



RESEARCH ARTICLE

# Comparison of the Effect of *Avocado/Soybean* Extract and Crocin on Pain Intensity and Radiographic Changes in Patients with Knee Osteoarthritis

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## ABSTRACT

*Introduction:* Osteoarthritis is a common joint disease, affecting many people worldwide, especially people over 65 years old. As effective medical treatment is lacking and the increased side effects of available drugs for osteoarthritis treatment, this study aimed to compare the outcome of Avosoy and Crocin extracts on pain intensity and radiographic changes in osteoarthritis patients.

*Materials and Methods:* This clinical trial was performed on osteoarthritis patients aged 40–75 years with joint injury of grade 2–3 confirmed by radiographic images. Patients were randomly divided into two groups of 30 patients. One group was given *avocado/soybean* extract (Avosoy) with vitamin D (Vit D; 50,000-IU/week) and 500mg calcium (Ca) daily. Another group received Crocin with Vit D (50,000-IU/week) and 500mg Ca daily. After four months of drug use, the final questionnaire was filled in both groups. The data were analyzed in SPSS 22 software after collecting information.

*Results:* No significant difference was found in the mean pain intensity before and after the intervention in the Avosoy group ( $P = 0.06$ ), but a significant decrease was found in the pain intensity of patients in the Crocin group ( $P < 0.001$ ). Furthermore, no significant difference was found in the mean severity of osteoarthritis symptoms before and after intervention in the Avosoy group ( $P = 0.051$ ), but a significant decrease in the severity of osteoarthritis symptoms and knee discomfort was found in the crocin group ( $P < 0.001$ ). Our findings revealed a decrease in difficulties with activities of daily life, recreation, and exercise in both groups, but no radiological changes were observed.

*Conclusion:* The present study demonstrated that treatment with Crocin has a better effect in decreasing the severity of pain, symptoms of osteoarthritis, and knee discomfort when compared with Avosoy, resulting in improvement of quality of life. Thus, its use could be recommended for patients suffering from osteoarthritis.

## KEYWORDS:

Avosoy; crocin; osteoarthritis

## ARTICLE HISTORY:

Received April 15, 2021

Accepted April 29, 2021

Published May 29, 2021

## DOI:

10.5455/jcmr.2021.12.01.16

VOLUME: 12

ISSUE: 1

ISSN: 2146-8397

## INTRODUCTION

Osteoarthritis is the most common chronic joint disease. Its prevalence is increasing because of the increase in the average age of the population and obesity. It is more common in women than men after the age of 50 years.<sup>1</sup> Knee osteoarthritis is the most common type.<sup>2</sup> According to the World Health Organization, osteoarthritis has been reported globally to be the sixth leading cause of years living with disability in 2000.<sup>3</sup> The disease worsens with age. Patients with advanced osteoarthritis of the knee (Grade 3 and 4) complain of severe pain and functional disability. Most conservative treatments in this group of patients are associated with poor results. Joint replacement surgery is the recommended treatment for this patient group. Besides, this surgery cannot be performed in some patients because of unsuitable physical conditions and age.

Given the limited lifespan of the prostheses used in this surgery, it makes sense to find a conservative treatment that delays the surgery.<sup>4</sup> Researchers believe that low levels of inflammation, growth of blood vessels and nerves from subchondral bone to articular cartilage, and metabolic disorders play a pivotal role in the pathology of osteoarthritis.<sup>5</sup> Inflammation leads to activation of the nuclear factor- $\kappa$ B signal pathway, which in turn is induced by matrix-degrading enzymes such as matrix metalloproteinases (MMPs) in cartilage cells.<sup>6</sup> These enzymes are involved in the destruction of cartilage and thus promote osteoporosis. Oxidative stress is a mediator of inflammation and has been responsible for muscle dysfunction in osteoarthritis.<sup>7</sup>

So far, no effective medical treatment has been found for osteoarthritis.<sup>8</sup> Medication interventions are more sedative and less focused on reducing symptoms or slowing the progression of the disease until the replacement of injured hip and knee joint. Analgesics (acetaminophen, topical capsaicin), oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs; naproxen and ibuprofen), and narcotics (tramadol and codeine) are currently used to treat the symptoms of osteoarthritis. However, each treatment method has its problems that may limit its widespread use. Analgesics can be addictive, while acetaminophen can cause serious side effects such as liver and kidney damage.<sup>5</sup> As a result of the side effects of some chemical drugs, patients are depending on herbal compounds as they have no side effects and also show a positive effect on the disease improvement. One of these drugs is Crocin, the biologically active component of saffron and has proven anti-inflammatory effects in cartilage.<sup>9-11</sup> The second herbal medicine is avocado/soybean unsaponifiables (Avosoy; ASU) derived from natural plant extracts of avocado and soy.<sup>5</sup> ASU is a complex mixture, including fat-soluble vitamins, sterols, triterpene, and furan fatty acids. ASU sterol content is one of the first participants in the biological activity of articular cartilage cells that can modulate the pathogenesis of osteoarthritis by inhibiting certain molecules and pathways involved in osteoarthritis. The anticatabolic properties of ASU prevent cartilage damage by inhibiting the release and activity of MMPs and increasing the tissue inhibitors of the catabolic

enzymes. The anabolic property of ASU can improve cartilage repair by stimulating collagen synthesis and aggrecan synthesis through inhibiting inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor, extracellular signal-regulated kinase, and prostaglandin E.<sup>5</sup>

Because of the high prevalence of osteoarthritis, especially in people over 65 years, the lack of effective medical treatment, and side effects of existing drugs, we decided to compare the outcomes of Avosoy and Crocin on pain intensity and radiographic changes among patients with knee osteoarthritis.

## MATERIALS AND METHODS

This clinical trial was performed on osteoarthritis patients aged 40–75 years with joint injury of grade 2–3 based on radiographic images. The tool and method of data collection was a questionnaire. The sampling method was nonprobability, and patients with inclusion and exclusion criteria were included in the study. Inclusion criteria included: osteoarthritis patients with grade 2–3, between 40–75 years, and informed consent. Exclusion criteria included: history of surgery, diabetic disorders, rheumatism, kidney disease, osteonecrosis and gout, patients without long-term use of anti-inflammatory drugs (2 months), patients without difficult jobs.

### SAMPLE SIZE

Based on previous studies, 30 people per group were considered for the present study.

### PROCEDURE

After obtaining informed consent, patients were randomly divided into two groups of 30 patients. One group was given avocado and soy extract with 500,000 IU vitamin D and 500mg calcium weekly. The other group received Crocin with 500,000 IU vitamin D and 500mg calcium daily. NSAID (Naproxen: 500 mg BID) was administered in case of unbearable pain to both group patients.

At the beginning of the study, knee radiographs were taken for all according to Kellgren-Lawrence criteria. The severity of osteoarthritis was determined as according to the clinical and radiological symptoms: 1- no symptoms, 2 - mild degenerative changes (osteoarthritis) in the knee, 3 - moderate degenerative changes in the knee, and 4 - advanced or severe degenerative changes in the knee.

The patient's pain was determined by the global and localized KOOS questionnaire that consisted of 42 patient-centered questions. Five questions were related to the severity of osteoarthritis symptoms and knee discomfort, and seven questions were about knee swelling, feeling of wear or sound in the knee joint, locking, the ability to straighten and bend the knee. The scoring was 1: never, 2: rarely, 3: sometimes, 4: often, and 5: always.. The questions of morning dryness and dryness after rest were scored from 1 (nothing), 2 (little), 3 (moderate), 4 (severe), and 5 (infinite).

Pain intensity was assessed with nine questions (1: never, 2: once a month, 3: once a week, 4: once a day, and 5: always).

Other questions like the amount of pain felt during the activity such as spinning on the knee, straightening, and bending the knee completely, walking on a flat floor, climbing stairs, sleeping at night, sitting, or lying down and standing were scored from nothing (1) to infinite (5).

Performing daily activities and tasks was composed of 17 questions like going down the stairs, going up the stairs, getting up from a sitting position, standing, bending, picking up objects, walking on a flat floor, getting on and off the car, shopping, wearing socks, lying in bed, bathing, sitting, sitting or getting up from the toilet, and doing heavy and light housework, and was given a score of 1 to 5 (nothing to infinite).

Sports and recreational activities were assessed with five questions in the field (difficulty in performing activities such as squatting, running, jumping, spinning and twisting on the knee, and kneeling) and were given a score of 1 to 5 (nothing to infinite).

Quality of life was assessed with the following four questions and was scored from 1 to 5 (at all, very little, to some extent, a lot and completely):

1. How often do you remember the discomfort in your knee?
2. Have you changed your lifestyle to do less harmful things for your knees?
3. To what extent has a lack of confidence in your knee made you comfortable?
4. How much trouble do you have with your knee in general?

These questionnaires were refilled in both groups four months after taking the drug.

## DATA ANALYSIS

Chi-square and Fisher's exact test was used to compare the background variables between the two groups. The study objectives were evaluated using the Kolmogorov-Smirnov test for the normality of the studied variables. Independent t- and Mann-Whitney tests were used to compare the scores of normally and abnormally distributed variables, respectively, in the two groups. Paired t-test was used to compare the scores of normally distributed variables in each group before and after the intervention. The Wilcoxon test was used for abnormally distributed variables. Data analysis was performed using SPSS software version 22 (SPSS, Chicago, IL). A P value of  $\leq 0.05$  was statistically significant.

## ETHICAL CONSIDERATIONS

A written letter of introduction was received from the university officials. The aim of the study was described to all research units, and written consent was obtained. The information of all patients was kept confidential. Furthermore, all ethics declarations of Helsinki and ethics research committees of the University of Medical Sciences were considered. The study was carried out after approval by the research council of the medical school (IR.BUMS.REC.1397.241).

## RESULTS

A total of 60 patients were included in the study, of which 23 were female (76.6%), and seven were male (23.3%) in the Avosoy group, and eight were male (26.6%), and 22 were female (73.4%) in the Crocin group. No statistically significant difference between the two groups in terms of gender was noted ( $P = 1$ ). The mean age of individuals in the Avosoy and Crocin group was  $64.73 \pm 5.15$  and  $65.27 \pm 5.28$ , respectively, but were not statistically significant in terms of mean age between the two groups ( $P = 0.69$ ). In the Avosoy group, nine were school/High school degree, followed by (12; 39.96%) diplomas, associate degree (2 Cases), and bachelor's degree (7 cases). In the Crocin group, 10 (33.3%) had a school/High school degree, followed by a diploma (8), associate degree (3 cases), and bachelor's degree (9;  $P$  for all = 0.76). No significant difference in terms of education between groups was noted.

The frequency of physical and nonphysical jobs in the two groups was examined and compared. In the Avosoy group, (40%) and 18 patients (60%) had physical and nonphysical professions, respectively. In Crocin group, 21 (70%) had physical jobs and 9 (30%) had nonphysical jobs, that there was no statistically significant difference between groups.

Grade 2 of the disease was observed in 23 (76.5%) and 20 (66.6%) patients in the Avosoy and Crocin group. Moreover, seven (23.5%) patients in the Avosoy group and 10 (33.4%) patients in the Crocin group had grade 3 osteoarthritis. No statistically significant difference was found between the two groups in terms of the grades of arthritis ( $P = 0.56$ ).

The mean of pre- and postintervention pain in the Avosoy group was  $30.77 \pm 3.933$  and  $29.9 \pm 3.33$ , respectively, with no significant difference. In the Crocin group, the mean of pre- and post-intervention pain was  $33.93 \pm 3.9$  and  $23.57 \pm 3.26$ , which showed a significant reduction in the patient's pain (Table 1).

The two groups were not the same in terms of pain intensity before the intervention. So, the score of changes in each patient was obtained and compared in the two groups. The results of the Mann-Whitney test showed that the Crocin group had a significant and greater decrease versus the Avosoy group.

The mean severity of osteoarthritis before and after the intervention was  $23.03 \pm 3.09$  and  $22.5 \pm 2.75$  in the Avosoy group, with no statistical difference (Table 2). A significant decrease in the severity of osteoarthritis symptoms and knee discomfort was found in the Crocin group. The results of the Mann-Whitney test showed that the Crocin group had a significant decrease in this variable versus the Avosoy group.

Statistical analysis showed an average difficulty in daily activities in the Avosoy group before ( $46.7 \pm 6.97$ ) and after the intervention ( $45.06 \pm 6.6$ ). But in the Crocin group, before the intervention, the difficulty level in daily activities was  $52.13 \pm 8.47$  and reached  $32.5 \pm 5.96$  after the intervention, indicating a significant reduction in the difficulty. As varying degrees of difficulty in performing daily activities before the intervention was seen in the groups, the change score of each patient was compared between the two groups. The results

**Table 1** Comparison of mean pain scores in the study groups.

Pain	Study group				P-Value
	Avosoy		Crocin		
	Mean ± SD	Middle (first to third quarter)	Mean ± SD	Middle (first to third quarter)	
Before intervention	30.77 ± 3.93	31 (28–33)	33.93 ± 3.9	32.5 (31–37)	P = 0.01
After the intervention	29.97 ± 3.33	30 (32–28)	23.57 ± 3.26	23 (21–25)	P < 0.001
Wilcoxon statistical test result	Z = -1.82 P = 0.06		Z = -4.82 P < 0.001		

**Table 2** Comparison of the mean score of osteoarthritis symptoms and knee discomfort.

Severe symptoms of osteoarthritis and knee discomfort	Study group				P-Value
	Avosoy		Crocin		
	Mean ± SD	Middle	Mean ± SD	Middle	
Before intervention	23.03 ± 3.09	23.03	25.7 ± 2.94	25.7	P = 0.001
After intervention	22.5 ± 2.75	22.5	20.3 ± 2	20.3	P = 0.001
The result of paired t-test	t = 2.04/P = 0.051		t = 9.89/P < 0.001		

**Table 3** Comparison of the average difficulty score in exercising and recreation.

Difficulty in sports and recreation	Study group				P-Value
	Avosoy		Crocin		
	Mean ± SD	Middle (first - third q quarter)	Mean ± SD	Middle (first-third quarter)	
Before intervention	20.33 ± 2.4	20 (19–21)	21.5 ± 2.53	20 (20–24)	P = 0.096
After the intervention	18.77 ± 2.56	19 (17–20)	14.67 ± 2.02	15 (14–15)	P < 0.001
Wilcoxon statistical test result	Z = -3.476/ P = 0.001		Z = -4.84/ P < 0.001		

of the Mann-Whitney test showed that the Crocin group had a significant decrease in this variable versus the Avosoy group ( $P < 0.05$ ).

The statistical analysis of the average difficulty in exercising and recreation was  $20.33 \pm 2.4$  before the intervention in the Avosoy group, which reached  $18.77 \pm 2.56$  after the intervention, showing a significant decrease in the Avosoy group (Wilcoxon test; Table 3). The mean difficulty of exercising and recreation in the Crocin group was  $21.55 \pm 2.53$  before the intervention, which reached  $14.67 \pm 2.02$  after the intervention, indicating a significant decrease compared to the Avosoy group. The results of the Mann-Whitney test showed that the Crocin group showed a decline significantly in difficulty of exercising and recreation than the Avosoy group.

Wilcoxon analysis showed that the mean quality of life was  $16.87 \pm 4.92$  in the Avosoy group before the intervention, which reached  $18.77 \pm 2.56$  after the intervention, with no significant decrease in the Avosoy group was observed. In the Crocin group, the mean quality of life was  $16.8 \pm 1.99$  before the intervention, which increased to  $14.67 \pm 2.02$  after the intervention, indicating a significant improvement in quality of life in the Crocin group. Since the quality of

life differed in preintervention variables in the groups, the change scores of each person were compared in the two groups. The results of the Mann-Whitney test revealed a significant decrease in this variable in the Crocin group versus the Avosoy group.

The frequency of tendonitis and bursitis in the study groups was examined. Only three patients (9.99%) in the Avosoy group and one patient (3.33%) in the Crocin group had tendonitis and bursitis. Therefore, no statistically significant difference was observed between the two groups ( $P = 0.612$ ).

The average frequency of radiculopathy is shown in Table 4. Our findings revealed that 17 patients (56.6%) in the Avosoy group and 25 patients (83.2%) in the Crocin group had radiculopathy. Significant differences were observed between the two groups in terms of radiculopathy ( $P = 0.047$ ).

Besides, 12 patients (39.96%) in the Avosoy group and 27 patients (89.91%) in the Crocin group exhibited musculoskeletal problems, which were statistically significant ( $P < 0.001$ ).

One patient (3.33%) in the Avosoy group and two patients (6.66%) in the Crocin group showed mental disorders, which were not statistically significant ( $P = 1.0$ ).



**Table 4** Comparison of the mean frequency of radiculopathy.

Radiculopathy	Studygroup		Total	Statistical analysis
	Avosoy frequency	Crocin frequency		
Yes	17 (56.6%)	25 (83.2%)	42 (100%)	$\chi^2 = 5.07/P = 0.047$
No	13 (43.4%)	5 (16.8%)	18 (100%)	
Total	30 (100%)	30 (100%)	60 (100%)	

## DISCUSSION

Knee osteoarthritis is a common degenerative joint disease in the middle-aged population. Among the lower limb joints, the knee joint is most affected.<sup>12</sup> To date, no effective medical treatment has been found for osteoarthritis, and it usually needs to be replaced in the later stages of the disease. Drug interventions are more sedative and have less focus on reducing symptoms or disease progression.<sup>13</sup> This study aimed to compare the effect of Avosoy and Crocin extracts on pain intensity and radiographic changes in patients with knee osteoarthritis. The study outcomes showed no significant differences in pain intensity, osteoarthritis symptoms, and quality of life in the Avosoy group, because of the limited study duration. So, further research needs to be performed for a longer period. A study by Christiansen et al.<sup>5</sup> in the United States examined the effect of ASU extract on osteoarthritis. They concluded that ASU improves joint function, while reducing joint pain and stiffness, leading to decreased dependence on analgesics. These findings were not consistent with the results of our study, which may be because of the study duration. Another research by Catunda et al.<sup>14</sup> examined the effect of ASU on joint pain and osteoarthritis of the temporomandibular joint. The results of this study were not consistent with the present study in reducing pain and improving quality of life, which could be because of a different osteoarthritis type.

In the Avosoy group, there was a significant difference in the difficulty of daily activities, recreation, and exercise, which could be because of the anticatabolic properties of ASU, which inhibits the activity of the MMPs and increases tissue inhibitors of these catabolic enzymes. Furthermore, ASU is capable of inhibiting fibrinolysis through stimulation of plasminogen activator inhibitor. Anabolic properties are capable of increasing cartilage repair by inducing collagen and aggrecan synthesis through suppressing inflammatory cytokines.<sup>5</sup> Głuszko et al.<sup>15</sup> examined the symptom-modifying effects of ASU capsules in the routine treatment of osteoarthritis in Poland. They concluded that most patients treated with ASU for 6 months showed a gradual alleviation in joint pain and improvement in functional ability. The outcomes of reducing pain intensity were not consistent with our study, but were consistent in improving functional ability and daily activities. In the Crocin group, there was a significant difference in pain intensity, osteoarthritis symptoms, quality of life, difficulty in daily activities, and difficulty in recreation and exercise, which could be due to the anticatabolic and antiinflammatory properties of Crocin via inhibiting the expression of NM- $\kappa$ B-induced MMPs.<sup>16</sup>

Li et al.<sup>17</sup> (2015) examined the antiinflammatory and anticatabolic properties of Crocin on rat intervertebral disc (IVD) degeneration by suppressing JNK activity and found that Crocin inhibited the downregulation of aggrecan and type II collagen, and concluded that Crocin effectively prevented degeneration-related inflammation and catabolism in rat IVDs. This study outcome was consistent with our study. Lei et al.<sup>18</sup> also studied the effect of Crocin on joint pain and muscle dysfunction in osteoarthritis mice and concluded that Crocin reduced the symptoms of osteoarthritis by alleviating oxidative stress and inflammation. This also was consistent with our findings. In both the study groups, a significant difference was observed in the difficulty of daily activities and difficulty in recreation, exercise before and after the intervention. But a higher significant decrease was found in the Crocin versus Avosoy group.

A radiographic review study by Mendía et al.<sup>19</sup> evaluated the efficacy and safety of ASU for the treatment of hip or knee osteoarthritis where no significant structural or significant change in the width of the joint space was found. This study was consistent with our study outcomes as we also did not observe any radiological changes in the knee in either group.

## CONCLUSION

In summary, this study showed that Crocin treatment is more effective than Avosoy treatment in decreasing the severity of pain and symptoms of osteoarthritis and knee discomfort, and could be capable of improving the quality of life, so its use could be recommended.

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