accompanied by inflammation.⁵ When compared between the curcuminoid group and diclofenac group it looked no statistically significant difference of age average in both groups. Judging from the level of education, the highest frequency

was the high school level, so that in filling out the questionnaire it was predicted that no large bias happened.¹⁵ When compared between the curcuminoid group and diclofenac group it did not look statistically significant differences in educational levels of both groups. The average duration suffering from osteoarthritis was 41.23 ± 32.60 months in the curcuminoid group and 40.37 ± 30.87 months in the diclofenac group. These data indicate that osteoarthritis is a chronic disease. Osteoarthritis is a degenerative disease, so that is chronic.¹⁶ When compared between curcuminoid group and diclofenac group it did not look statistically significant difference the duration of suffering of both groups.

Co-morbidities such as diabetes mellitus, dyslipidemia and hypertension were found in some subjects. Hypertension was the most frequent co-morbidity, followed by diabetes mellitus. Some elderly often have more than one disease in the body,¹⁷ this agrees with the data above that there were some accompanying diseases that occurred in some patients with osteoarthritis. When compared between the curcuminoid group and diclofenac group it looked no statistically significant difference in the percentage of co-morbidities in both groups.

Chainani (2003) reported the results of a meta-analysis that in vitro curcumin inhibits COX-2 enzyme activity, phospholipase, lipooxygenase, collagenase, elastase and hyaluronidase.¹¹ All NSAIDs work by inhibiting COX-2 enzyme activity, although each NSAID has different

Table 2. Cyclooxygenase-2 secretion by Synovial fluid's monocytes before and after treatment

Variable	Curcuminoid (Mean \pm SD)		P-value	95% CI		Diclofenac (Mean \pm SD)		P-value	95% CI	
	Before	After		Under	Upper	Before	After		Under	Upper
COX-2 Secretion	1.84 \pm 0.37	1.15 \pm 0.28	<0.001#	0.58	0.79	1.79 \pm 0.38	1.12 \pm 0.27	<0.001#	0.53	0.82

Description: # Wilcoxon Signed Ranks test; SD Standard Deviation; CI Confidence Interval

Table 3. Decreasing of COX-2 secretion by Synovial fluid's monocytes during treatment

Variable	Mean \pm SD		P-value	95% CI	
	Curcuminoid (n = 34)	Diclofenac (n = 39)		Under	Upper
Decreasing of COX-2 Secretion	0.70 \pm 0.51	0.67 \pm 0.45	0.89 #	-0.19	0.26

Description: # Mann Whitney; U test; SD Standard deviation; CI Confidence interval

capacities to inhibit that activity.¹⁸ Sodium diclofenac as a preferentially selective COX inhibitor is an NSAID that inhibit the COX-2 enzyme activity equal to its inhibitory in COX-1 enzyme activity, although in fact it is slightly more potent in inhibiting the activity of COX-2 enzyme. Inhibition of COX-2 enzyme activity would suppress the inflammation, whereas inhibition of COX-1 enzyme activity will cause some side effects such as gastrointestinal ulcers, bleeding and decreasing of kidney function.¹⁹

Monocytes are important cells in the process of inflammation and degeneration of the affected joint in osteoarthritis. If the activities of monocytes are suppressed then the process of inflammation and degeneration of the joints can be slowed.²⁰ COX-2 enzyme plays an important role in transforming arachidonic acid into prostaglandins. Monocytes are one of the cells that produce COX-2 in the synovial fluid. Inhibition of COX-2 activity becomes an important target to suppress the inflammation in the treatment of osteoarthritis.²¹

Diclofenac sodium is a powerful inhibitor of COX-2 and prostaglandin synthase activities, both of them are involved in Prostaglandin E-2 (PGE-2) production.²² Thickening of the synovium is one process that occurs in joints affected by osteoarthritis. Thickening of the synovium causes joints stiffness. Thickening of the synovium occurs due to excessive growth of synovial cells. In osteoarthritis, stimulation of COX-2 enzyme on cells in the synovium causes excessive growth of these cells. In osteoarthritis, the inhibition of COX-2 enzyme activity by curcumin from turmeric rhizome extract is able to reduce the excessive growth of the synovial cells. The combination of curcumin from turmeric rhizome extract and celecoxib could enhance the ability of celecoxib in inhibiting the excessive growth and increased apoptosis of synovial cells in osteoarthritis.²³

In the previous study for 2 years (1998-2000) with clinical analysis and examination of blood and synovial fluid of osteoarthritis patients, the researcher found that the combination of 15 mg curcuminoid from *Curcuma domestica* Val. rhizome extract and 100 mg of essential oil from *Curcuma xanthorrhiza* Roxb. was taken 2 times daily for 2 weeks time was comparable to the anti-inflammatory drug piroxicam for the

treatment of patients with knee OA by lowering the level of malondialdehyde (MDA) in the blood and synovial fluid and improving the clinical symptoms of the patients.²⁴

Alwi et al.⁸ evaluated the effect of curcumin on lipid profile of patients with acute coronary syndrome (ACS), as one of serial studies about the effect of curcumin on metabolic factor and inflammatory response in patients with ACS, they conclude the administration of low-dose curcumin showed a trend of reduction in total cholesterol level and LDL cholesterol level in ACS patients. Since the pathophysiology of ACS particularly depends on the roles of inflammation, thrombosis and distal embolization,²⁵ the benefit of curcuminoid for ACS should be thought to be beneficial for OA as well where the inflammation is one of the role in the OA pathophysiology.

Another advantage is that the combination of curcuminoid from *Curcuma domestica* Val. rhizome extract and essential oil from *Curcuma xanthorrhiza* Roxb. were cheaper, more effective in improving the physical condition, tends to improve the liver function, kidney and gastrointestinal tract, whereas piroxicam worsen those function.²⁶ In animal model, the study of curcuminoid from *Curcuma domestica* Val. rhizome extract proved that until the largest dose that is technically still able to be given to animal, the dose of 483.84 mg/kg or 128 times the usual dose for treatment in humans, it did not cause any symptoms of poisoning and death on white rats (wistar). The results of histo-pathological examination to the liver, kidney, stomach, heart, lung, pancreas, brain, spleen, ovary and testis showed no pathological signs after curcuminoid administration on dose of 120.96 mg/kg and a dose of 483.84 mg/kg.²⁷

Gastrointestinal damage caused by non-steroidal anti-inflammatory drugs (NSAIDs) remains a significant clinical problem. Other adverse effects of NSAIDs, including those associated with the renal and cardiovascular systems impairment, are of growing concern to practitioners.²⁸ The using of NSAIDs often has constraints by the presence of gastrointestinal side effects from mild dyspepsia to the occurrence of severe complications such as bleeding due to perforation of the stomach and duodenum. It is predicted between 10-20% of NSAID users have complaint of dyspepsia. Non-steroidal

anti-inflammatory drugs are mostly acidic and inhibit the synthesis of prostaglandins by inhibiting the activities of cyclooxygenase enzymes. Various efforts have been attempted to reduce the occurrence of side effects particularly on the gastrointestinal tract. The mode of administration (parenteral, suppositories, topical) and enteric-coated drug use are some effort of them. Through these ways the gastric side effects still occur, although the numbers are reduced. Recently there are 2 types of isoenzymes cyclooxygenase (COX) which have been found, namely cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Cyclo-oxygenase-1 is an enzyme that the body needs to maintain the physiological homeostasis. By inhibiting this enzyme the physiological homeostasis will be disrupted and will result in the side effects of drugs. Cyclooxygenase-2 occur in pathological conditions, such as inflammation. Non-steroidal anti-inflammatory drugs work more selectively suppressing the COX-2 than COX-1 promising less gastrointestinal side effects.²⁹ The differences of both enzyme activities have led to the hypothesis that the roles of these two enzymes are different. Cyclooxygenase-1 maintain the physiological functions of various organs such as maintaining the thickness of the gastric mucosa, increases gastric mucus production and improving the renal blood flow. Cyclooxygenase-2 has some effects on pathological processes such as inflammation. Experiments on animals and clinical findings strengthen the evidence of the influence of COX-2 in chronic inflammatory disorders and malignancy. The Presence of COX-2 on peripheral nerve endings and on the central nervous system has proven instrumental in helping the transmission of pain. The development of knowledge about the biology of COX-1 and COX-2 has given the impression of simplicity of understanding, where COX-1 is considered as a constitutive enzyme and COX-2 as an inducible enzyme. In fact it is not simple, because in various specific tissues the COX-2 enzyme also plays a role of physiological processes such as in ovulation and implantation.³⁰

In ancient times infectious diseases and malnutrition dominate in the community, but recently degenerative disease, metabolic and psychosomatic illnesses dominate. People believe that in order to prevent degenerative

diseases they can use traditional ingredients, for example concoction consisting of gandarusa leaves, brotowali steam, temu lawak and other turmeric rhizomes.³¹ Curcuminoid from *Curcuma domestica* Val. containing among other things as much as 3-4% (consisting of curcumin, desmethoxy-curcumin, bisdesmethoxy curcumin), as much as 2-5% volatile oil (composed of sesquiterpenes and phenylpropane derivatives), arabinose, fructose, glucose, starch, tannin and minerals (magnesium, manganese, iron, copper, calcium, sodium, potassium, lead, zinc, cobalt, aluminum and bismuth). The study of anti-inflammatory activity of curcumin has been done. If the components of curcuminoid are separated it revealed that curcumin has the strongest anti-inflammatory activity compared to the other components.³² In vitro studies have identified a number of different molecules involved in inflammation that are inhibited by curcumin including phospho-lipase, lipooxygenase, cyclooxygenase-2, leucotrienes, prostaglandins, thromboxanes, nitric oxide (NO), collagenase, elastase, hyaluronidase, matrix metallo proteinase-1 (MMP)-1, interferon, tumor necrosis factor- α (TNF- α) and interleukine-12 (IL-12).³² Curcumin is also able to prevent and treat gastric ulcers; it is anti hepatotoxic, kolagogum and anti-tumor.¹⁰

It still needs further study to explain the mechanism of action of diclofenac sodium and curcuminoid from *Curcuma domestica* Val. rhizome extract in suppressing the secretion of the COX-2 enzyme by synovial fluid's monocytes.

CONCLUSION

Curcuminoid from *Curcuma domestica* Val. rhizome extract significantly suppresses the secretion of COX-2 enzyme by synovial fluid's monocytes of patients with knee osteoarthritis. The ability of curcuminoid from *Curcuma domestica* Val. rhizome extract was not significantly different compared to diclofenac sodium in suppressing the secretion of cyclooxygenase-2 enzyme by synovial fluid's monocytes.

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