

# QUERCETIN SUPPLEMENTATION IN RHEUMATOLOGICAL DISEASES: A SCOPING REVIEW

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**ABSTRACT – Objective:** Quercetin is a flavonoid with anti-inflammatory properties and is used in a few rheumatic conditions. Herein, the authors review the rheumatological diseases in which quercetin has been investigated: rheumatoid arthritis, osteoarthritis, gout, and pre-hyperuricemia.

**Materials and methods:** A systematic search of articles published in PubMed/MEDLINE, Web of Sciences, LILACS, and Scielo from 1966 to August 2022 was done. No language restriction was used. The reference lists in the selected articles were analyzed to identify other publications.

**Results:** There are only 6 articles published in this field, involving a total of 284 patients. Rheumatoid arthritis was the most studied disease (n=3 articles), and then osteoarthritis (n=2), gout (n=1), and pre-hyperuricemic subjects (n=1). Age varied from 19 to 62.5 years old; females predominated, ranging from 83% to 100% in most studies. However, all participants were male in the two articles in which gout and pre-hyperuricemia were evaluated. Disease duration varied from 5.0 to 10 years. Quercetin dosage ranged from 45 mg to 2000 mg/day. Regarding outcome, all studies except one showed a good result after quercetin treatment, with improved pain, morning stiffness, disease activity score-28 joints (DAS28), uric acid, inflammatory biomarkers, and other parameters in the studied diseases.

**Conclusions:** This review shows that quercetin use in some rheumatic diseases has good effects, although new studies to confirm these findings are needed.

**KEYWORDS:** Quercetin, Rheumatic diseases, Rheumatoid arthritis, Osteoarthritis, Gout, Hyperuricemia.

## INTRODUCTION

Quercetin is an essential flavonoid which is present in red onions, apples, berries, and red wine<sup>1</sup>. Therefore, it is frequently found as a secondary plant metabolite in fruits and vegetables. Many studies have shown that quercetin has antioxidant, anti-inflammatory, anticancer, immunomodulatory, and vasodilating effects<sup>1</sup>. This flavonoid has shown promising results in improving inflammation, mainly after physical exercise<sup>2</sup>. In fact, in a clinical trial, F2-isoprostanes, a parameter of increased oxidative stress, were significantly reduced after quercetin supplementation in athletes<sup>2</sup>. In addition, quercetin can diminish arthritis in animal models and decrease pain sensitivity by inhibiting nociceptive effects in several animal models of nociception and clinically in humans<sup>3</sup>. Furthermore, this flavonoid was evaluated in rheumatoid arthritis, osteoarthritis, gout, and pre-hyperuricemia concerning rheumatic diseases.



Considering this, we performed a scoping review on the safety and efficacy of quercetin in these rheumatic diseases.

## MATERIALS AND METHODS

### Literature review

We performed a systematic search of articles published in PubMed, MEDLINE, LILACS (Literatura Latino Americana e do Caribe em Ciências da Saúde), and Scielo from 1966 to August 2022 using the following MeSH entry terms: “quercetin” and “rheumatic” OR “rheumatologic” OR “fibromyalgia” OR “rheumatoid arthritis” OR “spondyloarthritis” OR “Sjögren’s syndrome” OR “myositis” OR “systemic sclerosis” OR “vasculitis” OR “osteoarthritis” OR “gout.”

We used equivalent strategies in other databases. All related articles are without language restriction. The reference lists in the selected papers were analyzed to identify other publications. Two authors (JFC and EAH) initially performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. A third reviewer resolved disagreements arising in consensus meetings.

We designed a standardized form to extract information from relevant articles regarding authors, year of publication, the number of patients investigated, demographic data, disease duration, study follow-up, quercetin posology, outcomes, and side effects (Table 1).

### Statistical Analysis

We used descriptive statistics in the results.

## RESULTS

A total of 6 articles published in this field were found, involving 284 patients<sup>3-8</sup>. The countries in which the studies were performed are Japan (n=2), Iran (n=1), Korea (n=1), Ukraine (n=1), and United Kingdom (n=1). Rheumatoid arthritis was the most studied disease (n=3 articles), and then osteoarthritis (n=2), gout (n=1), and pre-hyperuricemic subjects (n=1). One study included patients with osteoarthritis and rheumatoid arthritis<sup>7</sup>. Age varied from 19 to 62.5 years old; females predominated, ranging from 83% to 100% in most studies. Although two articles evaluated gout and pre-hyperuricemia, all participants were male. Disease duration varied from 5.0 to 10 years. Follow-up ranged from 4 weeks to 12 months. Quercetin dosage varied from 45 mg to 2000 mg/day.

Regarding outcome, all studies except one<sup>8</sup> showed a good effect after quercetin treatment, with improved pain, morning stiffness, disease activity score-28 joints (DAS28), uric acid, inflammatory biomarkers, and other parameters in the studied diseases (Table 1). Concerning side effects, the majority (3/6) revealed no side effects, and 2/6 did not describe the adverse effects and in 1/6 articles; indeed, the authors observed mild effects similarly in melatonin and control groups (Table 1).

## DISCUSSION

This is the first study in which a scoping review on the therapeutic effects of quercetin in rheumatic diseases has been performed. The study strengths are (1) the inclusion of studies with patients with international criteria for rheumatic diseases and (2) the inclusion of all kinds of study designs on using quercetin in rheumatic diseases. In this way, the authors believe that all published cases of quercetin in rheumatic patients were collected.

Given the results, there is some improvement with quercetin supplementation in all rheumatic conditions. It is well known that gout, osteoarthritis, and rheumatoid arthritis have different inflammation and oxidative stress grades. Therefore, it is reasonable to have evaluated a substance with antioxidative and anti-inflammatory properties, such as quercetin, showing a positive result in these conditions<sup>1</sup>.

Table 1. Studies on quercetin use in rheumatic diseases.

Author, reference	Study design	Country	N, age, gender	Rheumatic disease	Disease duration	Treatment regimen	Follow-up	Outcome	Side effects
Javadi et al <sup>3</sup>	Randomized, double-blind, placebo-controlled clinical trial	Iran	50, 60 yo 100% females	Rheumatoid arthritis	60 months	Quercetin (500 mg/day) or placebo group for 8 weeks	8 weeks	Improved early morning stiffness, morning pain, and pain after activity ( $p<0.05$ ) Decreased the number of patients with active disease, DAS28, and HAQ and TNF levels ( $p=0.04$ ).	None
Bae et al <sup>4</sup>	Randomized, placebo-controlled, double-blind, Three-treatment cross-over design trial	Korea	20, 52.1 _ 10.3 yo, 95% females	Rheumatoid arthritis	10.2 _ 5.9	Quercetin + vitamin C (166mg +133mg/capsule), lipoic acid (300mg/capsule) or placebo for 4 weeks	4 weeks	No significant differences in clinical and laboratory features were seen.	ND
Kanzaki et al <sup>5</sup>	Randomized, double-blind, placebo-controlled study	Japan	40, 56.5 yo, 83% females	Knee osteoarthritis	ND	1200 mg glucosamine hydrochloride, 60mg chondroitin sulfate, and 45 mg quercetin glycosides per day or placebo	16 weeks	Improved walking ability and painfulness at weeks 8, 12, and 16 ( $p<0.01$ ). Improved walking stairs at weeks 8, 12, and 16 ( $p<0.01$ ).	Similar in both groups: cold symptoms, myalgia/muscle stiffness, arthralgia, gastric distress, and diarrhea

Continued

Table 1 (Continued). Studies on quercetin use in rheumatic diseases.

Author, reference	Study design	Country	N, age, gender	Rheumatic disease	Disease duration	Treatment regimen	Follow-up	Outcome	Side effects
Matsuno et al <sup>6</sup>	Single-blinded clinical trial using the “up-and-down” method	Japan	22 RA: 58 ± 10yo, 91% female 46 OA: 62.5 ± 9.4 yo, 85% females	Rheumatoid arthritis and knee osteoarthritis	RA: 7.9 ± 10 years OA: 8.5 ± 6.7 years	Glucosamina 1.2g, chondroitin 111mg, and quercetin 45mg	3 weeks	Improved scores for the ability to walk and climb up and down stairs in the OA group ( $p<0.05$ ).	None
Kondratiuk et al <sup>7</sup>	Prospective controlled trial	Ukraine	84, 56.7 yo, 100% males	Gout and systemic hypertension	ND	Quercetin 1000 mg 2 times per day for 30 minutes before meals for 6 months, then maintenance dose was 500 mg 2 times per day for another 6 months	12 months	Improved echocardiographic parameter of diastolic function left ventricular, reduced uric acid by 33.7%, normalized creatinine by 13%, and reduced systolic blood pressure by 5.5% and diastolic blood pressure by 3.6%.	ND
Shi et al <sup>8</sup>	Randomized, double-blinded, placebo-controlled, cross-over trial	United Kingdom	22, 19-60 yo, 100% males	Pre-hyperuricemia (uric acid concentration in the higher but still considered healthy range).	—	500mg quercetin daily for 4 weeks or placebo 4 weeks		Reduced uric acid in -26.5 µmol/L ( $p=0.008$ )	None

Abbreviations - DAS28: diseases activity score 28 joints; HAQ: Health Assessment Questionnaire Disability Index; ND: not described; OA: osteoarthritis; yo: years old; TNF: tumor necrosis factor.

In this line, quercetin seems to be an add-on therapy to the immunosuppressive treatment (conventional or biological) disease modifying antirheumatic drugs (DMARDs) RA (rheumatoid arthritis) for the different rheumatic diseases studied herein. Regarding RA, there is an improvement in subjective data such as morning stiffness and morning and after-activity pain. Although, a reduction in disease activity scores, including DAS28 and tumor necrosis factor (TNF), was observed<sup>4</sup>. Another study on RA did not report any significant difference after quercetin supplementation<sup>5</sup>. Matsuno et al<sup>6</sup> analyzed the quercetin supplementation in patients with RA and osteoarthritis, and these authors observed that OA patients had a significant improvement in pain, daily activities (walking and climbing up and down stairs), and alterations in the synovial fluid concerning the hyaluronic acid properties.

Regarding osteoarthritis studies, both reports demonstrated improvement parameters after quercetin, including walking ability and the performance of climbing stairs<sup>5,6</sup>. Improvements were also observed after quercetin supplementation in patients with gout/hyperuricemia: a reduction in uric acid levels was observed in one trial<sup>8</sup>, and the second one showed an improvement in the left ventricular diastolic function, a reduction of 33% in uric acid levels, a creatinine reduction, and an additional normalizing of the blood pressure<sup>7</sup>.

Regarding the mechanism by which quercetin may reduce uric acid, there is evidence that quercetin can inhibit xanthine oxidase (XO). In fact, XO has one high affinity binding site for quercetin, and van der Waals forces and hydrogen bonds predominately drive the binding process. Moreover, molecular docking confirmed that the binding site for quercetin is located in the isoalloxazine ring of XO's flavin adenine dinucleotide domain, blocking the electron transference<sup>9</sup>.

This scoping review verified that the sample size of all included articles was small. In addition, most authors in their papers did not use standard and, currently, international parameters to assess disease activity or evaluate improvements or worsening of the studied diseases. Furthermore, no comparison between quercetin and classical treatments used in rheumatic diseases was available in the literature. In addition, the number of participants was low, and future studies should include large patient samples with more long-term follow-ups. Also, incorporating other rheumatic diseases would enable a better understanding of the course of quercetin in rheumatic conditions.

## CONCLUSIONS

A few studies in the literature evaluate quercetin in rheumatological diseases, and only four rheumatic diseases were addressed. Most studies herein analyzed demonstrated that quercetin supplementation might have a positive effect on patients. However, new studies with a higher number of participants, including other rheumatic diseases, are necessary.

### CONFLICT OF INTEREST:

The authors have no conflict of interest to declare.

### FUNDING:

No funding was found for this study.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

It is not applicable since it is a review article.

### AVAILABILITY OF DATA AND MATERIAL:

All material is available from the corresponding authors upon request.

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