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Curcuma longa and *Boswellia Serrata* for improving functional status in osteoarthritis patients: From bench to bedside evidences

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ABSTRACT

Background: The management of osteoarthritis (OA) represents a real challenge. Curcumin is a highly pleiotropic molecule with an excellent safety profile.Some previous studies showed the extract of *Curcuma longa* and *Boswellia Serrata*(CB extract) is a promising potential as therapeutic interventions against OA. **Aims and Objective:** This study aimed to measure the effectiveness and safety of CB extract for improving functional status in patients with OA. **Materials and Methods:** A randomized controlled trial (RCT) in OA patients. 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). Subjects were randomized to 3 different group (Group 1: CB extract and NSAID; group 2: CB extract; group 3: NSAID). Each subject would be followed up 3 times: baseline (visit I), 2 weeks after baseline (visit II), and 4 weeks after baseline (visit III). The measurement of functional status with WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index). **Results:** There were 105 osteoarthritis patients. Seven subjects were lost to follow up and three subjects were excluded from the study due to medication side effect. Ninety-five subjects (group 1: 36; group 2: 29, group 3: 30) remained for complete analysis. Delta (Δ) WOMAC score defined as the result of subtraction between WOMAC score at visit I and WOMAC score at visit III. Group 1 showed the greatest reduction of WOMAC score after 4 weeks of treatment (ΔWOMAC = 12.08 ± 18.6). Group 3 has the least WOMAC score reduction (ΔWOMAC = 6.9 ± 16). There was no statistically different of ΔWOMAC score between groups (p = 0.367). There were no statistically different of the prevalence of AE between groups at the visit II (p: 0.119) and at the visit III (p: 0.767). **Conclusion:** CB extract is effective and safe for improving functional status in OA patients.

Key words: *Curcuma longa*; *Boswellia serrate*; Osteoarthritis; WOMAC

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INTRODUCTION

The management of osteoarthritis (OA) is a challenge. As a multifactorial disease evolving over decades, OA is one of the most disabling rheumatic diseases. In addition, no cure has been discovered to date. There is growing interest in the medical management of OA. However, this area requires new therapeutic strategies and approaches to deal with OA in a rapidly growing elderly population.[1]

Many pre-clinical evidences support the use of curcumin in OA. Most of the biological effects observed and published for curcumin in chondrocytes and OA between 2002 and 2009 were reported in previous narrative review.[2,3]

Over the last few decades many scientific and clinical studies have focused on the potential of curcumin for treating various pathological conditions.[4] Curcumin was investigated mainly for its anti- inflammatory and

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anti-oxidant potency. Recently, these therapeutic effects have been reviewed in depth by Gupta et al.[5,6]

Only a few clinical studies have been published with curcumin. Curcumin was tested in patients suffering rheumatoid arthritis. In addition to be safe and not related to any adverse events, curcumin (500 mg) was the most effective to improve disease activity score (DAS) and American College of Rheumatology (ACR) score. Curcumin was administered alone or in combination with diclofenac sodium (50 mg).[7] Despite the paucity of published clinical data on curcumin and the overall poor quality of the trials, there is scope for promising future studies on curcumin in OA. However, since the in vitro effect was so well- documented and proven, the clinical efficacy needs to be further studied in OA patients. This study aimed to measure the effectiveness of *Curcuma longa* and *Boswellia Serrata* (CB extract) for improving functional status in OA patients.

MATERIALS AND METHODS

Study design

This was a randomized controlled trial (RCT) in OA patients. Computerized generated block randomization with openepi software is used in this study. 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), 2 weeks after baseline (visit II), and 4 weeks after baseline (visit III). The measurement was using WOMAC (Western Ontario and McMaster Universities Osteoarthitis Index).

Subjects

Subject Inclusion criteria for this study are: male or female patients, age >18 years old, and has knee osteoarthritis with Kellgren-Lawrence grade II or III. Subject with a known hypersensitivity to CB extract, ibuprofen, diclofenac sodium, participation in other clinical trial in the last 1 month before this study, pregnant or has a pregnancy program, 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 100 subjects were enrolled for achieving normal distribution.Subjects were randomized to 3 different group (Group 1: CB extract and NSAID; group 2: CB extract; group 3: NSAID). Each medication was taken two times per day for 4 weeks.

Variable

Demographic profile including sex, age, occupation, marital status, education background, comorbidity, and the degree of OA. The degree of knee OA was measured using Kellgren-Lawrence (KL) grading scale. WOMAC (Western Ontario and McMaster Universities Osteoarthitis Index) commonly used as a standardized questionnaires to evaluate the functional status of patients with osteoarthritis. It consists of 3 categories of questions, 5 questions for pain, 2 questions for stiffness, and 17 questions for physical functioning of the joints. Each question is scored on a scale of 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme), thus score range for pain, stiffness, and physical functioning are 0-20, 0-8, and 0-68 respectively. The total score for all questions is 96. The higher score indicates the worse OA symptom. Any adverse event (AE) in this trial would be reported and monitored strictly. This study was approved by Duta Wacana Christian University School of Medicine Ethical Research Committee, Yogyakarta, Indonesia. The number of ethical clearance is 867/C.16/FK/2018.

Analysis

The analysis of this study is intention to treat based. After normality test with Kolmogorov-Smirnov test, numeric variables analyzed using t-test or wilcoxon signed rank test. Based on the result of homogenity test, ANOVA or Kruskal Wallis test used to identify the mean differences between three groups. The significant level was set at $p < 0.05$.

RESULTS

There were 105 subjects at the beginning of the study. Most of the study subjects were female (80%) with mean aged 63 years. About 57.1% of subjects have osteoarthritis with KL grade II. Seven subjects were lost to follow up and three subjects were excluded from the study due to medication side effect. Ninety-five subjects (36 subjects from group 1, 29 subjects from group 2, 30 subjects from group 3) remained for complete analysis (Table 1).

Table 1: The subjects' characteristics

Characteristics	n (%)
Age (mean)	63.24±8.77
Gender	
Male	21 (20%)
Female	84 (80%)
Marital status	
Married	78 (74.3%)
Not married	27 (25.7%)
Occupation	
Employe	70 (66.7%)
Not employe	35 (33.3%)
KL Grade	
Grade II	60 (57.1%)
Grade III	45 (42.9%)
Comorbidity	
Yes	79 (75.2%)
No	26 (24.8%)

Table 2: The result of WOMAC

Group	WOMAC I (n=105)			WOMAC III (n=95)			p
	Min. Score	Max. Score	Mean. Score	Min. Score	Max. Score	Mean. Score	
All subjects	3	73	39.7±19	0	84	27.9±21	<0.001
Group 1	5	73	41.4±19	2	84	30.3±22	<0.001
Group 2	5	73	33.9±17	0	79	26.4±20	<0.001
Group 3	3	69	34.3±20	1	65	26.7±21	0.016

Table 2 showed the mean of WOMAC score at visit I and visit III from all subjects and from each group. The highest mean of WOMAC score was in group 1 and the least was in group 2. The reduction of WOMAC score from visit I to visit III is statistically significant in all groups.

Delta (Δ) WOMAC score defined as the result of subtraction between WOMAC score at visit I and WOMAC score at visit III. The highest mean of WOMAC score was in group 1 (Table 3 and Figure 1). However, group 1 showed the greatest reduction of WOMAC score after 4 weeks of treatment (ΔWOMAC = 12.08 ± 18.6). Group 3 has the least WOMAC score reduction. There was no statistically different of ΔWOMAC score between groups (Table 3).

Group 3 was the most frequently group with reported AE, whereas group 2 has the least reported AE. Abdominal pain was the most common type of AE (n = 7). All of them were seen in group 3. Three subjects need to discontinue the medication due to the AE, two among them were subjects in group 3 and one among them was subject in group 2. No fatal AE was reported in all groups and no subject needed an inpatient treatment due to the AE. After a further investigation, only one case (dizziness) of AE that related to the administration of CB extract and 5 cases (abdominal pain) related to the administration of NSAID. There were no statistically different of the prevalence of AE between groups at the visit II (p: 0.119) and at the visit III (p: 0.767).

Table 3: The mean of ΔWOMAC score

Medication	Mean ΔWOMAC	p
Group 1 (n: 36)	12.08±19	0.367
Group 2 (n: 29)	7.2±14	
Group 3 (n: 30)	6.9±16	

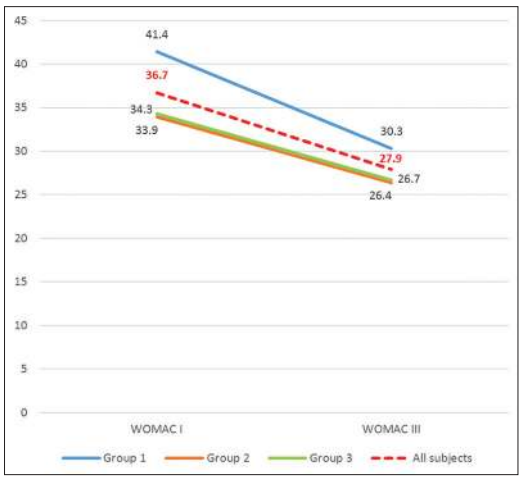

Figure 1: The comparison of WOMAC score mean

DISCUSSION

Pre clinical evidences

The anti-inflammatory property of curcumin has been investigated and explained by studies showing how curcumin acts on inflammatory pathways. Curcumin (50 μM) was shown to inhibit NF-κB activation and translocation induced by IL-1β and the consequent expression of NF-κB induced pro-inflammatory genes, COX-2 and VEGF.[8] Another study has described its effect on signaling and its inhibitory potency in chondrocytes in agarose constructs.[9] Curcumin (0.01-100 ng/ml) was used for its potency to inhibit activator protein (AP)-1 and reverse the IL-1β stimulated production of nitric oxide (NO) and prostaglandin E_2 (PGE_2).

Curucmin was able to produce an anti-inflammatory effect by inhibiting the pro-inflammatory mediators, i.e. PGE2, NO, IL-6 and IL-8. However, in contrast to NSAIDs, curcumin inhibited COX-2, but not COX-1 gene expression.[10] The anti-inflammatory potency of curcumin was also demonstrated in another connective tissue cell type. Curcumin (5μM) was shown to modulate inflammation in human tenocytes by the inhibition of COX-2 through its effect on NF-κB and on other related and equally important cell signaling pathway - the phosphatidylinositol-3 kinase/Akt pathway.[11]

Clinical evidences

Our study show promising result. The result similar with other clinical studies. The clinical efficacy of curcumin was tested in OA patients receiving a patented complex with phosphatidylcholine that improved curcumin bioavailability.[12] This study investigated efficacy and safety of the compound on a longer term (8 months). The evaluation included the measurement of several markers of inflammation (IL-1β, IL-6, sCD40L, sVCAM-1, ESR). One hundred OA patients were included in this study. The add on of curcumin to standard therapy, significantly

reduced pain and stiffness and improved joint function. All WOMAC scores were improved by the treatment with add on curcumin therapy including social and emotional function. Finally, the markers of inflammation were significantly decreased in the treatment group between enrollment and after 8 months of treatment.

A recent study showed that CL extract, BS extract, or its combination was beneficial in OA patients. About 201 subjects were investigated in a three-arm, parallel-group, randomized, double-blinded, placebo-controlled trial to identify the effects of 333 mg curcuminoids and a combination of 350 mg curcuminoids and 150 mg boswellic acid. The administration of combination of curcumin and boswellic acid had a superior effect size (physical performance tests and the WOMAC joint pain index) than curcuminoid alone.[13]

Further research

The promising in vitro results and the interesting clinical observations gathered here for curcumin should refocus efforts to develop therapies based on new formulations of curcumin. Well-designed clinical studies are needed to determine and document the efficacy of curcumin and combination products with curcumin in OA patients.

Hence, curcumin represents a new paradigm since it is not yet a recommended intervention in OA but should be considered based on its safety and efficacy. In addition, taken altogether, these data highlight the needs in OA research for the near future as good quality and well-designed trials.

CONCLUSION

CB extract is effective and safe for improving functional status in OA patients. Further clinical studies are warranted to determine the efficacy of curcumin and its combination products for OA patients.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors declare that they do not have any conflicts of interest.

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Authors Contribution:
RTP- Concept and design of the study, literature search, collected data and statistically analyzed and interpreted, manuscript preparation; **VOW-** Reviewed the literature, participated in drafting, helped and approved in preparing the manuscript to be published.

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APPENDIX

PATIENT NAME | DOB

WESTERN ONTARIO AND MCMASTER OSTEOARTHRITIS INDEX (WOMAC)

Please circle the appropriate rating for each item.

RATE YOUR PAIN WHEN...	NONE	SLIGHT	MODERATE	SEVERE	EXTREME	HOSPITAL USE ONLY
Walking	0	1	2	3	4	
Climbing stairs	0	1	2	3	4	
Sleeping at night	0	1	2	3	4	
Resting	0	1	2	3	4	
Standing	0	1	2	3	4	TOTAL
RATE YOUR STIFFNESS IN THE...	NONE	SLIGHT	MODERATE	SEVERE	EXTREME	HOSPITAL USE ONLY
Morning	0	1	2	3	4	
Evening	0	1	2	3	4	TOTAL
RATE YOUR DIFFICULTY WHEN...	NONE	SLIGHT	MODERATE	SEVERE	EXTREME	HOSPITAL USE ONLY
Descending stairs	0	1	2	3	4	
Ascending stairs	0	1	2	3	4	
Rising from sitting	0	1	2	3	4	
Standing	0	1	2	3	4	
Bending to floor	0	1	2	3	4	
Walking on even floor	0	1	2	3	4	
Getting in/out of car	0	1	2	3	4	
Going shopping	0	1	2	3	4	
Putting on socks	0	1	2	3	4	
Rising from bed	0	1	2	3	4	
Taking off socks	0	1	2	3	4	
Lying in bed	0	1	2	3	4	
Getting in/out of bath	0	1	2	3	4	
Sitting	0	1	2	3	4	
Getting on/off toilet	0	1	2	3	4	
Doing light domestic duties (cooking, dusting)	0	1	2	3	4	
Doing heavy domestic duties (moving furniture)	0	1	2	3	4	TOTAL

PATIENT SIGNATURE | DATE

REVIEWED BY PHYSICAL THERAPIST | DATE

WOMAC TOTAL SCORE /96

Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire