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The effect of curcuminoid turmeric rhizome extract on interleukin 1β concentration in osteoarthritis patient

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ABSTRACT

Background: Cytokine Interleukin (IL) 1β is increased in synovial fluid and cartilage of patients with osteoarthritis (OA). Curcuminoid blocks lipopolysaccharides causing the suppression of IL 1β production. The capability of curcuminoid to decrease IL 1β secretion by the synovial fluid monocytes has not been previously studied.

Objective: This study aimed to explore the activity of curcuminoid of turmeric rhizome extract (C. *domestica Val.*) in blocking the IL 1β secretion by the knee synovial fluid monocytes of patients with osteoarthritis.

Methods: This research was a prospective randomized open and blinded endpoint (PROBE) study. The subjects of the study were osteoarthritis patients who were divided into 2 groups. Subjects were administered 30 mg of turmeric rhizome curcuminoid extract (treatment group) and 25 mg diclofenac sodium capsules (control group) twice a day for 4 weeks. Knee synovial fluid was taken before and after treatment. The capability examination of IL 1β secretion by synovial fluid monocytes was conducted by culturizing the monocyte cells. Level of IL 1β was measured by ELISA

Results: There were 80 subjects eligible to participate in the study according to the inclusion/exclusion criteria. The decrease of means of IL 1β concentration of the curcuminoid group after the 4-week therapy was 70.24±81.46 pg/ml, while the decrease of means of diclofenac sodium was 61.90±60.42 pg/ml, with no significant difference between groups (p=0.691;95%CI:0.681-0.699).

Conclusion: Curcuminoid of turmeric rhizome (C. *domestica Val.*) extract has the capability which is not weaker than that with diclofenac sodium in decreasing the IL 1β secretion by synovial fluid monocytes of the OA patients' joints.

Latar Belakang: *Kadar sitokin interleukin (IL) 1β meningkat pada kartilago dan cairan synovial pada pasien dengan osteoarthritis. Kurkuminoid menghambat lipopolisakarida sehingga produksi IL 1β menurun. Kemampuan kurkuminoid dalam menurunkan sekresi IL 1β oleh monosit cairan sinovial belum diketahui.*

Tujuan: *Tujuan dari penelitian ini yaitu untuk mengetahui aktivitas kurkuminoid ekstrak rimpang kunyit (C. domestica Val.) dalam menghambat sekresi IL 1β oleh monosit cairan sinovial pada pasien dengan osteoarthritis.*

Metode: *Penelitian ini merupakan penelitian prospektif, acak, terbuka dan tersamar. Subjek dari penelitian ini adalah pasien osteoarthritis yang dibagi dalam 2 kelompok. Subjek diberikan 30 mg ekstrak rimpang kunyit (kelompok perlakuan) dan 25 mg natrium diklofenak (kelompok kontrol) 2 kali sehari selama 4*

minggu. Cairan sinovial lutut diambil sebelum dan sesudah terapi. Pemeriksaan kemampuan sekresi IL 1β oleh monosit cairan sinovial dilakukan dengan mengkultur sel monosit. Kadar IL 1β diukur menggunakan ELISA.

Hasil: *Terdapat 80 subjek yang memenuhi syarat penelitian. Rerata penurunan konsentrasi IL 1βpada kelompok kurkuminoid setelah 4 minggu terapi adalah 70.24±81.46 pg/ml, sedangkan rerata penurunan kelompok natrium diklofenak adalah 61.90± 60.42 pg/ml. Tidak ada perbedaan yang bermakna antar kelompok (p = 0.691; 95% CI 0.681-0.699).*

Kesimpulan: *Kurkuminoid ekstrak rimpang kunyit (C. domestica Val.) memiliki kemampuan yang tidak lebih lemah daripada natrium diklofenak dalam penurunan sekresi IL 1β oleh monosit cairan synovial pada sendi pasien dengan OA.*

INTRODUCTION

Osteoarthritis (OA) is a cartilage disorder with a systemic and chronic inflammation-inducing disability on an elderly person. The cartilage disorder involves a painful degradation process of cartilage, bone and synovial fluid and is associated with genetic, metabolic, biochemical and biomechanical factors.[1,2]

It is estimated that 27 million adults in the US suffer from OA.[3] Prevalence of OA in Indonesia reached 15.5% for men and 12.7% for women of 40-60-year-old people.[4] Osteoarthritis has been reported to be the cause of the fourth most critical disability for women and the eighth for men.[5]

Osteoarthritis is characterized by progressive cartilage degradation and coincidence with the metabolism changes of the synovial fluid, subchondral bone, hyaline articular cartilage, ligament, capsule, and periarticular muscle.[6] It involves leukocyte activation in synovial fluid which produces inflammation mediators such as protease, prostaglandin E2 (PGE2) and cytokines. Interleukin 1 β (IL 1β) is one of the cytokines which is particularly secreted by monocytes, macrophages, and chondrocytes involved in cartilage degradation.[2,7] IL 1β activates degradation enzymes such as matrix metalloproteinases (MMPs) and collagenases, which cause inflammation responses in the joint and cartilage destruction.[8] Cytokine IL 1β is increased in synovial fluid and cartilage of patients with OA.[2,9]

Management of OA include efforts to reduce inflammation symptoms especially joint pain and swelling, and also the progressivity of joint destruction, which finally will increase the life quality of OA patients.[4] Based on the guidance of the American Pain Society in 2004 for the patient management of mild joint pain, acetaminophen is the first choice for medicine and the other non-steroidal anti-inflammatory drugs (NSAID) as the second choice. To treat medium and severe pain or inflammation, the main choice of treatment is the COX-2 selective barriers, except for those patients with high-risk hypertension and kidney disease.[2,10] One of the frequently used of NSAIDs is diclofenac sodium.[10,11]

Diclofenac sodium is an antiinflammatory agent often used in OA. The most common side-effect from diclofenac sodium is gastroenteropathy.[10] In OA, cartilage degradation occurs and progressive decrease of proteoglycan. IL 1β plays an important role in progressivity of cartilage degradation and has the responsibility as a medium for chondrocyte response to OA. The increasing concentration of IL 1β which is particularly secreted by monocyte fluid of joint induces the inflammation process.[7]

Curcuminoid is the secondary metabolite from turmeric rhizome (*Curcuma domestica* Val./C. *domestica Val*.) and temulawak (C. *Xanthorriza*). Curcuminoid has been shown to possess the antiinflammatory and analgesic activities with the low side effects to gastrointestinal tracts.[12] Curcuminoid can block the lipopolysaccharides (LPS) causing the suppression of IL 1β and TNFα productions.[13]

The ability of curcuminoid in decreasing the IL 1β secretion by the synovial fluid monocyte has not previously been studied. This study aimed to examine the activity of curcuminoid of turmeric rhizome extract (C. *domestica Val*.) compared with diclofenac sodium in blocking the IL 1β secretion by the knee synovial fluid monocytes of OA patients.

METHODS

This research was a prospective, randomized, open, blinded end-point (PROBE) study and has received appropriate ethical approval (Number: KE/FK/23/EC) from the Medical and Health Research Ethics Commission of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University with research permit No. 070/248 RSUD Kota Yogyakarta. The subjects of the study were patients with OA who have been diagnosed based on the 1986 American College of Rheumatology (ACR) criteria who visited the Rheumatology Clinic of RSUP Dr. Sardjito and Internal Medicine Clinic of RSUD Kota Yogyakarta who met the following inclusion criteria: (1) OA patients who have been diagnosed based on the 1986 ACR, (2) were getting ready not to take anti-inflammation medicine 1 week before synovial fluid testing, (3) able to take synovial fluid from the knee joints minimum 2 cm3 and (4) were prepared to participate in the complete study by signing the informed consent form. Subjects were excluded from the study with the following exclusion criteria: (1) liver dysfunction (the increase of transaminase enzyme having been more than 3 times the upper limit of normal values) or kidney dysfunction (creatinine serum is more than 3 mg/dl, (2) gastritis disease, peptic ulcer or duodenal ulcer, (3) hypersensitivity to curcuma or diclofenac sodium, (4) consuming anti-coagulant or other anti-inflammatory agents, (5) previous surgery of OA joint, (6) administered joint corticosteroid/ visco-supplement injection for the last 3 months, and/or (7) any contraindications of intra-articular injection.

The sample size was calculated based on the formula for the hypothesis test with different means of two populations. When the dropped out (DO) estimation was 20%, the minimal samples for either group was 25 subjects. Eligible patients were randomly assigned to receive either 30 mg of turmeric rhizome curcuminoid extract that contained 90% curcumin (curcuminoid group) or 25 mg diclofenac sodium capsules (diclofenac sodium group). The therapy was given twice a day for 4 weeks. Knee synovial fluid was taken on day 0 (before therapy) and after 4 weeks (the end of therapy) to measure the IL 1β concentration by monocytes in the knee synovial fluid.

The measurement of IL 1β secretion by synovial fluid monocyte was performed by culturizing the monocyte cells in the growth media and examination of IL 1β concentration. The observation examined the capability of synovial fluid monocytes in secreting IL 1β before the therapy and after the 4-week therapy using ELISA method.

Statistical analysis was performed using SPSS version 21 (IBM Corp., Chicago). The mean differences of the curcuminoid group and the diclofenac sodium group were analyzed with t-test and significance difference was set at $p<0.05$. The concentration change of IL 1β before and after therapy was analyzed with paired t-tests with 95% confidence interval and a significant difference was set at $p<0.05$.

RESULTS

There were 110 subjects participated in this study. They were gathered in the Pharmacology clinic test room, Faculty of Medicine Public Health and Nursing, Gadjah Mada University, Yogyakarta, for re-anamnesis, physical, and basic laboratory examinations. There were 80 subjects eligible to participate in the study according to the inclusion/exclusion criteria (Fig.1). There were 6 subjects (5 in the curcuminoid group and 1 in the diclofenac sodium group) who were not able to complete the therapy. In the curcuminoid group, 1 subject received treatment in the hospital for a bladder infection, 1 for chronic obstructive lung disease, 1 for swollen joint, 1 for hematuria and 1 stopped the therapy without any reason. In the diclofenac sodium group, there was 1 subject with abdominal complaint after taking medicine for 7 days so they discontinued the therapy and 1 completed the study, but could not be analyzed because of no post-therapy synovial fluid was taken. Therefore, at the end of the study, there were 7 subjects considered dropped out (5 from the curcuminoid group and 2 from the diclofenac sodium group).

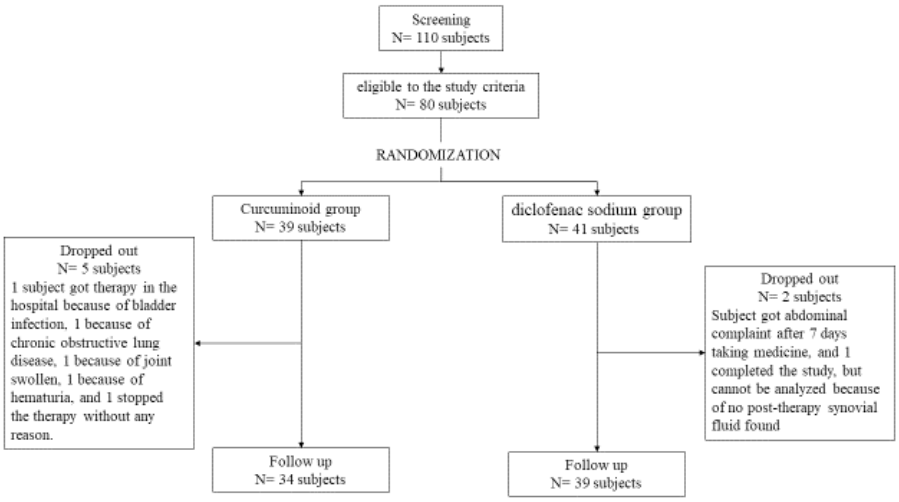

Figure 1. Diagram of subjects involved from the beginning until the end of study

The basic characteristic subjects of the study, sexual status and body weight were normally distributed, while age, OA duration and pre-study IL 1β concentration were not normally distributed. There were no significant differences between the basic characteristic of subjects in both groups (Table 1). In these two groups, the women subjects were more than the men subjects. The mean age of all the subjects was 64.31 ± 8.79 years (range 50-80 years), suffering duration of OA 3.24 ± 3.5 years (range 1 month-23.33 years) and IL 1β concentration mean 100.021 ± 98.13 pg/ml (range 2.84-350.119 pg/ml).

Table 1. The basic characteristic of subjects

Variable	Curcuminoid group (n=39) mean + SD	Diclofenac sodium group (n=41) mean + SD	p	95% CI
Female sex	24	29	0,472	0,433-0,699
Body weight (kg)	62,91+11,38	63,28+11,64	0,886	-5,50-4,76
Age (year)	64,05+8,83	64,56+8,86	0,763	0,669-0,856
OA duration (year)	2,94+3,48	3,40+2,38	0,089	0,043-0,182
IL lβ concentration (pg/ml)	105,95+102,38	94,39+94,84	0,528	0,390-0,610

The mean of IL 1β concentration before the intervention for the curcuminoid group was 105.95 ± 102.38 pg/ml (median 64.25 pg/ml with range 3.34 – 350.12 pg/ml, while for the diclofenac sodium group it was 94.39 ± 94.84 pg/ml (median 41.43 pg/ml with range 2.84 – 325.464 pg/ml).

The mean and median of IL 1β concentration before and after 4 week therapy (Table 2) show the decrease of IL 1β concentration of the curcuminoid group from 110.74 ± 107.79 pg/ml (median 70.51; range 3.34 – 350.12 pg/ml) to 40.49 ± 54.33 pg/ml (median 11.10 ; range 0 – 214.59 pg/ml). The decrease of IL 1β concentration of diclofenac sodium from 88.46 ± 93.40 pg/ml (median 33.84; range 2.84 – 325.46 pg/ml) to 26.5 ± 43.64 pg/ml (median 6.22; range 0 – 180.70 pg/ml). The above data were not normally distributed, so that Wilcoxon signed ranks test was used to

know the decrease before and after the therapy. There were significant differences (p < 0.001) between IL 1β concentration in week 0 compared with week 4 in both the curcuminoid group and diclofenac sodium.

Table 2. IL 1β concentration in week 0 compared to week 4

Group		IL 1β concentration (pg/ml)		*p*	95% CI
		Week 0	Week 4		
Curcuminoid	Mean	110,74+107,79	40,49+54,33	<0,001	0,000-0,084
(n=34)	Median	70,51	11,10		
Diclofenac sodium	Mean	88,46+93,40	26,5+43,64	<0,001	0,000-4,074
(n=39)	Median	33,84	6,22		

In week 0 there was no significant difference between curcuminoid group and diclofenac sodium group (110.74±107.79 vs 88.46±93.40 pg/ml; p = 0.261; 95% CI -24.667 -69.225) nor for week 4 (40.49±54.33 vs 26.5±43.64 pg/ml; p = 0.223; 95% CI -81.939 -36.815). There were significant differences before and after treatment in both groups but there was no significant difference between the average decrease in IL 1β concentration in the curcuminoid group and diclofenac sodium group. Table 2 showed the IL 1β concentration between week 0 and week 4 on both groups. There were significant differences between week 0 and week 4 in the curcuminoid group (110.74±107.79 vs 40.49+54.33 pg/ml; p<0.001; 95% CI 0.000-0.084) and in the diclofenac sodium group (70.24±81.46 vs 61.90+69.42 pg/ml; p<0.001; 95% CI 0.000-4.l074) (Table 2).

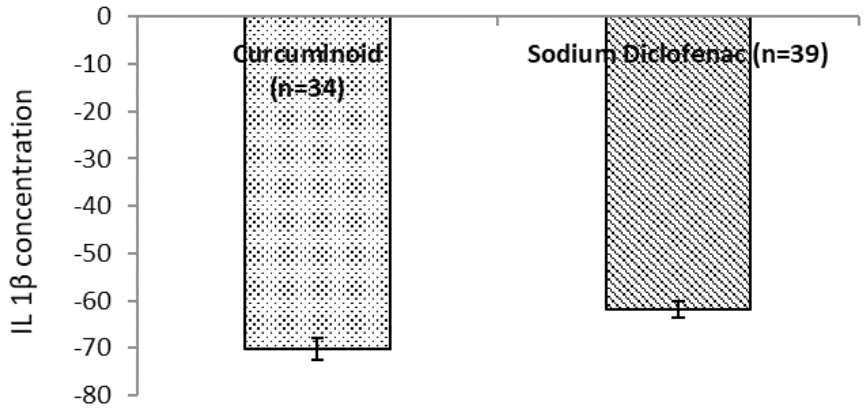

Figure 2. IL 1β concentration decreased in curcuminoid and diclofenac sodium groups for 4 weeks

The decrease of means of IL 1β concentration of curcuminoid group after 4 weeks of therapy was 70.24±81.46 pg/ml, while the decrease of means of diclofenac sodium was 61.90±60.42 pg/ml, and there was no significant difference between both groups (p = 0.691; 95% CI 0.681-0.699)(Fig.2).

DISCUSSION

During the inflammation processes, polymorphonuclear (PMN) leukocytes play an important role in initial defence to phagocytosis. Polymorphonuclear leukocytes have a short survival. Inflammatory mediators including IL I, GCSF, LPS, and an alkaline condition serve

to prolong the survival of PMN. After the phagocytosis process, PMN leukocytes will die by apoptosis. Apoptosis dysregulation will induce exudative cells to remain in the inflammation site, which in turn influence the pathogenesis process of chronic inflammation disease including OA.[14,15]

Kertia et al. conducted a study of the influence of giving turmeric rhizome curcuminoid extract combination and temulawak rhizome atsiri oil compared with piroxicam on leukocyte count in the synovial fluid of patients with OA. There was no significant difference found between the reduction of leukocyte count in the treatment group (the combination of turmeric rhizome extract curcuminoid and temulawak rhizome atsiri oil) and piroxicam group.[16]

This study aimed to compare curcuminoid of turmeric rhizome extract (C. *domestica* Val.) with diclofenac sodium toward the capability of IL 1β secretion by the monocytes of the knee synovial fluid of patients with OA. In this study, the curcuminoid group was given a capsule containing 30 mg curcuminoid of turmeric rhizome extract. The curcuminoid of turmeric rhizome contains 90% curcumin.[12,13,17]

Turmeric rhizome is included in the monograph of WHO herbal medicine with known efficacy and safety.[18] Some studies show that curcumin is effective in acute and chronic inflammation-related diseases.[18–20] The systematic review for safety test of curcuminoid given for the healthy person or patients showed that its curcuminoid and metabolite content are well-tolerated. The most common side effects are flatulence (1000 and 2000 mg/day), constipation (1500 mg/day), nausea (1500 and 1890 mg/day), diarrhea (1890 and 2000 mg/day) and itching (1500 mg/day).[21] Curcuminoid consumption till 8 g/day for 4 months by patients with colorectal adenocarcinoma induces some mild side effects.[22]

In this study, the group consumed 90 mg curcuminoid per day in 3 dosages of turmeric rhizome extract for 7 days. Three persons were excluded from the study. One patient suffered from OA knee joint pain and swelling more serious because of excessive activity for ± 3 days during the patient's child's marriage. One patient suffered from hematuria, vesica urinary mass was found in USG examination, and was referred to the surgery department of RSUP DR Sardjito for further treatment. One patient quitted the therapy without any reason and did not come at evaluation time in the second week of study. After curcuminoid tablets had been given for almost 3 weeks, there were 2 patients treated at the hospital, one of them was diagnosed as bladder infection and suspected as bladder stone and the other suffered from chronic obstructed lung disease in acute onset.

Curcuminoid affects to decrease acid secretion, to increase mucin and to accelerate gastric ulcer healing in animal trials.[18] Curcumin's mechanism of action as anti-inflammatory agents is to inhibit COX-2 expression.[19] Curcumin blocks the activity of MMP-9 and MMP-2 which play a role in the formation of gastric ulcers because of indometacin.[20] In the diclofenac sodium group, one patient suffered from epigastric pain after 7 days consuming of the medicine. This patient was asked to stop consuming diclofenac sodium and administered H2 and sucralfate therapy. The gastric pain complaint was reduced after consuming the above medicine. Gastric pain or other gastrointestinal disorder ware not found in the curcuminoid group.

In this study, IL Iβ concentration which was secreted by synovial fluid monocyte of OA patient was measured. The measurement at the beginning of the study was 100.02 ± 198.13 pg/ml. Westacott et al. (1999) found IL 1β concentration of synovial fluid of the OA patient 27.8 ±4.5 pg/ml (range 20-128) and RA 130.3 ±22 pg/ml (range 80-970) while in the healthy person it was 20 pg/ml.[23] Whereas Srivastava et al (2016) found IL 1β in monocyte of blood of the OA patient at levels of 126.4 ± 19.94.[24]

Diclofenac sodium as a NSAID has the effect to suppress IL 1β by blocking Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) cascade.[3,15,20,25] The cascade of NF-κB will cause the occurrence of decreasing IL 1β production in the subject given diclofenac sodium. In this study, the significant decrease of IL 1β concentration

was found in the synovial fluid monocyte after administration of diclofenac sodium, from 88.4 ± 93.40 pg/ml (median 33.84 pg/ml; range 2.84 – 325.46) to 26.5 ± 43.64 pg/ml (median 6.22 pg/ml; range 0–180.70).

Curcuminoid has been known to have the anti-inflammatory activity toward the inflammation process and to reduce pain. These effects occur by blocking some inflammatory mediators.[8,12,26] Some studies on cell cultures showed that curcumin suppressed the production of IL 1β as the consequence of IκBα degradation and by blocking the activity of IκB kinase (IKK) to NF-κB cascade.[27–29] In this study, there was a significant decrease of IL 1β concentration secreted by synovial fluid monocyte in the curcuminoid group from 110.74 ± 107.79 pg/ml (median 70.51 pg/ml; range 3.34 – 350.12) to 40.49 ± 54.33 pg/ml (median 11.10 pg/ml; range 0 – 214.59).

Currently, there is another drug besides NSAID that has been proven to be used for osteoarthritis therapy, namely diacerein. Diacerein affects similar to NSAID and has a better effect than paracetamol. The mechanism of action of diacerein is to inhibit the IL 1β system so that the IL 1β concentration is decreased in the synovial fluid of osteoarthritis patients. In this study showed that curcuminoid can reduce IL 1β concentration in the 4-weektherapy. So that curcuminoid can be developed as an alternative anti-IL 1β drug with a mechanism similar to diacerein.[30]

At the end of the study, the mean difference of IL 1β concentration after the 4-week treatment between both groups showed only the insignificant difference (70.24 ± 81.46 and 61.90 ± 69.42 pg/ml; p<0.691). This result confirmed that curcuminoid has the comparable effect with diclofenac sodium in suppressing the monocyte secretion of IL 1β in the synovial fluid of patients with OA.

In early OA (less than 1 year) or during the acute condition, there are infiltration of mononuclear cells, increased pro-inflammation mediators including cytokine and expression of transcription factors. This causes the IL 1β concentration of synovial fluid, especially in cases of OA, in the beginning, to be higher than that of the previous level. In the patients with OA, the concentration of IL 1β of synovial fluid at the beginning of the study was 542.0 ± 102.1 pg/ml and in previous OA 202.5 ± 36 pg/ml, p<0.001). In OA when acute inflammation is occurring, the effusion of synovial fluid, inflammation of PMN leucocyte, as well as the IL 1β and TNFα secretion becomes higher than the time without acute inflammation.[31] The effect of curcuminoid in decreasing TNFα level and reactive oxygen intermediates (ROI) on patients with OA is similar to sodium diclofenac.[32, 33]

The weakness of this study was that the subjects of the study were not differentiated between the beginning OA (suffered less than 1 year) and the chronic OA (more than 1 years). The OA patients with the acute inflammation condition were also not differentiated from the condition without the acute inflammation which might cause a greater range of IL1β concentration (2.84 – 350.119 pg/ml).

The IL 1β secreted by monocyte is influenced by a gene which encodes pro-inflammatory NF-κB protein. The gene product which is regulated by NF-κB is also able to give the feedback to activate NF-κB through the NF-κB cascade.[20] Further study is needed to know the effect of curcuminoid of turmeric rhizome extract in suppressing NF-κB in OA patients. If the effect of curcuminoid is known to suppress NF-κB in the synovial fluid, it is possible that the pro-inflammatory proteins in OA are involved.

It is recommended to do additional studies to know the clinical benefits of curcuminoid of turmeric rhizome extract in suppressing NF-κB and decreasing IL 1β secretion. There is some clinical evidence and hope that the decreasing IL 1β will reduce the inflammation and joint pain in patients with OA and also block the OA progressivity.

CONCLUSION

It can be concluded that curcuminoid of turmeric rhizome (C. domestica Val.) extract has a comparable effect to diclofenac sodium

in decreasing IL 1β secretion by synovial fluid monocyte of the OA patients' joints. Additional studies are recommended to know the effectivity of curcuminoid of turmeric rhizome extract compared with the standard therapy in suppressing the inflammatory processes and blocking the joint destruction through the blocking of NF-κB, IKK and IκBα degradation which play an important role in the NF-κB cascade.

CONFLICT OF INTEREST

None declare.

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REFERENCES

1. Klippel J. Primer on the rheumatic diseases. 12th ed. Georgia: Arthritis Foundation; 2001. p. 573–582.
2. Loeser R. Pathogenesis of osteoarthritis [Internet]. Up to date. 2018 [cited 2019 Aug 15]. Available from: www.uptodate.com/contents/table-of-contents/rheumatology/osteoarthritis
3. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Practise Research Clinical Rheumatology . 2014;28(1):5–15.
4. IRA. Rekomendasi IRA untuk diagnosis dan penatalaksanaan osteoartritis. Jakarta: Ikatan Reumatologi Indonesia; 2014.
5. WHO. Osteoarthritis. In: Priority medicines for Europe and the World 2013 Update. Geneva: World Health Organization; 2013.
6. Hunter DJ, Bierma-zeinstra S. Osteoarthritis. Lancet. 2019;393:1745–59.
7. Noormartany. Gambaran petanda biologi cairan tubuh pada penyakit osteoartritis. In: Pramudito R, Wachjudi R, Hamijoyo L, editors. Osteoarthritis Course. Bandung; 2005. p. 9–13.
8. Lopes EBP, Filiberti A, Husain SA, Humphrey MB. Immune contributions to osteoarthritis. Current Osteoporosis Report. 2017;1–8.
9. Bay-jensen AC, Thudium CS, Mobasheri A. Development and use of biochemical markers in osteoarthritis : Current update. Current Opinion in Rheumatology. 2017;29:1–8.
10. NPC. Management of acute pain and chronic noncancer pain. In: Pain: Current understanding of assessment, management, and treatments. Washington: National Pharmaceutical Council; 2005. p. 61–71.
11. Depkes. Pedoman penggunaan obat opioit dalam penatalaksanaan nyeri. Jakarta: Departemen Kesehatan RI Direktorat Jendral Pelayanan Kefarmasian dan Alat Kesehatan Jakarta; 2002. p. 42–61.
12. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis : A randomized open-label parallel-arm study. Trials. 2019;20(214):1–11.
13. Yin H, Guo Q, Li X, Tang T, Li C, Wang H. Curcumin suppresses IL-1 β secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. The Journal of Immunology. 2018;200:2835–46.
14. Tateiwa D, Yoshikawa H, Kaito T. Cartilage and bone destruction in arthritis : pathogenesis and treatment strategy : A literature review. Cells. 2019;8(818):1–31.
15. Van Dalen SC, Blom AB, Walgreen B, Sloetjes AW, Helsen MM, Geven EJ. IL-1 β -mediated activation of adipose-derived mesenchymal stromal cells results in PMN reallocation and enhanced phagocytosis : A possible mechanism for the reduction of osteoarthritis pathology. Frontiers in Immunology. 2019;10(1075):1–13.
16. Kertia N, Sudarsono, Imono A, Mufrod, Catur E, Rahardjo P. Pengaruh pemberian minyak atsiri temulawak dan ekstrak kunyit dibandingkan dengan piroksikam terhadap angka lekosit cairan sinovia penderita osteoarthritis lutut. Majalah Farmasi Indonesia. 2005;16:155–61.
17. Ahmed S, Anuntiyo J, Malemud C, Haqqi T. Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis: A

review. Evidence-Based Complementary and Alternative Medicine. 2005;2:301–8.
18. WHO. WHO monographs on selected medicinal plants. 1999. 115–124 p.
19. Zhang Z, Luo D, Xie J, Xian Y, Lai Z, Liu Y. Curcumin's metabolites, tetrahydrocurcumin and octahydrocurcumin, possess superior anti-inflammatory effects in vivo through suppression of TAK1-NF-κB pathway. Frontiers in Immunology. 2018;9(1181):1–12.
20. Kumar SSD, Houreld NN, Abrahamse H. Therapeutic potential and recent advances of curcumin in the treatment of aging-associated diseases. Molecules. 2018;23(835):1–14.
21. Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances: Review. Phytotherapy Research. 2018;1–11.
22. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: Lessons learned from clinical trials. Journal of the American Association of Pharmaceutical Scientists. 2013;15:195–218.
23. Westacott C, Wicher J, Barner I, Thompson D, Swan A, Dieppe P. Synovial fluid concentration of five differents cytokines in rheumatic disease. Annals of the Rheumatic Diseases. 1999;49:676–81.
24. Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS. Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee : A four-month , double-blind , randomized , placebo-controlled trial. Inflammopharmacology. 2016;
25. Barcelos RP, Bresciani G, Cuevas MJ, Martínez-flórez S, Soares FAA, Gozalez-Gallego J. Diclofenac pretreatment modulates exercise-induced inflammation in skeletal muscle of rats through the TLR4 / NF-κB pathway. Applied Physiology, Nutrition, and Metabolism. 2017;42(7):757–64.
26. Kim L, Kim JY. Chondroprotective effect of curcumin and lecithin complex in human chondrocytes stimulated by IL-1 b via an anti- inflammatory mechanism. Food Sci ence and Biotechnology. 2019;28(2):547–53.
27. Zhang Y, Zeng Y. Curcumin reduces inflammation in knee osteoarthritis rats through blocking TLR4 / MyD88 / NF- κ B signal pathway. Drug Development and Research. 2019;1–7.
28. Wang J, Ma J, Gu JH, Wang F-Y, Shang X-S, Tao H-R. Regulation of type II collagen, matrix metalloproteinase-13 and cell proliferation by interleukin-1 β is mediated by curcumin via inhibition of NF- κ B signaling in rat chondrocytes. Molecular Medicine Reports. 2017;16:1837–45.
29. Henrotin Y, Priem F, Mobasheri A. Curcumin : A new paradigm and therapeutic opportunity for the treatment of osteoarthritis : Curcumin for osteoarthritis management. Springerplus. 2013;2(56):1–9.
30. Cooper C, Kanis JA, Pavelka K, Bruye O, Leeb BF, Maheu E. Diacerein : Benefits , risks and place in the management of osteoarthritis . An opinion-based report from the ESCEO. Drugs Aging. 2016;33:75–85.
31. Bigoni M, Sacerdote P, Turati M, Franchi S, Gandolla M, Gaddi D. Acute and late changes in intraarticular cytokine levels following anterior cruciate ligament injury. Journal of Orthopaedic Research. 2012;1–7.
32. Hudiyanti V, Kertia N, Sumardi. Effect of curcuminoid versus diclofenac sodium on monocytes secretion of tumor necrosis factor α in knee osteoarthritis. Acta Interna - The Journal of Internal Medicine. 2012;2(1): 27-32.
33. Kertia N, Asdie AH, Rochmah W Marsetyawan. Ability of curcuminoid from Curcuma domestica Val. in reducing the secretion of reactive oxygen intermediates by synovial fluid monocytes in patients with osteoarthritis. The Indonesian Journal of Biotechnology. 2011;16(1):111-7