Quercetin supplementation and muscular atrophy in animal models: A systematic review and meta-analysis

Weiqun Lin, Yongyi Zhao, Cuibing Liu, Yinghua Yan, and Qiaowen Ou

Department of Clinical Nutrition, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, People's Republic of China

ABSTRACT

Muscle atrophy is a degenerative condition characterized by secondary inflammation, free radical injury, and metabolic dysregulation. Evidence regarding the effects of quercetin on skeletal muscle atrophy is currently controversial and unclear. We hypothesized that quercetin, a anti-inflammatory and antioxidant properties phytochemical, may play an important role in muscle atrophy, and we conducted a comprehensive systematic review and meta-analysis to summarize the effects of quercetin supplementation on muscular atrophy based on studies performed in animal models. Three atrophy biomarkers (muscle mass, fiber size, and function) with enough eligible studies (n = 6, 7, and 4, respectively) were combined in the final meta-analysis. Next, we calculated the overall and stratified effects of quercetin administration on muscular atrophy. No significant effects were observed on muscle mass and muscle function; however, we observed protective effects of quercetin on muscle fiber diameter and area ([Standardized Mean Difference (SMD): 0.82, 95% Confidence interval (CI): 0.36, 1.28], and [SMD: 0.94, 95% CI: 0.25, 1.62], respectively). This study suggests that quercetin could have histological protection effect on muscle fiber. Thus, it could become a promising complementary therapy for muscle atrophy that occurs due to various clinical conditions.

Abbreviations: SMD, Standardized Mean Difference; CI, Confidence interval; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; Nr2f2, nuclear factor erythroid 2-related factor; HO-1, heme oxygenase-1; PPAR-y, peroxisome proliferator-activated receptor-γ; SIRT-1, silent mating type information regulator 2 homolog 1; PGC-1α, PPAR-γ coactivator-1α; FABP4, fatty acid binding protein 4; DMD, Duchenne muscular dystrophy

Introduction

Muscle atrophy is a degenerative and debilitating condition that is characterized by progressive protein degradation and degressive protein synthesis in skeletal muscles. The leading causes of muscular atrophy include congenital myopathies, different forms of muscular dystrophy, and acquired disorders that include spinal cord injury, malnutrition, cancer cachexia, and organ failure. Skeletal muscle atrophy leads to decrease in muscle mass and muscle strength, which eventually leads to weakness, decline in ability decline, wheelchair confinement, and various other debilitating adverse outcomes. This debilitating condition can reduce patients' quality of life and, increase medical costs.
and mortality. Therefore, developing effective, evidence-based countermeasures is critical in delaying or attenuating the progression of muscular atrophy.

The major pathological changes in muscular dystrophy include decrease in size and number of muscle fibers, transition of fiber types, infiltration of inflammatory cells and ectopic fat storage\cite{3}, which leads to decline in strength and function of the skeletal muscles. Extensive studies have been conducted to explore effective treatments (including myostatin antagonists and androgen receptor modulators) that may help restore the dynamic balance between muscle protein degradation and synthesis, with the goal of maintaining motor capacity and prolong life expectancy in patients with muscle atrophy. Unfortunately, though some therapies reportedly reduced muscle wasting, only a few contributed in maintaining muscle function.\cite{4,5} Physical exercise is currently the most validated non-therapeutic treatment for reservation muscle mass and function; however, maintenance of a regular physical exercise program is not applicable to frail atrophic patients, who are mostly bedridden, due to increased chances of accidents and injuries.\cite{6}

Alternative practical interventions that could help preserve muscle function, ease suffering, and improve quality of life are urgently needed. Meanwhile, pathophysiologists have demonstrated that characteristic secondary pathological changes occur in patients with muscle atrophy, including inflammation; free radical injury; and metabolic dysregulation; changes in hormone levels and sensitivity\cite{7,7} and in mechanism of some of the defense regulation pathways such as Nrf2/HO-1, IKK/IκB/NF-κB and SIRT1/PGC-1α.\cite{8} Studies have found that protecting muscle tissue from these secondary damaging changes may help mitigate detrimental effects on muscle function.\cite{9} Therefore, alternative pharmaceutical and nutraceutical interventions to address these secondary changes have arisen as promising therapeutic strategies.

Quercetin is a flavonoid compound present in fruits and vegetables, and is well-known for its health benefits because of its antioxidant, anti-inflammatory, anti-aging effects.\cite{10,11} In recent years, with new advances in \textit{in vivo} and \textit{in vitro} studies, the potential effects of quercetin on skeletal muscle have gradually come into focus. A study conducted in 2009 found that short term quercetin supplementation has the potential to improve physical capacity by enhancing skeletal muscle mitochondrial biogenesis.\cite{12} This demonstrated effect of quercetin has important implications for enhancing physical performance, muscle strength, and muscle mass. In this context, researchers have investigated the relationship between quercetin supplementation and, skeletal muscle mass and functionality.\cite{13} According to the results of studies conducted to date, researchers have extended the conceptual framework regarding the potential muscle function-promoting mechanism of quercetin from traditional anti-inflammatory and antioxidant properties to enzymatic and cell receptor activity modulation in skeletal muscle and relevant neural pathways.\cite{14} However, very been few large-scale, high-quality studies conducted on this subject, and the results of those studies have not been entirely consistent.\cite{15,16} A meta-analysis integrating the overall findings from many studies, hence, would be a sought-after addition to the literature.

We hypothesized that quercetin may play an important role in muscle atrophy. Systematic reviews on the muscle-protective effects of quercetin have been scarce, while studies have mainly focused on the effects of quercetin supplementation on sports performance improvement in healthy athletes rather than that on anti-muscular atrophy performance in patients in a pathological state.\cite{17} This was the starting aspect of the current study as well. However, given the small number of clinical trials investigating the anti-muscular atrophy properties of quercetin, it was difficult to conduct a reliable meta-analysis in humans.\cite{18} Hence, we performed a comprehensive systematic review and meta-analysis of animal studies to evaluate muscle pathology and function, in order to provide a scientific assessment of the effects of quercetin supplementation on muscle atrophy based on the available literature. We sought to summarize the anti-muscular atrophy effects of quercetin and explore the potential translational applications of alternative nutraceutical strategies in human clinical applications. We aimed to answer the following questions: 1. What are the effects of quercetin supplementation on muscular atrophy? 2. Are these differences related to factors such as pathological models, sex, or intervention strategies?
Methods and materials

Search strategy

The systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement\textsuperscript{[19]} and the protocol was registered in the PROSPERO international prospective register (registration ID: CRD42021241046).

Selection criteria

Systematic literature searches were independently conducted by two researchers (CBL, YYZ) in order to identify animal studies investigating the effects of quercetin on muscle senility, wasting, and atrophy. Searches were conducted using the PubMed, Web of Science, EMBASE, and Scopus databases on February 23 and August 26, 2022. These searches were conducted without any language restrictions, and the relevant articles published since database inception were included for preliminary screening. The search terms were as follows: (quercetin OR quercetin sulfate OR methylated quercetin OR quercetin glucoside OR quercetin glucuronide) AND (muscle OR muscle atrophy OR cachexia OR muscle waste OR skeletal muscle OR sarcopenia) AND animal.

Study selection criteria

Two independent researchers screened the titles and abstracts to search for relevant studies for additional screening. The inclusion criteria were as follows: (1) animal studies conducted in a murine model; (2) studies focusing on the impact of quercetin on skeletal muscles; (3) investigations conducted in muscle-atrophy-specific pathological models; (4) quercetin or modified quercetin was used as treatment and compared with an appropriate placebo or non-exposed control group; (5) a supplementation duration of >7 days; (6) intervention via oral administration; and (7) quercetin was not tested in combination with pharmacological interventions. The exclusion criteria were as follows: (1) ex vivo studies, in vitro studies, and studies in humans; (2) animal studies in fruit-fly (Drosophila melanogaster), rabbits, and other non-murine animals; (3) studies evaluating non-quercetin interventions; (4) an intervention duration of <7 days; (5) studies with administration routes other than oral administration; (6) studies without adequate controls; and (7) studies not evaluating muscle-associated outcomes. A group discussion was held to reach a final consensus in case of any discrepancies.

Data extraction

Studies that met the selection criteria in the preliminary screening were used for secondary screening for relevant characteristic information. Two independent authors were assigned to fill out the data extraction form with detailed information from eligible studies. The following details of the included articles were extracted: authors, publication year, country, subject (species or strain), age, sex, method of inducing muscle atrophy, intervention duration, intervention dosage, sample size, intervention route, and detailed information on the outcomes of interest (sample types, central measures, dispersion parameters, units of measure, \(p\)-values). If the available data of the eligible studies were presented only graphically, we would communicate with the corresponding author to request the original data. For studies in which the original data were unavailable, the Get Data Graph Digitizer\textsuperscript{[20]} was used to estimate the quantitative data. In cases where different doses of quercetin were assessed in the same study, we compared each intervention dose separately, as described previously.\textsuperscript{[21]}

Quality assessment

Quality assessment was performed following the Cochrane collaboration guidelines.\textsuperscript{[22]} Further quality assessments were conducted according to the Essential 10 criteria specified in the ARRIVE
guidelines (version 2.0) for animal research.[23] A slight modification in our methodology was that the criteria that were not suitable for animal research assessments were deleted from our evaluation schema.[24] The scoring system used in this study was established to evaluate the bias and quality of eligible studies in 10 categories, as described in a previous investigation.[25] Studies that met < 50%, 50–75%, and > 75% of the Essential 10 criteria were rated as low-, moderate-, and high-quality research, respectively.

Statistical analysis

Given the small number of animal studies evaluating atrophy-related biomarkers of interest, only muscle atrophy markers with enough eligible studies (n ≥ 3) were included in the final analysis. Namely, three atrophy biomarkers (muscle mass, cross-section fiber, and force) that satisfied this condition were selected for additional analyses. The effect size of quercetin on muscle atrophy indices was evaluated by calculating standardized mean differences (SMDs) and 95% confidence intervals (CI). The $I^2$ statistic was used to estimate the heterogeneity among animal studies. The random-effects model was applied to analyses with statistically significant heterogeneity ($I^2 ≥ 50%$), whereas studies with $I^2 < 50%$ used the fixed-effects model.[26] As previously described, a sensitivity analysis was implemented to determine the specific studies that significantly impacted the heterogeneity in the current study.[27] The potential source of intra-study heterogeneity was identified using planned subgroup analyses (with more than five eligible studies). Potential confounding factors were determined, including basic characteristics (country, disease model, animal age) and intervention mode (duration, dosage, composition of the supplementation). Publication bias was assessed through the visual assessment of the funnel plot, Begg’s test, and Egger’s test. The meta-analysis was conducted via Review Manager software 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and publication bias was performed via Stata software 12.0 (StataCorp LP, College Station, TX, USA). A p-value of $p ≤ .05$ was considered to indicate the threshold for statistical significance.

Results

Study characteristics

Initially, 6,241 articles were retrieved and 11 were included in the final meta-analysis after conducting a series of literature retrievals, scans, and evaluation (Figure 1). All the eligible studies were published between 2013 and 2021[9,28–37] and the intervention duration ranged from 2–36 weeks (Table 1). Eligible studies investigated skeletal muscle function in mice (n = 10)[9,29–37] and rats (n = 1).[28] All the included studies investigated the protective effect of orally administered quercetin administered by diet (n = 9)[9,28,29,31,33–37] or gavage (n = 2).[30,32] A total of 251, 186, and 49 animals were enrolled in the meta-analyses regarding skeletal muscle mass, cross-sectional fibers, and specific force, respectively. Four studies evaluated the protective effects of quercetin on skeletal muscle in mice models of spontaneous Duchenne muscular dystrophy (DMD).[9,32,36,37] Two of the 11 included articles used high-fat diet-induced obesity mice to investigate the muscular health-promoting effects of quercetin.[28,29] Two eligible studies were conducted on tumor-bearing murine models.[30,31] Two were conducted in surgically induced atrophy models.[33,34] One eligible study investigated animals without any comorbidities.[37]

Quality assessment

Quality assessment was conducted according to the ARRIVE guidelines (version 2.0) and the Cochrane Collaboration guidelines (i.e., the aforementioned Essential 10 criteria and Cochrane Handbook guidelines). We evaluated the study design, sample size, inclusion criteria, randomization, blinding procedures, outcome measures, statistical methods, animal models, and the quality of the experimental results
in the retrieved studies. The results are presented in Table 2 and Supplementary Figure 1. The average quality score for the Essential 10 assessment was 69.69 ± 13.00%. Four eligible studies were classified as high-quality, while one was judged to be low-quality. All the experiments were well-designed with suitable intervention groups and comparable control groups, although no studies explained how to calculate the number of experimental animals in detail. Randomization was reported in only four studies; therefore, the adequacy of this methodological aspect was questionable. Only four studies indicated the use of blinding and clearly reported the blinding strategy. Seven studies were deemed to be at high risk of incomplete outcomes because the numbers of animals presented in the Methods and Results sections were not consistent. In summary, the majority of eligible studies were classified as high or moderate quality investigations, indicating that no significant bias was found in these studies.

**Effect of quercetin on muscle mass**

**Gastrocnemius muscle**

Five studies[28–31,35] comprising of 91 experimental animals (73 mice, 18 rats) with various health conditions (i.e., obesity,[28,29] tumors[30,31] or DMD[35]) were selected for assessment of the effect of quercetin on the absolute gastrocnemius muscle mass. The overall effect of quercetin on gastrocnemius mass was 0.09 (95% CI: −0.66, 0.84, \( p = .82 \)), with considerable heterogeneity \( I^2 = 62\% \) (Table 3, Figure 2). A sensitivity analysis was performed, and a study conducted using a DMD model was found to be responsible for the observed heterogeneity (\( I^2 \) from 62% to 32%); the intervention effects of quercetin on the gastrocnemius remained stable after eliminating this study (SMD: 0.32, 95% CI: −0.20, 0.93, \( p = .30, I^2 = 32\% \)). A series of subgroup analyses were then performed, and studies conducted by researchers in Asia were found to be homogeneous and showed a notable effect on the gastrocnemius mass (SMD: 1.08, 95% CI: 0.00, 2.17, \( p = .05, I^2 = 0\% \)) (Tables 4 and 5, Supplementary Tables 1 and 2).
Table 1. General characteristics of studies included in the systematic review.

| Author, year, country | Species | Age | Sex | Duration, design | Diseases/health status/medication | Dose of quercetin/day (mg/d) | Outcome parameters |
|-----------------------|---------|-----|-----|-----------------|-----------------------------------|-----------------------------|-------------------|
| Velazquez, 2013, USA | C57BL/6, Apc(-/-) mice | 15 weeks | Male | 3 weeks, quercetin | Spontaneous adenomatous polyposis coli mouse model | 25 mg/kg of body weight by gavage | GAS weight, SOL weight |
| Arias, 2014, Spain | Wistar rats | 6 weeks | Male | 16 weeks, quercetin | HFD-induced obesity | 0.045% by diet | GAS weight |
| Le, 2014, Korea | C57BL/6 mice | 8 weeks | Male | 9 weeks, quercetin | HFD-induced obesity | 0.05% or 0.1% quercetin by diet | GAS weight, SOL weight, fiber diameter |
| Assi, 2015, France | BALB/c mice | 7 weeks | Male | 22 days, antioxidant cocktail | Colon 26 tumor-bearing mice | 81.5 mg/kg of body weight by gavage | GAS weight, SOL weight, EDL weight, fiber diameter |
| Mukai, 2016, Japan | C57BL6 mice | 7 weeks | Male | 20 days, quercetin | Sciatic nerve induced atrophy | 0.2% by diet | Fiber area |
| Selsby, 2016, USA | C57BL6 mice | 2 months | Male | 12 months, quercetin | Spontaneous DMD model | 0.0% by diet | Specific force, fiber area |
| Spaulding, 2016, USA | C57BL6 mice | 2 months | Male | 12 months, quercetin | Spontaneous DMD model | 0.2% by diet | SOL weight, EDL weight, specific force, fiber area |
| Kohara, 2017, Japan | ICR mice | 6 weeks | Male | 3 weeks, EMIQ | Functional overload created by synergist ablation surgery | 0.003% by diet | Fiber area |
| Spaulding, 2019, USA | DBA2/J (DBA) mice, D2-Mdx mice | 4 months | Male | 7 months, quercetin | Spontaneous DMD model | 0.2% by diet | GAS weight, SOL weight, EDL weight, fiber area |
| Spaulding, 2020 USA | DBA2/J (DBA) mice, D2-Mdx mice | 4 months | Male | 7 months, quercetin | Spontaneous DMD model | 0.2% by diet | Specific force |
| Sakuka, 2021, Japan | C57BL/6 mice | 19 months | Female | 6 months, EMIQ | - | 0.03% EMIQ by diet | SOL weight, EDL weight |

DMD, Duchenne muscular dystrophy; EDL, extensor digitorum longus muscle; GAS, gastrocnemius muscle; HFD, high-fat diet; SOL, soleus muscle; EMIQ, enzymatically modified isoquercitrin

Soleus muscle
A meta-analysis of data from eight study arms that enrolled a total of 100 animals revealed that quercetin administration had no effect on the absolute mass of the soleus muscle as compared to the placebo groups (SMD: 0.05, 95% CI: −0.36, 0.47, p = .79, I² = 50%) (Table 3, Figure 3). [9,29–31,35,37] No intra-study heterogeneity was found in sensitivity analyses after excluding each study from the meta-analysis. When the studies were stratified according to basic characteristics and intervention methods, no statistically significant intervention effects were observed in the subgroups (Tables 4 and 5; Supplementary Tables 1 and 2).

Extensor digitorum longus muscle
With regard to the extensor digitorum longus muscle, four studies with 44 animals were eligible for the meta-analysis. [9,31,35,37] Figure 4 and Table 3 showed no statistically significant difference between the experimental and control groups (SMD: 0.00 95% CI: −0.77, 0.76, p = .99, I² = 51%). The heterogeneity
Table 2. Quality assessment based on the ARRIVE guidelines.

| No. | Essential 10 | Criteria                                                                 | Velazquez | Arias | Le | Assi | Mukai | Selsby | Spauling | Kohara | Spauling | Spauling | Spauling | Sakuka |
|-----|--------------|---------------------------------------------------------------------------|-----------|-------|----|------|-------|--------|----------|--------|----------|----------|----------|--------|
| 1   | Study design | Included control and experiment groups                                    | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
|     |              | Reported the experimental unit                                             | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
| 2   | Sample size  | Specified the total number of animals and the number of animals            | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
|     |              | in each experimental group                                                |           |       |    |      |       |        |          |        |          |          |          |        |
|     |              | Explained how the sample size was calculated                              | 0         | 0     | 0  | 0    | 0     | 0      | 0        | 0      | 0        | 0        | 0        |        |
| 3   | Inclusion and exclusion criteria | Described criteria used in animal inclusion and exclusion | 1         | 0     | 0  | 1    | 1     | 1      | 1        | 1      | 1        | 0        | 0        |        |
|     |              | Reported the number of animals excluded and explained the reason          | 0         | 0     | 0  | 0    | 0     | 1      | 0        | 1      | 1        | 0        | 0        |        |
|     |              | Reported the exact number of animals in each experimental group            | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
| 4   | Randomization | Described the process of animal randomization into different groups       | 0         | 1     | 0  | 0    | 0     | 1      | 0        | 1      | 0        | 0        | 0        |        |
|     |              | Described the strategy for minimizing confounders                         | 1         | 0     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 0        |        |
| 5   | Blinding     | Reported blinding methods                                                  | 0         | 0     | 0  | 0    | 0     | 1      | 1        | 0      | 1        | 1        | 0        |        |
| 6   | Outcome measures | Clearly defined all evaluated outcomes                                    | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
|     |              | Specified primary outcome measures                                         | 0         | 0     | 0  | 0    | 0     | 0      | 0        | 0      | 0        | 0        | 0        |        |
| 7   | Statistical methods | Illustrated details of the statistical methods for each analysis        | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
|     |              | Described whether the study data met the requirements of each statistical approach | 1         | 1     | 0  | 1    | 0     | 0      | 0        | 0      | 0        | 0        | 0        |        |
| 8   | Experimental animals | Species-related details for the study animals (e.g., species, strain, sex, age) | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
|     |              | Further relevant information, including health status                     | 1         | 1     | 1  | 1    | 1     | 0      | 1        | 1      | 1        | 1        | 1        |        |
| 9   | Experimental procedures | Described the details of the experimental procedure (e.g., What, When, Why) | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |
| 10  | Results      | Reported the results of each analysis with a measure of precision (e.g., SD, SEM, CI) | 1         | 1     | 1  | 1    | 1     | 1      | 1        | 1      | 1        | 1        | 1        |        |

Quality assessment

- **Score of 18 = 100%**
- **Total score (%):** 72, 67, 56, 72, 44, 78, 83, 72, 83, 83

Quality classification

- **M =** high quality
- **H =** moderate quality
- **L =** low quality

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1 Refer to the study conducted by Spauling in 2016; 2 refer to the study conducted by Spauling in 2019; 3 refer to the study conducted by Spauling in 2020

* Studies that meet all 18 criteria will be scored 100%.

CI, confidence interval; SD, standard deviation; SEM, standard error of the mean

1 = Yes; 0 = No; H = high quality; M = moderate quality; L = low quality
Table 3. Pooled estimates of effect size for the results of quercetin interventions as compared with respective controls.

| Outcome          | Mean   | 95% CI       | p-Value | Sample size, (n) | I² (%) |
|------------------|--------|--------------|---------|-----------------|--------|
| Absolute GAS mass (mg) | 0.09   | -0.66, 0.84  | 0.82    | 91              | 62     |
| Absolute SOL mass (mg) | 0.05   | -0.36, 0.47  | 0.79    | 100             | 5      |
| Absolute EDL mass (mg) | 0.00   | -0.77, 0.76  | 0.99    | 60              | 51     |
| Fiber diameter (µm) | 0.94   | 0.25, 1.62   | <0.01   | 93              | 52     |
| Fiber area (µm²) | 0.86   | 0.40, 1.32   | <0.01   | 93              | 47     |
| Specific force (n/cm²) | 0.37   | -0.22, 0.96  | 0.22    | 49              | 19     |

CI, confidence interval; GAS, gastrocnemius; EDL, extensor digitorum longus; SOL, soleus

Figure 2. Effect of quercetin supplementation on gastrocnemius muscle mass (mg). The forest plot illustrates the standardized mean difference (SMD) calculated by random-effect models in gastrocnemius muscle mass. The Le study consisted of 2 sub studies: low dosage (0.05% by diet) quercetin supplementation (Le a) and high dosage (0.1% by diet) quercetin supplementation (Le b); and the Velazquez study consisted of 2 sub studies: quercetin supplement in C57BL/6 mouse model (Velazquez a) and APC Apc<sup>Min/+</sup> mouse model (Velazquez b). SD = standard deviation; CI = confidence interval.

Table 4. Subgroup analysis: stratification by basic characteristics.

| Factor subgroups | Absolute GAS mass (mg) | Absolute SOL mass (mg) | Fiber diameter (µm) | Fiber area (µm²) |
|------------------|------------------------|------------------------|---------------------|-----------------|
|                  | DM (95% CI)            | DM (95% CI)            | DM (95% CI)         | DM (95% CI)     |
| **Age (years)**  |                        |                        |                     |                 |
| ≤8               | 0.14 (−0.65, 0.93)     | 1.05 (−0.24, 2.35)     | 0.94 (0.25, 1.62)   | 1.28 (0.72, 1.84) |
| >8               | −0.04 (−1.69, 1.62)    | −0.35 (−0.90, 0.19)    | −                    | 0.00 (−0.80, 0.81) |
| **Country**      |                        |                        |                     |                 |
| Asia             | 1.08 (0.00, 2.17)      | 0.54 (−0.18, 1.25)     | 1.23 (0.69, 1.76)   | 1.28 (0.72, 1.84) |
| EU/ N. America   | −0.29 (−1.05, 0.60)    | −0.18 (−0.69, 0.32)    | −0.06 (−1.04, 0.92) | 0.00 (−0.80, 0.81) |
| **Disease**      |                        |                        |                     |                 |
| Without disease  | 0.02 (−0.83, 0.87)     | 0.1 (−0.38, 0.58)      | 2.70 (1.29, 4.11)   | 0.88 (0.09, 1.67) |
| With disease     | 0.57 (−0.66, 1.80)     | −0.18 (−1.52, 1.16)    | 4.04 (2.66, 5.43)   | 1.12 (0.10, 2.13) |

DM, difference in mean; CI, confidence interval; GAS, gastrocnemius; SOL, soleus

Disease status indicates health condition, and disease indicates that the included subjects were diagnosed with obesity, Duchenne muscular dystrophy, a surgical disability, or a tumor.

Significance level: * p-value ≤ 0.05.

For more detailed information (DMs, 95% CIs, sample sizes, p-values, I² statistics), please refer to the Supplementary Material (Table S1 and Table S2).
between studies was reduced to 0% after removing a study on D2-mdx mice, whereas the pooled effect was maintained after this removal (SMD: 0.30, 95% CI: −0.28, 0.87, p = .31).

### Effect of quercetin on cross-sectional fibers

**Fiber area**

Regarding the fiber area, four studies with eight arms were included to estimate the pooled effects of quercetin supplementation on the muscle fiber area.\(^{9,33–35}\) Using the forest plot, we observed that oral intervention of quercetin increased the cross-sectional area of muscle fibers, which was statistically significant (SMD: 0.86, 95% CI: 0.40, 1.32, \(p = .0002\)) with an \(I^2\) of 47% (Figure 5 and Table 3). After
removing a study that used a surgically induced atrophy model, a decrease in heterogeneity was found ($I^2$ value change from 47% to 37%), while the difference between the groups remained unchanged. The subgroup analysis categorized studies according to intervention methods and basic characteristics. Studies including animals aged ≤ 8 weeks, studies performed in Asian countries, and studies administering quercetin for ≤ 8 weeks respectively, showed decreased heterogeneity and notable protective effects with regards to cross-sectional fiber area (SMD: 1.28, 95% CI: 0.72, 1.84, $p < .01$, $I^2 = 16$%) (Tables 4 and 5 and Supplementary Tables 1 and 2).

**Fiber diameter**

Oral supplementation of quercetin resulted in a statistically significant increase in cross-sectional fiber diameter in comparison to the placebo group (SMD: 0.94, 95% CI: 0.25, 1.62, $p < .01$, $I^2 = 52$%) (Figure 6 and Table 3). Through the leave-one-out sensitivity analysis, two studies identified as a substantial source of study heterogeneity, which when removed, the remaining eligible studies became homogeneous after these two studies were removed ($I^2$ from 52% to 0%), while the overall effect on fiber diameter was not affected (SMD: 0.94, 95% CI: 0.35, 1.53, $p < .01$, $I^2 = 0$%). However, subgroup analyses that stratified studies according to basic characteristics and intervention modes did not influence the overall effects on fiber diameter (Tables 4 and 5; Supplementary Tables 1 and 2).
Table 6. Assessment of publication bias.

| Muscle markers | Study arms | Begg’s test | Egger’s test |
|----------------|------------|-------------|--------------|
|                |            | p           | p (correction) | SE       | 95% CI | p       |
| GAS mass (mg)  | 7          | 0.099       | 0.133        | 2.86     | −0.87, 13.85 | 0.073 |
| SOL mass (mg)  | 8          | 0.46        | 0.54         | 2.63     | −4.05, 8.83 | 0.4    |
| EDL mass (mg)  | 4          | 1.00        | 1.00         | 4.23     | −27.22, 9.20 | 0.17   |
| Fiber diameter (µm) | 7 | 0.45 | 0.55 | 4.39 | −8.32, 14.26 | 0.53 |
| Fiber area (µm²) | 7 | 0.29 | 0.37 | 2.71 | −3.39, 10.53 | 0.25 |
| Specific force (n/cm²) | 4 | 0.5 | 0.73 | 5.27 | −26.28, 19.11 | 0.57 |

CI, confidence interval; EDL, extensor digitorum longus; GAS, gastrocnemius; SE, standard error; SOL, soleus.

Effect of quercetin on specific force

Four studies reported about skeletal muscle-specific force following chronic quercetin supplementation.\(^9,32,35,36\) The meta-analysis showed that 7–12 months of quercetin treatment had a negligible to small effect on a specific force (SMD: 0.37, 95% CI: −0.22, 0.96, \(p = .22, \ I^2 = 19\%\) (Figure 7 and Table 3). In an additional sensitivity study, exclusion of studies performed by Selsby et al.\(^{32}\) and Spaulding et al.\(^{36}\) decreased the intra-study heterogeneity without impacting the overall effect (SMD: 0.58, 95% CI: −0.06, 1.23, \(p = .08, \ I^2 = 0\%\) (SMD: 0.15, 95% CI: −0.52, 0.82, \(p = .66, \ I^2 = 0\%\) (Tables 4 and 5, Supplementary Tables 1 and 2).

Publication bias

Publication bias was estimated by visualizing the symmetry of the derived funnel plots (Supplementary Figure 2), Egger’s rank correlation test, and Begg’s linear regression test (Table 6). Our results suggested no publication bias with regard to muscle mass, cross-sectional fiber diameter and area, and muscle force.

Discussion

In the present study, we systematically summarized the effects of quercetin supplementation on skeletal muscle mass, muscle fiber, and muscle strength based on in vivo studies conducted in murine animal models. A quantitative analysis of the included studies showed a favorable effect of oral quercetin intervention on the skeletal muscle fiber diameter and area, as compared to the placebo controls. In contrast, no significant effects were observed on muscle mass and function after quercetin supplementation. Subgroup analyses indicated a statistically significant improvement in the gastrocnemius muscle mass for studies conducted in Asia. However, no significant publication bias was observed. Moreover, despite a large amount of statistical heterogeneity among studies, the overall effect of quercetin supplementation on muscle atrophy remained robust after omitting heterogeneous studies in the sensitivity analyses. Quercetin appears to be a promising complementary therapy for muscle atrophy, while further studies are still warranted before its clinical application.
Muscle atrophy is a debilitating and destructive muscle disorder that develops in patients due to aging, chronic disease, genetic deficiencies, advanced-stage cancer, and other diseases. The major pathophysiological changes underlying muscular atrophy include a decrease in muscle fiber thickness and loss of muscle fibers, resulting in the attenuation of muscle mass and function.\textsuperscript{[38]} It has been suggested that a reasonable and valid curative effect evaluation system for muscle atrophy should include, not only morphological and pathological changes but also functional changes in skeletal muscle.\textsuperscript{[39]} However, the medical effects of quercetin administration on muscular physical performance and histopathological changes in humans, especially in patients with muscle atrophy, have rarely been reported. Herein, we synthetically reviewed pre-clinical studies that examined the anti-muscular atrophy properties of quercetin in murine models and comprehensively evaluated the effects of quercetin supplementation on muscle mass, histological changes, and muscle function.

We found that studies conducted in this area have evaluated effects and mechanisms concerning “muscle atrophy or sarcopenia” in different rodent models, with most of them focusing on the function of quercetin on fatigue delay and physical performance improvement.\textsuperscript{[12,40]} However, some of the major traits of patients with atrophy, including severe lose of grip strength and motor ability deficits, are not given enough attention, and there is a lack of primary data that can be used in a systematic review and meta-analysis. Moreover, determining the potential of quercetin as an anti-atrophy complementary therapy requires more than a simple measurement of muscle mass and fiber size. To evaluate the effects of quercetin on muscle tissue from a functional perspective, we adopted evaluations of specific force (i.e., excursive muscle flesh experiments) to validate the observed effects of quercetin on muscle strength. The results of these studies were consistent, with no statistically significant differences found in subjects that were supplemented with quercetin. Even publication bias, sensitivity, and heterogeneity analyses demonstrated the reliability and robustness of the present result, which was similar to results with respect to other muscle function indices,\textsuperscript{[30,41]} leading us to wonder if negative functional results may “sit in a file drawer.” Current data are insufficient to answer this question. More studies that report the effects of quercetin on a series of objective scientific indices (muscle motor ability, grip strength, motor coordination) are needed to address this gap in the literature.

Contrary to the popular belief that the maintenance of muscle strength depends on minimizing the loss of muscle mass,\textsuperscript{[42,43]} several studies have found that changes in muscle mass account for a small proportion of muscle strength.\textsuperscript{[44,45]} Moreover, the disproportionate changes in muscle strength and muscle mass with respect to physical exercise observed in some earlier studies also indicated that improvements in muscle quality, and not muscle mass, may play a critical role in maintaining muscle function during muscle atrophy.\textsuperscript{[45,46]} Muscle quality largely depends on the size and composition of the constituent motor units.\textsuperscript{[47]} Herein, we generated relevant primary data from 14 studies and reported that dietary quercetin intervention exerts beneficial effects by preventing histopathological damage during muscle atrophy rather than preserving skeletal muscle mass. Some of the latest results also revealed that quercetin supplementation increased locomotor activity by promoting fiber-type conversion in elderly mice.\textsuperscript{[37,48]} Our results can aid in interpreting the anti-atrophy effects of quercetin on muscle fiber parameters. However, caution should be taken in utilizing these findings because only histopathological changes were confirmed, and few relevant studies have so far been conducted.

Quercetin, a type of natural dietary polyphenolic flavonoid, is a secondary metabolite found commonly in many vegetables and fruits. Some \textit{in vitro} studies have reported its mild adverse effect on embryonic development, and potential damaging effect due to its oxidation product quercetin-quinine.\textsuperscript{[49]} Generally quercetin is safe and well tolerated, in both animal and human subjects, and no teratogenic and mutagenic effects have been reported in short- and long-term studies.\textsuperscript{[50,51]} The presence of two antioxidant pharmacophores in the quercetin molecule, the catechol group and the OH group, makes it a natural radical scavenger and an anti-inflammatory agent.\textsuperscript{[49]}

Nowadays, quercetin is available as an over-the-counter medicament in the form of capsules, and is consumed, sometimes excessively, by health-conscious individuals as a beneficial dietary additive,
assuming it to be a natural and safe nutraceutical. For years, quercetin has been known as a low-toxicity phytochemical since neither acute nor chronic toxicity has been found in animals supplemented with large quantities of quercetin (and its conjugated metabolites).

Although it is not certain whether these interventions were the cause, two studies have reported animal deaths during quercetin interventions. Moreover, pre-clinical studies have reported that daily intake of quercetin, with or without other antioxidants, reduced the survival in cancer cachexia and enhanced cachexia-related complications, which was suggestive of the health-damaging effect of long-term and excessive usage of quercetin in combination with other antioxidants. However, it remains unclear how patients with muscle atrophy may benefit from prolonged quercetin supplementation.

Besides potential interactions with antioxidants, studies on quercetin applications face major challenges about its true efficacy, and competition with the pharmaceutical and biotechnology industries. Several issues need to be addressed in future investigations: (1) antagonistic/synergistic and interaction effects between quercetin and therapeutic drugs, other nutritional substances, and gut microbiota; (2) impact of administration routes, dosage, and time intervals on the overall effect of long-term supplementation; (3) the active pharmaceutical ingredient of quercetin; and (4) the absorption, distribution, and metabolism of modified quercetin and its metabolites. As a commercial nutraceutical, we believe that a full evaluation of the clinical underpinnings of findings in atrophy patients who self-prescribe quercetin as prolonged supplementation is critically needed. Moreover, we suggest that nutritional supplements for therapy and health promotion should be provided under the credible advice of registered nutritionists or physicians rather than self-prescription practices.

Generally, our study illustrated a potential anti-atrophic effect of quercetin on skeletal muscle fibers, though no statistically significant effects on muscle mass and function were observed. To date, the molecular mechanisms of the action of quercetin on muscle atrophy have not been completely understood. Several underlying mechanisms reported by previous studies may help explain the anti-atrophy features of quercetin seen in various investigations. The known anti-inflammatory and antioxidant defense Nrf2/HO-1 (nuclear factor erythroid 2-related factor- (Nrf2-) heme oxygenase-1 (HO-1)) axis, that can play a critical role in various pathology conditions, was shown to be induced by exercise and caloric restriction. Nrf2 deficiency worsen muscle wasting and frailty though impairing mitochondrial biogenesis and dysregulation. Phytonutrients intervention have been reported to induced Nrf2/HO-1 pathway activation recently, and quercetin intervention attenuates metabolic disorder-induced muscle wasting by inhibiting TNF-α-induced atrophic factors (MuRF1 and MAFbx/atrogin-1) via the Nrf2/HO-1 pathway, accompanied by inactivation of NF-κB. The nuclear receptor, peroxisome proliferator-activated receptor (PPAR)-γ, is involved in the metabolism and myosteatosis of skeletal muscle. Evidence indicates that quercetin directly inhibits the transcription of PPAR-γ and fatty acid binding protein 4 (FABP4) in muscle satellite cell adipogenesis (i.e., resident stem cells for muscle regeneration and function maintenance). Moreover, activation of silent mating type information regulator 2 homolog 1 (SIRT-1) in skeletal muscle was shown to induce the PPAR-γ coactivator-1α (PGC-1α) deacetylation and activation, thereby inducing mitochondrial biogenesis and transition of muscle fiber type which simulated protective effect of exercise. Quercetin supplementation not only promotes mitochondrial biogenesis by activating SIRT-1 and PGC-1α, but also preserves mitochondrial function by scavenging hydrogen peroxide originating from mitochondrial damage. These pre-clinical mechanistic theories may help interpret the potential anti-atrophic effects of quercetin on muscle mass and function. However, most of these mechanisms have not been substantiated in human participants. Therefore, more clinical studies are needed to translate this mechanistic understanding to clinical practice.

The present study presents several notable strengths and limitations. The current meta-analysis is the first to perform a complete and systematic evaluation of the effects of quercetin on muscle function, histology, and morphology. We also applied strict criteria and procedures to improve the included studies’ quality and reduce the distortion of the analysis. However, in addition to the substantial advantages of this work, some limitations should be considered. First, there was considerable heterogeneity between studies evaluating muscle mass and fiber size. Though random-effects models and
subgroup meta-analyses were utilized to minimize this heterogeneity and identify its sources, some heterogeneity was inevitable, and the source of this heterogeneity was unclear. Second, the animal models employed in the included studies varied substantially. Moreover, although all of these models attempted to mimic the pathological state of disease-induced muscle atrophy, they cannot truly reflect the clinical manifestations of in human patients with atrophic in the real world. We also cannot rule out the effects of gaps between clinical and scientific research on interpretation of the findings reported herein. Finally, since studies investigating muscle function were limited in number and scope, we could not adequately analyze the effects of quercetin on these parameters; thus, more clinical studies and an integrated evaluation system are urgently needed to improve our knowledge of muscle atrophy. However, the present study results provides an objective and comprehensive assessment of the anti-muscular atrophy effects of quercetin based on available pre-clinical data.

**Conclusion**

Our meta-analysis suggests that quercetin has a histopathological protective anti-muscular atrophy effect (Figure 8). Quercetin is a promising complementary therapy for muscle atrophy; however, there are still hurdles to overcome before its clinical application. Our work may pave way for future research directions and clinical guidelines.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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**ORCID**

Weiqun Lin  [http://orcid.org/0000-0002-6420-5625](http://orcid.org/0000-0002-6420-5625)

Yongyi Zhao  [http://orcid.org/0000-0001-7765-9039](http://orcid.org/0000-0001-7765-9039)

Qiaowen Ou  [http://orcid.org/0000-0002-1832-9790](http://orcid.org/0000-0002-1832-9790)

**Author contributions**

Conceptualization and methodology, W.Q.L.; article screening and selection, Y.H.Y., C.B.L. and Y.Y.Z.; data curation, C.B.L. and Y.Y.Z.; formal analysis and writing-original, W.Q.L.; writing-review and editing, W.Q.L. and Q.W.O.; project administration, Q.W.O.; funding acquisition, W.Q.L. and Q.W.O. All authors read and approved the final manuscript.

**Author declarations**

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