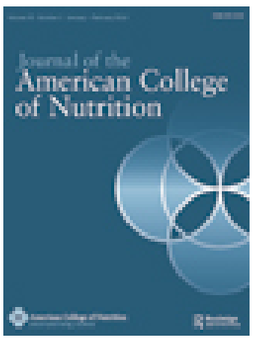

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Original Research

The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial

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Key words: quercetin, rheumatoid arthritis, clinical symptoms, DAS-28, HAQ, hs-TNFα

Objective: Previous studies have shown that the bioflavonoid quercetin has anti-inflammatory and anti-nociceptive effects. We investigated the effect of quercetin supplementation on inflammation, disease severity, and clinical symptoms in women with rheumatoid arthritis (RA).

Methods: The present study was a randomized, double-blind, placebo-controlled clinical trial in which 50 women with RA were allocated into a quercetin (500 mg/day) or placebo group for 8 weeks. Plasma levels of high-sensitivity tumor necrosis factor-α (hs-TNFα), erythrocyte sedimentation rate (ESR), clinical symptoms including early morning stiffness (EMS), morning and after-activity pain, and tender (TSC) and swollen joint counts (SJC) were determined. Disease activity and functional disability were assessed by Disease Activity Score 28 (DAS-28), physician global assessment (PGA), and a health assessment questionnaire (HAQ) at the beginning and end of the study.

Results: Quercetin supplementation for 8 weeks significantly reduced EMS, morning pain, and after-activity pain ($p < 0.05$). DAS-28 and HAQ scores decreased in the quercetin group compared to placebo and the number of patients with active disease significantly decreased in the quercetin group. Plasma hs-TNFα level was significantly reduced in the quercetin group compared to placebo ($p < 0.05$). There were no significant differences in TJC and SJC between groups but TJC significantly decreased in the quercetin group after the intervention. Supplementation had an effect on ESR but it was not significant ($p > 0.05$).

Conclusions: Five hundred milligrams per day quercetin supplementation for 8 weeks resulted in significant improvements in clinical symptoms, disease activity, hs-TNFα, and HAQ in women with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a common and important rheumatic disease affecting women 2–3 times more than men with a worldwide of prevalence 0.5%–1% [1]. RA is a chronic inflammatory systemic disease that affects all joints, connective tissues, muscles, tendons and fibrous tissues of the body. In this disease, inflammatory changes take place in the synovial membrane and joint structure, including synovial cell hyperplasia and proliferation, along with penetration of inflammatory cells, such as T cells of synovial membranes, and production of inflammatory cytokines derived from macrophages such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α). This leads to pain, atrophy, and deformation of joints, muscles distortion, bones erosion, and osteoporosis. It results in dysfunction, disability, and decreased quality of life and even leads to premature death in the long term [2].

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There is a relationship between inflammation and oxidative stress in the body in which increased reactive oxygen species (ROS) through activation of nuclear factor-κB (NF-κB) leads to transcription of genes associated with inflammation and inflammatory cytokines production. These factors in turn raise ROS production and ultimately lead to apoptosis inhibition, synovial cell proliferation, and joint damage [3]. Quercetin is one of the most important phenolic compounds and most abundant bioflavonoids in foods of plant origin such as fruits and vegetables [4]. Previous studies have shown that quercetin has strong antioxidant [5,6] and anti-inflammatory effects, including inhibition of immune cells such as macrophages and the secretion of inflammatory cytokines such as interferon-γ (IFN-γ), TNF-α, and IL-2 [7,8]. Quercetin suppresses the secretion of inflammatory cytokines by regulating gene expression associated with transcription factors (NF-κB) [9,10]. In some studies, quercetin has been shown to reduce arthritis in animal models [11–13]. In addition, it reduced pain sensitivity by inhibition of nociceptive effects in several animal models of nociception and clinically in humans [14–16]. We hypothesized that quercetin has a therapeutic effect on subjects with RA. Studies on the effects of quercetin on clinical symptom of RA patients are scarce. The objective of this study was to investigate the effect of quercetin as an adjunctive treatment on the clinical symptoms and disease activity in patients with RA.

METHODS

One hundred women with a previous diagnosis of RA, according to American College of Rheumatology 1987 criteria [17], were referred from the rheumatology clinics of 2 hospitals to participate in the study following the initial examination by an academic rheumatologist. Patients could participate in this study if they were aged 19–70 years, were not suffering from any chronic diseases (including acute heart, kidney, and liver diseases), were not taking any antioxidant supplements, type and dose of medications were not changed at least one month prior of the study, and were not smokers. Pregnant and lactating women were not included in this study. The exclusion criteria were the need to change medications, possible side effects, or unwillingness to continue the study.

This study was a double-blind, placebo-controlled randomized clinical trial including 50 eligible women with RA. The sample size estimation yielded 22 patients in each group to detect with 80% power a difference of 0.35 in health assessment questionnaire (HAQ) means assuming an SD of 0.4 [18] and using a 2-sided significance level of 0.05. Considering the probable withdrawal of patients during the intervention, 25 patients with RA were recruited for each group. Written consent was obtained from all patients. Patients were allocated into 2 groups using permuted block randomization with blocks size 2 and a random number table. To conceal treatments, another person who was not involved in the study encoded the identical boxes of the capsules and generated the random sequence. Quercetin and placebo capsules were identical in shape and color and had no odor. Capsules were packaged in identical boxes with 60 capsules in each box. Patients in the quercetin group received one 500 mg quercetin capsule per day (Solaray, Park City, UT), and patients in the placebo group received an identical placebo capsule containing lactose (Daroupakhsh, Tehran, Iran) daily for 8 weeks, in addition to their ongoing conventional treatment. Patients were asked to take capsules after lunch with one glass of water. The dose and type of medications were constant from the previous month to the end of the study. Patients were asked not to alter their usual diet or physical activity during the study and they were regularly in touch with investigators and monitored. We evaluated the physical activity of patients by the International Physical Activity Questionnaire [19] and diet using a 24-hour recall questionnaire for 2 days and the data were analyzed using Nutritionist IV (Version 4.1, First Data Bank Division, Hearst Corporation, San Bruno, CA). Compliance was assessed by counting the remaining capsules. Patients who had used less than 80% of supplements were excluded. At the beginning and end of the intervention, clinical symptoms were assessed and 10 ml venous blood samples taken after at least 8–10 hours of fasting. Three milliliters of blood was removed for erythrocyte sedimentation rate (ESR) measurement and the remainder was transferred into tubes containing EDTA and centrifuged for 10 minutes (2000 *g*). The plasma was stored at -80°C for biochemical measurements.

The study was approved by the ethics committee of the Iran University of Medical Sciences and recorded in the Iranian Registry of Clinical Trial (No. IRCT138807252394N2). This study was conducted in accordance with the provisions of the World Medical Association's Declaration of Helsinki.

At the beginning and end of the intervention, the physician global assessment (PGA) and the number of tender (TJC) and swollen joints (SJC) were determined by an academic rheumatologist with examination of patient joints and Disease Activity Score–28 (DAS-28) was calculated with ESR and the number of swollen and tender joints [20]. Early morning stiffness (EMS) was recorded in minutes. The morning pain and pain after activity was measured using a visual analogue scale (VAS) and a 0–100 scale (*no pain* to *severe pain*). Quality of life and disability were determined using a validated HAQ for a Persian population [21]. The questionnaire contains 8 sections including "dressing," "standing up," "eating," "walking," "hygiene," "hand stretching," "gripping," and "activity" that review functional disability and personal health. The questions were scored using a range of 0–3, where 3 is an indicator of more severe disability. Plasma hs-TNFα was measured using enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN) with a sensitivity of (0.038–0.191 pg/ml) according to the manufacturer's protocol. ESR was measured using the Westergren method.

SPSS statistical software (Version 18, SPSS Inc., Chicago, IL) was used for data analysis. The Kolmogorov-Smirnov test was used to test normality. Normally distributed quantitative values were reported as mean ± SD and not normally distributed quantitative values were reported as medians (25th and 75th percentiles). Qualitative data were reported as frequency (percent). For normally distributed quantitative variables, independent *t*-tests were used to compare the 2 groups at the beginning. Paired *t*-tests were used to compare the mean values at the beginning and end of the study in each group. If the distribution of the quantitative variable was not normal, the Mann-Whitney U test was used to compare the medians between 2 independent groups and Wilcoxon's signed-rank test was performed to compare before and after the intervention in each group. Analysis of covariance adjusted for baseline was used to compare the 2 groups at the end of the study. Chi-square test or Fisher's exact test was used to study the association between qualitative variables and groups. $p < 0.05$ was considered statistically significant.

RESULTS

Of 50 patients who participated in the study, 10 patients were excluded due to the need to increase or change medications, supplement intake less than 80%, and unwillingness to continue the study. Twenty patients in each group completed the study (Fig. 1). There was no significant difference in baseline characteristics including weight, body mass index, age, disease duration, physical activity, and medications between 2 two groups (Table 1). There was no significant difference in macro- and micronutrient intake between the 2 groups before the intervention. There was no significant difference between the 2 groups with regard to drug type and no patients had intra-articular injection.

Medication doses and physical activity were unchanged during the study. No side effects were reported by patients except for one patient in the placebo group with stomach pain, who was excluded from the study.

After the intervention there was a significant difference in hs-TNFα levels between the 2 groups ($p = 0.04$) and in the quercetin group compared to the beginning of the study ($p = 0.03$). Furthermore, supplementation had an effect on ESR but it was not significant (Table 2).

The disease activity score, clinical symptoms, and HAQ score were not significantly different between the 2 groups at the beginning of the study (Table 3). After the intervention, pain in the morning and after activity and EMS decreased in the quercetin group compared to the placebo group ($p = 0.005$, $p = 0.01$, and $p = 0.03$, respectively) and also compared to the beginning of the study ($p = 0.004$, $p = 0.001$, and $p = 0.01$, respectively), but this difference was not statistically significant in the placebo group. TJC and SJC were not statistically different between the 2 groups; however, TJC significantly decreased in the quercetin group after the intervention ($p = 0.03$). Quercetin supplementation decreased the DAS-28 and HAQ score in the quercetin group ($p = 0.001$ for both) and the differences were significant compared to the placebo group ($p = 0.04$ and $p = 0.008$, respectively). PGA showed no statistically significant difference between the 2

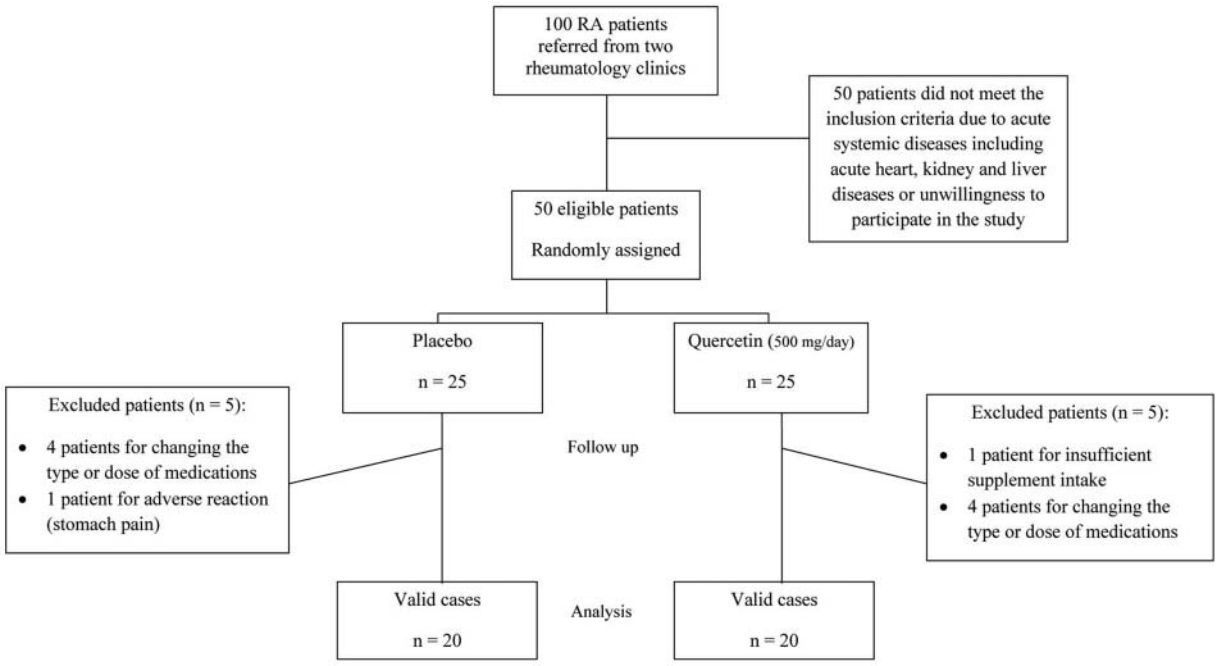

Fig. 1. Flowchart of the study.

Table 1. Baseline Characteristics of Patients (Intention to Treat Analysis)[a]

Variables	Quercetin Group ($n = 25$)	Placebo Group ($n = 25$)	p
Age (years)	46.55 ± 9.94	48.00 ± 8.39	0.62*
Disease duration (month)	62.05 ± 45.94	58.40 ± 36.30	0.78*
Physical activity (MET/min/week)	601.50 (406.50, 1635.00)	426.50 (166.50, 1033.88)	0.23¶
Weight (kg)	69.28 ± 10.30	76.83 ± 14.03	0.06*
BMI (kg/m^2)	27.99 ± 4.48	30.70 ± 4.61	0.07*
RF (IU/ml)	25.00 (16.75, 35.50)	20.50 (18.25, 37.75)	0.96¶
DMARDs:			
Methotroxate	23 (92)	23 (92)	—
Hydroxychloroquine	18 (72)	20 (80)	0.51§
Sulfasalazine	4 (16)	2 (8)	0.38§
Cyclosporine	3 (12)	2 (8)	0.64§
Prednisolone	19 (76)	19 (76)	—
NSAIDs	6 (24)	8 (32)	0.53§

MET = metabolic equivalent of task, BMI = body mass index, RF = rheumatoid factor, DMARDs = disease-modifying antirheumatic drugs, NSAIDs = nonsteroidal anti-inflammatory drugs.

[a]Values are expressed as mean ± SD for normally distributed variables, medians (25th and 75th percentiles) for not normally distributed variables, and frequency (%) for qualitative variables.

*Independent *t*-test.

¶Mann-Whitney U test.

§Fisher's exact test.

groups after the intervention, but it was significantly different in the quercetin group compared to the baseline. This means that there was a significant reduction in the number of patients with active disease in the quercetin group after the intervention ($p = 0.04$).

DISCUSSION

To our knowledge, the present study was the first study that examined the effect of quercetin supplement alone on the severity and symptoms of RA in women. The results showed that quercetin supplement as an adjunctive treatment had beneficial effects on pain, stiffness, disease activity, inflammatory factors (hs-TNFα), and well-being in women with RA.

In vitro studies suggest that quercetin has anti-inflammatory effects. For example, one study in mice with induced chronic arthritis showed that oral intake of quercetin significantly improved clinical symptoms, arthritis score, and healing [11]. Other studies showed that 30 μM quercetin decreased gene expression and production of IL-8, 1L-6, IL-1β, and TNFα, which are the major inflammatory cytokines in the pathogenesis of rheumatoid arthritis, and it also inhibited the activity of NF-κB and P38-kinase protein [22,23]. Boots et al. [24] showed that quercetin supplementation in untreated patients with sarcoidosis, an autoimmune condition, decreased the plasma TNFα/IL-10 ratios. Nieman et al. [25] found that 3 weeks' supplementation with quercetin in athletes decreased IL-8 and TNFα within the days of competition (a 3-day period of intensified exercise after 3 week supplementation) in the quercetin group compared to the

Table 2. Biochemical Outcomes before and after 8-Week Supplementation[a]

	Quercetin Group ($n = 20$)	Placebo Group ($n = 20$)	p
hs-TNFα (pg/ml)			
Before	2.52 (1.55, 4.45)	2.28 (1.71, 3.71)	0.90¶
After	2.40 (1.43, 2.81)	2.46 (1.62, 4.53)	0.04†
p-Value‡	0.03	0.66	
ESR (mm/h)			
Before	19.00 ± 8.62	21.10 ± 12.38	0.54*
After	16.85 ± 9.61	21.95 ± 17.52	0.35†
p-Value**	0.31	0.75	

hs-TNFα = high sensitivity tumor necrosis factor α, ESR = erythrocyte sedimentation rate.

[a]Values are expressed as medians (25th and 75th percentiles) for hs-TNFα and as mean ± SD for ESR.

*Independent *t*-test.

**Paired *t*-test.

¶Mann-Whitney U test.

‡Wilcoxon signed-rank test.

†Analysis of covariance adjusted for baseline.

Table 3. Clinical Outcomes before and after 8-Week Supplementation[a]

	Quercetin Group ($n = 20$)	Placebo Group ($n = 20$)	*P*
EMS (min)			
Before	7.50 (0.00, 23.75)	10.00 (0.00, 23.75)	0.61¶
After	0.00 (0.00, 0.00)	4.50 (0.00, 20.00)	0.03†
p-Value ‡	0.01	0.59	
Morning pain (mm)			
Before	36.70 ± 19.09	35.10 ± 24.39	0.82*
After	21.45 ± 15.88	40.25 ± 27.00	0.005†
p-Value**	0.004	0.39	
Pain after activity (mm)			
Before	57.35 ± 27.55	45.75 ± 24.89	0.17*
After	35.85 ± 21.98	50.80 ± 24.38	0.01†
p-Value**	0.001	0.53	
SJC			
Before	0.00 (0.00, 2.00)	1.00 (0.00, 1.00)	0.86¶
After	0.00 (0.00, 1.00)	0.00 (0.00, 1.75)	0.36†
p-Value‡	0.13	0.84	
TJC			
Before	1.00 (0.00, 2.75)	0.50 (0.00, 2.00)	0.62¶
After	0.00 (0.00, 1.00)	0.50 (0.00, 2.00)	0.33†
p-Value‡	0.03	0.62	
DAS-28			
Before	3.22 ± 0.93	3.13 ± 1.10	0.77*
After	2.65 ± 0.98	3.11 ± 1.29	0.04†
p-Value**	0.001	0.93	
HAQ			
Before	0.59 ± 0.37	0.67 ± 0.42	0.52*
After	0.35 ± 0.28	0.68 ± 0.41	0.008†
p-Value **	0.001	0.93	
PGA (active/inactive disease)			
Before	15(75)/5(25)	14(70)/6(30)	0.72§
After	8(40)/12(60)	12(60)/8(40)	0.21
p-Value	0.04	0.69	

EMS = early morning stiffness, SJC = swollen joint count, TJC = tender joint count, DAS-28 = Disease Activity Score–28, HAQ = health assessment questionnaire, PGA: physician global assessment, mm = milimeters of visual analogue scale.

[a]Values are expressed as mean ± SD for normally distributed variables, medians (25th and 75th percentiles) for not normally distributed variables, and frequency (%) for qualitative variables.

*Independent *t*-test.

**Paired *t*-test.

¶Mann-Whitney U test.

‡Wilcoxon signed-rank test.

†Analysis of covariance adjusted for baseline.

§Chi-square.

placebo. These studies showed that the anti-inflammatory effects of quercetin could be better demonstrated in patients with severe inflammation. In our study, quercetin decreased inflammatory cytokine hs-TNFα possibly through suppression of gene expression of cytokines based on previous studies [8,26,27], but it seems that some of other inflammatory factors like ESR need a longer duration of supplementation to produce a significant change.

In our study, clinical symptoms including pain, EMS, disease activity, and HAQ score were improved following supplementation. Some animal studies showed that quercetin supplementation had positive effects on synovial cells, controlling and reducing clinical symptoms and severity of arthritis (animal immobility, pain and swelling) and inflammation in animals with arthritis similar to RA [12,28], which is in agreement with our results. Previous studies have also shown that quercetin is partly responsible for pharmacological effects that are possibly mediated through 5-HT_{1A} serotonin receptor [29]. I addition, a study of patients with chronic prostatitis showed that disease symptoms such as pain and the quality of life significantly improved after supplementation with quercetin for one month [16]. Bae et al. observed a tendency toward reduction of pain in RA patients who consumed quercetin and vitamin C compared to α-lipoic acid [15]. Other antioxidants such as selenium and α-tocopherol in RA patients did not change biochemical factors such as rheumatoid factor, C-reactive protein, and ESR; however, they caused a significant decrease in clinical symptoms such as pain [30–32]. Quercetin, like other antioxidants, may have an anti-nociceptive effect

through different mechanisms such as modulation of GABA and 5-HT receptors or endogenous release of glucocorticoids [14]. On the other hand, quercetin decreased TNFα, which plays an important role in some aspects of pain [33] and, according to previous studies, anti-TNF antibodies can decrease pain-related behavior in some neuropathy models [34]. In the present study, quercetin supplementation improved well-being and HAQ score in RA patients, whereas in a previous study [15], quercetin and vitamin C together showed no significant effect on HAQ score, probably due to the small sample size. The effect of quercetin on disease activity (DAS-28 and PGA) was determined for the first time in our study and the supplement had a positive effect on these factors.

Our study has some strong points such as a larger sample size and longer duration of intervention compared to previous studies and more comprehensive review of symptoms and disease activity, but one of our limitations was that the study population included patients with mild to moderate disease activity, though the efficacy of the supplements is more likely to be reflected in the severe inflammation. We were uncertain of the long-term effect of quercetin on humans and thus we were cautious about increasing the duration of the study, though it seems that the effect of quercetin on some of inflammatory factors such as SJC and ESR require a longer duration. Therefore, more studies are needed to confirm these results in an even larger population over a longer time period.

In conclusion, quercetin supplementation had beneficial effects on clinical symptoms such as EMS, pain, inflammatory factors (TNFα), and HAQ score as well as well-being in women with RA, but it had no significant effect on ESR and SJC.

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