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Potential Therapeutic Effects of *Curcuma longa* extract in Patients with Osteoarthritis: A Randomized Controlled Trial

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Abstract:

Baground: Osteoarthritis (OA) is the most common degenerative joint disorder in the elderly and a major public health problem in worldwide. Non-steroidal anti-inflammatory drug (NSAID) is a common medication given in OA patients, but its use was limited due to many side effects. Previous studies showed that *Curcuma Longa* extracts may exhibit benefic effects in the treatment of OA. To determine the effective and safety of *Curcuma Longa* extracts for reducting pain in patients with osteoarthritis.

Methods: A randomized controlled trial (RCT) in OA patients. Subjects were randomized to 3 different group. Group I: CB extract (350 mg of Curcuma longa and 150 mg Boswellia serrata) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium), group II: CB extract, group III: NSAID. Each subject would be followed up 3 times: baseline, second weeks, fourth weeks after baseline. The pain severity was measured using visual analogue scale (VAS). The analysis is intention to treat based.

Results: There were 105 subjects enrolled at the study. Subjects were dominated by female (80%) with mean aged 63 years. Ninety-five subjects (group I: 36; group II: 29, group III: 30) remained for complete analysis. Group I showed the greatest reduction of VAS score after the second and fourth weeks of treatment (more than 50%). Group III has the least VAS score reduction after fourth weeks from baseline. There was statistically different of VAS score reduction between groups (P<0.001). The most frequent AE were reported from subjects in group III.

Conclusion: CB extract is effective and safe for reducting pain in OA patients.

Keywords: *Boswellia serrata*, *Curcuma longa*, Pain, Osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint disease and a major cause of pain and disability in older people [1]. Global estimation of OA are reported as 9.6% of men and 18% of women has symptomatic OA at age ≥60 years [2]. In the Asia-Pacific region, the prevalence of knee osteoarthritis was 7.5% in China, 5.78% in rural India, 10.20% in Bangladesh and 5% in Indonesia [3-4].

The management of osteoarthritis (OA) is a challenge. The conventional treatment of OA is restricted primarily to the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injection and analgesics. However, therapy with NSAIDs and analgesics can lead to adverse effects as gastrointestinal and cardiovascular problems, especially if it is used for long periode [5]. This situation shows the need for new agents that treat pain and reduce the progression of the disease.

Curcuma longa is commonly known as turmeric. It is cultivated in Asia and some tropical countries [6]. *Curcuma longa* constituents include the three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin[7]. Curcumin is a highly pleiotropic molecule that has been shown to possess anti-inflammatory, hypoglycemic, antioxidant, wound-healing, and antimicrobial activities[8]. Some promising effects have been observed in patients with various pro-inflammatory diseases[9], including metabolic syndrome, arthritis, and anxiety [10].

Panahi et al. (2014) and Srivastava et al. (2016) reported that *Curcuma longa* suppresses inflamation and brings clinical improvement including decrease level of Visual Analog Scale (VAS) and The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC score) [11-12]. Curcuminoids represent an effective and safe alternative treatment in patients with osteoarthritis.

The data in Indonesia are very limited. Further well-controlled studies are therefore required to examine the long-term effects of curcumin against patients with osteoartritihis. This study aimed to determine the efficacy and safety of *Curcuma longa* extracts for reducting pain in patients with osteoarthritis.

METHOD

Design

This was a Randomized Controlled Trial (RCT) at Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia in patients with osteoartrithis. The treatment used in this trial were CB extract (350 mg of Curcuma longa and 150 mg Boswellia serrata) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium). Each subject would be followed up 3 times: baseline (visit I), second weeks after baseline (visit II) and fourth weeks (Visitie III). The pain severity was measured using visual analogue scale (VAS).

Subjects

The study population of this study were all patients with osteoartrithis at Bethesda Hospital and Panti Rapih Hospital. The inclusion criteria were as follows: Male or female patients, age >18 years old with Kellgren-Lawrence grade II or III knee osteoarthritis. Subject with a known hypersensitivity to CB extract, ibuprofen, diclofenac sodium, pregnant or has a pregnancy program, participation in other clinical trial in the last 1 month before this study, incompetent to give a consent and answer the questionnaire, or receiving other pain treatment in the last 24 hours before this study was excluded in this study. The minimum sample requirement was 25 subjects

in each group. Total of 105 subjects were enrolled for achieving normal distribution.

Variables and Measurement

The data about clinical characteristics profile consist of sex, age, occupation, marital status, education background, and comorbidity. The degree of knee osteoarthritis was using Kellgren-Lawrence grading scale. The Kellgren Lawrence grading system is a radiological classification of knee osteoarthritis. It progresses from grade 0 to grade IV and based on x-rays. Each subject would be followed up 3 times: baseline (visit I), the second weeks after baseline (visit II) and the fourth weeks (Visiti III). We use Visual Analogue Scale (VAS) for knowing decrease of pain after treatment. We measured the decrease of VAS score from baseline to visite II and from baseline to the last follow up in the fourth weeks. Pain outcomes were divided into 2 groups <50% and > 50%.

The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between the two ends of the scale—"no pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm). Any AE was recorded in case report form, reported to principal investigator, and followed-up by researcher.

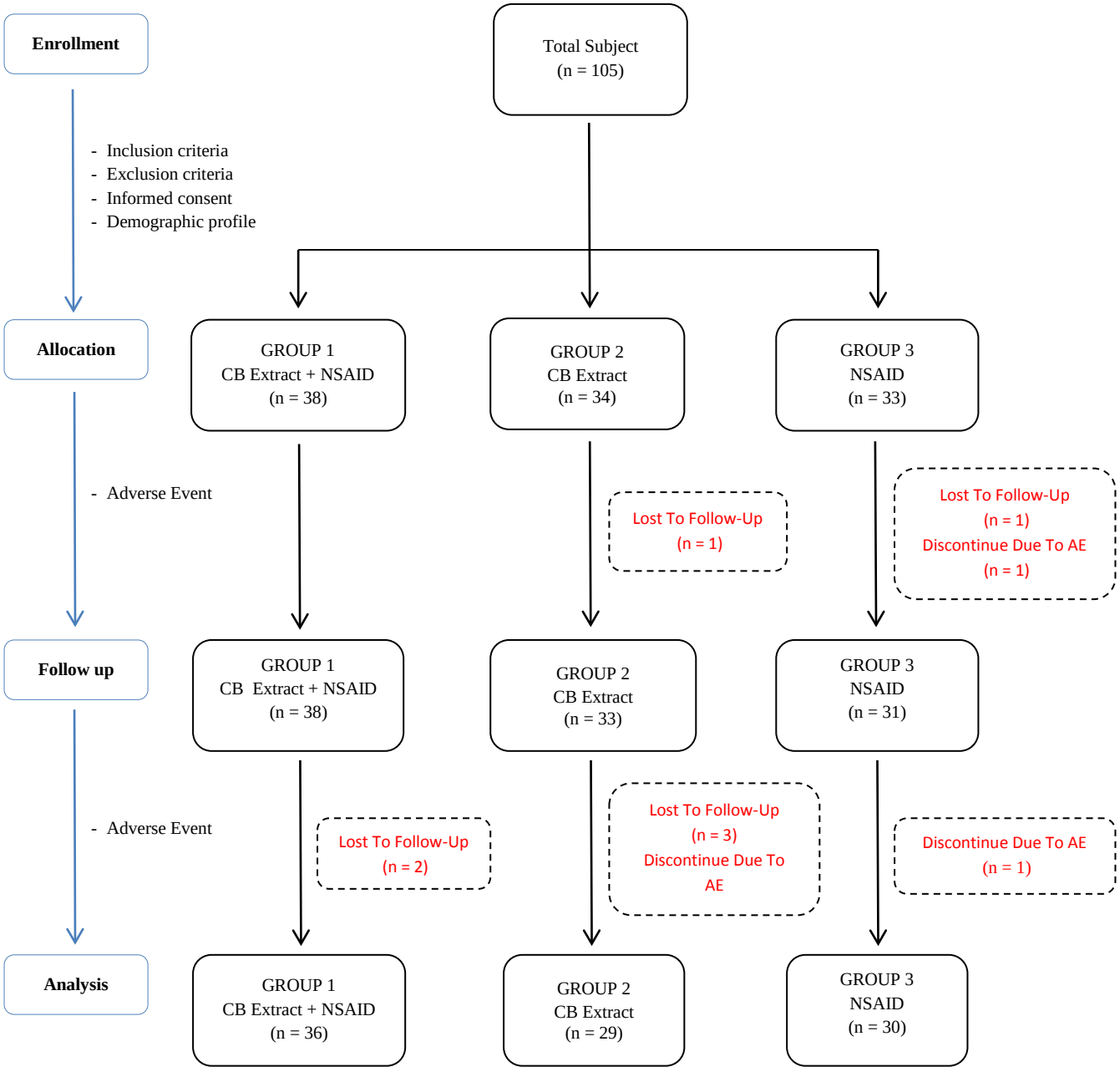


Figure 1. The Flow Diagram of The Research

Analysis

The analysis of this study is intention to treat based. The participants demographic profile mentioned in percentage. We describe about the reduction of pain among the groups using graphic.

Ethical Clearance

This study used primary and secondary data. Research Ethics Committee of Duta Wacana Christian University School of Medicine had approved the study. The number of ethical clearance is 867/C.16/FK/2018.

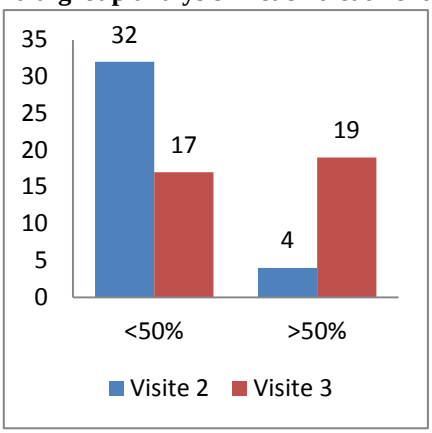
RESULTS

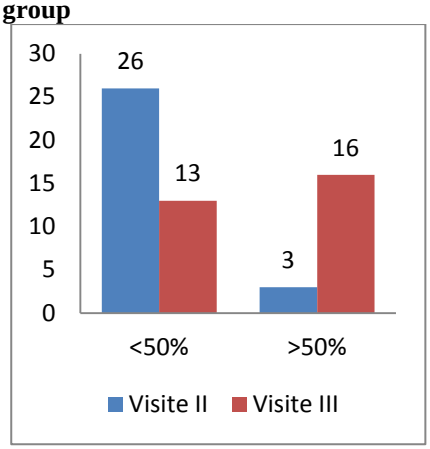
There were 105 subjects at baseline, consist of 38 subjects in group 1, 34 subjects in group 2, and 33 subjects in group 3. After 4 weeks of study, remained 95 subjects for complete analysis consist of 36 subjects in group 1, 29 subjects in group 2, and 30 subjects in group 3 (Figure 1). Subjects were dominated by age 60s, female, married, has an occupation, has a KL grade 2, and has a comorbidity (Table 1).

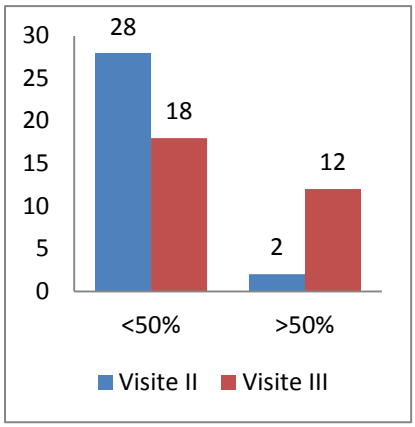
Table 1. Baseline characteristics of the subjects

Characteristics	Group 1	Group 2	Group 3
Age (mean)	63.8 ± 7.8	62.8 ± 9.2	62.9 ± 9.5
Gender			
Male	5 (13.2%)	9 (26.5%)	7 (21.2%)
Female	33 (86.8%)	25 (73.5%)	26 (78.8%)
Marital status			
Married	27 (71.1%)	29 (85.3%)	22 (66.7%)
Single	11 (28.9%)	5 (14.7%)	11 (33.3%)
Educational background			
Elementary school	9 (23.6%)	3 (8.8%)	4 (12.1%)
Junior high school	9 (23.6%)	4 (11.8%)	2 (0.6%)
Senior high school	7 (18.4%)	15 (44.1%)	16 (48.5%)
Bachelor degree	9 (23.6%)	7 (20.6%)	7 (21.2%)
Others	4 (10.5%)	5 (14.7%)	4 (12.1%)
Occupation			
Working	27 (71.1%)	26 (76.5%)	17 (51.5%)
Unemployment	11 (28.9%)	8 (23.5%)	16 (48.5%)
KL Grade			
Grade II	22 (57.8%)	18 (52.9%)	20 (60.6%)
Grade III	16 (42.2%)	16 (47.1%)	13 (39.4%)
Comorbidity			
Yes	25 (65.7%)	27 (79.4%)	27 (81.8%)
No	13 (34.3%)	7 (20.6%)	6 (18.2%)

Intra-group analysis in each treatment group



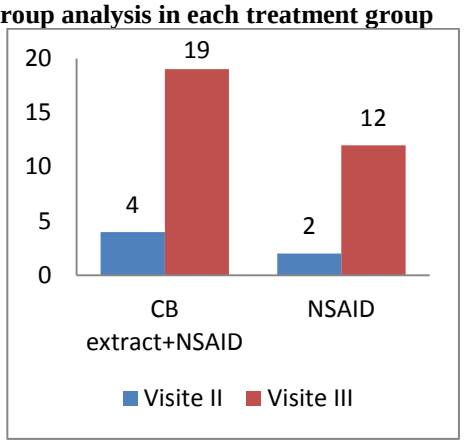




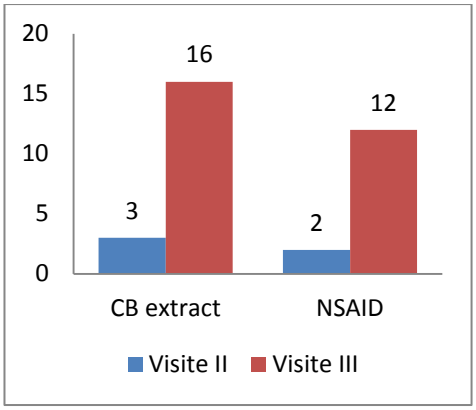
Graph 1. Combination CB extract and NSAID **Graph 2**. CB extract **Graph 3**. NSAID

Measurement of pain reduction in patients performed 2 analyzes namely intra-group and inter-group analysis. In the intra-group analysis the results were obtained. (Graph 1) CB extract and NSAID groups at the time of the second visit there were 4 patients who experienced a decrease in pain> 50% and at the third visit to 19 patients (p = 0.002). (Graph 2) CB Extract group at the time of the second visit there were 3 patients who experienced a decrease in pain> 50% and at the third visit there were 16 patients (p = 0,0002). (Graph 3) the NSAID group found> 50% less pain relief than the other groups, from 2 to 12 patients (p = 0,0004).

Inter-group analysis in each treatment group



Graph 4. Comparison combination CB extract and NSAID with NSAID between visite II and visite III



Graph 5. Comparison CB extract with NSAID between visite II and visite III

Tabel 2. The Adverse Event in each group at visit II and visit III

Group	Type of Adverse Event			
	Visit II	Correlation to CB extract/NSAID	Visit III	Corelation to CB extract/NSAID
Group I (Total n = 5)	Angioedema (n =1)	Not correlated	a. Flank pain (n = 1) b. Constipation (n = 1) c. Nausea and loss of appetite (n = 1) d. Malaise and dizziness (n = 1)	Not correlated
Group II (Total n = 4)	a. Dizziness (n = 1) b. Urticaria (n = 1)	a. Correlated to CB extract b. Not correlated	a. Nausea and loss of appetite (n = 1) b. Dizziness (n = 1)	Not correlated
Group III (Total n = 7)	Abdominal pain (n = 5)	Correlated to NSAID	a. Abdominal pain (n = 1) b. Muscle pain/spasm (n = 1)	a. Correlated to NSAID b. Not correlated

Intergroup analysis compared the combination group of CB + NSAID extract with NSAID and CB extract with NSAID. (Graph 4) the combination of CB + NSAID extract showed there were 15 patients who experienced a decrease in pain> 50% while in the NSAID group there were 10 patients. There was no significant difference between the two groups (p = 0.532). (Graph 5) CB extract group showed there were 13 patients who experienced a decrease in pain> 50% while in the NSAID group there were 10 patients. There was no significant difference between the two groups (p = 0.905).

The highest AE was seen in group 3. Group 2 had the least AE. One AE was correlated to CB extract and 5 AE were correlated to NSAID.

DISCUSSION

Efficacy of *Curcuma longa* extract

Our study showed that the greatest reduction of VAS score after the second and fourth weeks of treatment (more than 50%) in group 1(CB extract and NSAID). This study confirmed some previous studies. In another recent study, curcumin alone (0.5 g) and in combination with diclofenac sodium (0.05 g) in 45 patients with rheumatoid arthritis. Mean VAS scores among RA patients in the curcumin group showed the highest reduction in VAS score (59.9%) from baseline (68.57±17.14) to end of treatment (27.5±9.35). Percentage changes in VAS score were statistically significant ($p<0.05$) [13].

At the baseline, 85.71% of the subjects were in the moderate/severe pain category in the CB group and 78.57% in the celecoxib group. At the end of the study, only 21.43% of subjects in the CB group were in the moderate/severe pain category whereas 50% of celecoxib group remained in the moderate/severe pain category. There was a significant improvement in pain scores within CB group and celecoxib group in a period of 12 weeks, but there was no significant difference between the groups ($p >0.05$) [14].

Panahi et al. (2014) reported curcuminoids (1500 mg/day in 3 divided doses; n= 19) or matched placebo (n = 21) for 6 weeks. Treatment with curcuminoids was associated with significantly greater reductions in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analogue scale (VAS) and Lequesne's pain functional index (LPFI) scores during the study compared with placebo. Curcuminoids represent an effective and safe alternative treatment for OA [15].

160 patients with osteoarthritis of knee were randomly enrolled into two groups to receive either *Curcuma Longa* extract or placebo along with the standard

drug regimen. Over all significant improvement the VAS score was observed in the patients of CL extract group as compared to placebo group. Clinically, the VAS and WOMAC scores became better, and simultaneously, the levels of biomarkers, viz., IL-1β, reactive oxygen species and malondialdehyde (MDA) were also significantly ($p < 0.05$) improved [12].

The last study by Haroyan et al. (2018) in 201 patients with osteoarthritis. The effects of CuraMed® 500-mg capsules (333 mg curcuminoids) and Curamin® 500-mg capsules (350 mg curcuminoids and 150 mg boswellic acid) taken orally three times a day for 12 weeks. Combining Curcuma longa and Boswellia serrata extracts in Curamin increases the efficacy of OA treatment. Outcome efficacy measures included OA physical function performance-based tests, the WOMAC recommended index of joint pain, morning stiffness, limitations of physical function, and the patients' global assessment of disease severity [15].

The mechanism of curcumin as anti inflammatory agent

Most of the anti-inflammatory properties of curcuminoids are due to the inhibition of NF-κB, and effect that leads to the suppression of several key regulators of inflammation such as cyclooxygenase-II, activator protein-1, JNK, MAPK and PI3K/Akt [16]. Curcuminoids can effectively reduce the release of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β (IL-1β), IL-6, macrophage chemotactic protein-1 and prostaglandin E2. These anti-inflammatory properties have been verified in cultured chondrocytes [17-19].

Along with inflammation, oxidative stress plays an important role in the development and progression of OA. Free radicals produced by abnormal chondrocytes can impair intra-articular segments and components of joints such as proteins, lipids and nucleic acids. Reactive oxygen species can disturb cartilage matrix homeostasis and promote MMP expression, chondrocyte apoptosis and production of mediators involved in pain [20-21]. Curcuminoids are potent antioxidants and have been shown to modulate oxidative stress through various mechanisms.

Safety profile of curcumin

This study showed that CB extract is safe. No serious adverse event was reported in a trial by Panahi et al. (2014). Adverse events were mild gastrointestinal symptoms that were reported from 7 cases of the curcuminoids group and 4 cases of the placebo group. The frequency of these adverse events was not significantly different between the two groups ($p > 0.05$) [11]. In a study by Chandra and Goel (2012) reported adverse event more frequently in diclofenac sodium than in curcumin and curcumin + diclofenac sodium groups. Adverse events reported in the curcumin group were mild fever and a throat infection [13].

CONCLUSION

CB extract proved to be effective for pain treatment in OA patients and has a good safety profile.

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Authors Contribution:

RP - Concept and design of the study, manuscript preparation, statistically analyzed and interpreted, critical revision of the manuscript.

FB - Concept and design of the Study, collected data, preparing first draft of manuscript, critical revision of manuscript and review of the study.

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