Systematic Review

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Does Quercetin Supplementation Promote Biological Changes and Performance in Athletes? A Systematic Review

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Background: Summarize the available evidence in the literature regarding the repercussions generated by quercetin supplementation in amateur and professional athletes.

Methods: Searches were conducted in four databases, Cochrane Library (23 articles), PubMed/Medline (37 articles), Scopus (70 articles), and Excerpta Medica Database (EMBASE) (72 articles), which were subjected to eligibility criteria.

Results: Out of 202 articles found, 95 duplicates were removed, and 107 articles were analyzed for the inclusion process. Then, 784 studies were excluded after title/abstract evaluation, resulting in 17 articles of which 13 were included in this systematic review. After quercetin supplementation, alterations in aspects related to the inflammatory response were observed, mainly through modifications in the formation of interleukin (IL)-1β, interleukin 2 (IL-2), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 12 (IL-12), and tumor necrosis factor alpha (TNF-α). Responses were also observed in biochemical parameters, such as reduction of xanthine oxidase, and plasma free radicals. There were also changes related to anthropometry and body composition, in lean body mass (LBM). Some repercussions on performance were also observed, such as an increase in Sprint time (s), and training efficacy, a decrease post-run muscular pain through the Visual Analog Score (VAS), and recovery time in hours.

Conclusion: This systematic review indicates that quercetin supplementation does not improve exercise performance, but may exert positive effects on training development, which might trigger better performance as training progresses. On the inflammatory and oxidative-related parameters, just a few evidence pointed to an improved biochemical profile, wherein the slight enhancement may not justify the supplementation costs.

Keywords: quercetin; performance; sports nutrition; physical activity; athletes

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Introduction

Quercetin, a polyphenolic flavonoid, is naturally present in a wide variety of plant foods, including onions, apples, cabbage, grapes [1]. Studies have indicated that quercetin has anti-inflammatory, hepatoprotective, cardioprotective, and antioxidant effects, along with a beneficial influence on the immune system. It positively impacts oxidative stress and chronic inflammatory responses. Consequently, numerous studies have concentrated on dietary supplementation with quercetin, assessing its bioactive properties in various health contexts [2,3].

The antioxidant action of quercetin primarily stems from its influence on enzymatic activity, the formation of reactive oxygen species, and specific signal transduction pathways, which occur due to the body's production of free oxygen radicals [4]. As these radical's form, the enzyme superoxide dismutase (SOD) rapidly neutralizes the O_2 so that it is converted into hydrogen peroxide (H_2O_2), which is then decomposition into H_2O [5]. For these reactions to proceed effectively, the presence of reduced glutathione (GSH) is essential, as it acts as a hydrogen donor. This underscores the importance of quercetin, as it stimulates the production of GSH [6,7].

Quercetin is described as possessing anti-inflammatory properties, exerting its effects on various cell types. It protects cells in the gastrointestinal tract, stabilizing mast cells, and regulates inflammatory processes [8]. The anti-inflammatory action of quercetin occurs in macrophages by inhibition the production of tumor necrosis factor alpha (*TNF-*α) induced by lipopolysaccharide (LPS). Additionally, it potentially decreasing the mRNA levels of *TNF-*α and interleukin (*IL*)*-1*α induced by LPS in glial cells, thereby reducing neuronal apoptosis resulting from microglial activation [8–10].

Studies have investigated quercetin supplementation in various settings, particularly in the context of physical activity, due to its potential anti-inflammatory, antioxidant, and cardioprotective benefits [11–13]. However, a limitation of quercetin supplementation is its reduced gastrointestinal absorption, leading to decreased bioavailability. Therefore, supplementation typically occurs with the co-ingestion of other substances [14]. Quercetin supplementation has been linked to enhanced performance, including reductions in running times in specific sports compared to non-supplemented conditions. This is attributed to quercetin's ability to alleviate training-induced pain, decrease fatigue levels, improved effort efficiency, and enhance the quality of rest, thereby directly impacting overall performance [15]. In intense exercise, quercetin supplementation has demonstrated the ability to reduce important inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin 6 (IL-6), with reported improvements in antioxidant action and endothelial function [16,17].

On the other hand, studies have not found significant improvements in aspects related to the benefits of quercetin supplementation in physical activity, showing no substantial reductions in inflammation or oxidative stress. Therefore, this raises questions about optimal dosage, given the variations observed in the literature [18,19].

Considering the impacts of quercetin supplementation, physical activity can potentially benefit as exercises induces inflammatory processes and oxidative stress while also demanding cardiovascular capacity, all of which influence exercise efficiency and quality. However, despite the interest in quercetin supplementation, there are gaps in understanding its potential benefits or limitations in terms of biological and performance outcomes. These range from specific mechanisms of action when quercetin is targeted for physical practice to determining the ideal dosage.

Therefore, this study aims to investigate the biological and performance repercussions associated with quercetin supplementation in physical exercise. It analyzes the effects of this intervention on physiological parameters, biomarkers of oxidative stress and inflammation, as well as performance in athletes.

Methods

The present study followed the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA, **Supplementary File**) guidelines.

Study Selection and Eligibility Criteria

The eligibility criteria were previously established in advance to minimize the occurence of systematic biases. The inclusion and exclusion criteria followed the Population, Intervention, Comparator, Outcomes, Study Design (PICOS) framework (Population/Intervention/Control/Outcomes/Study Design) (Table 1). Thus, the following inclusion criteria were applied: (a) Only studies in English were selected, (b) without restriction on publication time, (c) involving athletes at various levels (amateur and professional/elite), (d) who underwent quercetin supplementation, (e) of both sexes, (f) age between 18 and 40 years old, (g) studies that included the Placebo group as a comparator, (h) evaluated inflammatory response, biochemical and anthropometric/body composition outcomes, (i) assessing neuromuscular, aerobic performance, and Physical Effort Load outcomes. Exclusion criteria: (a) articles that did not use quercetin supplementation or without a Placebo group, (b) athletes undergoing pharmacological and other nutritional strategies, as well as those with associated physical or psychological pathologies, (c) studies that did not evaluated athletes neuromuscular and aerobic performance components, (d) studies involving individuals under 18 years or over 45 years of age, (e) studies involving animals

Table 1. PICOS strategy.

	Inclusion criteria	Exclusion criteria
Population	Amateur and professional/elite athletes	Any other population
Intervention	Quercetin supplementation	No quercetin supplementation
Comparator	Control	Any other comparison group
Outcomes	Inflammatory response, biochemistry, anthropometric/body composition performance outcomes	Any other outcome
Study Design	Intervention Studies	Animal's Studies; Commentary: review, letters, duplicates, and missing data used in different studies were excluded

PICOS, Population, Intervention, Comparator, Outcomes, Study Design.

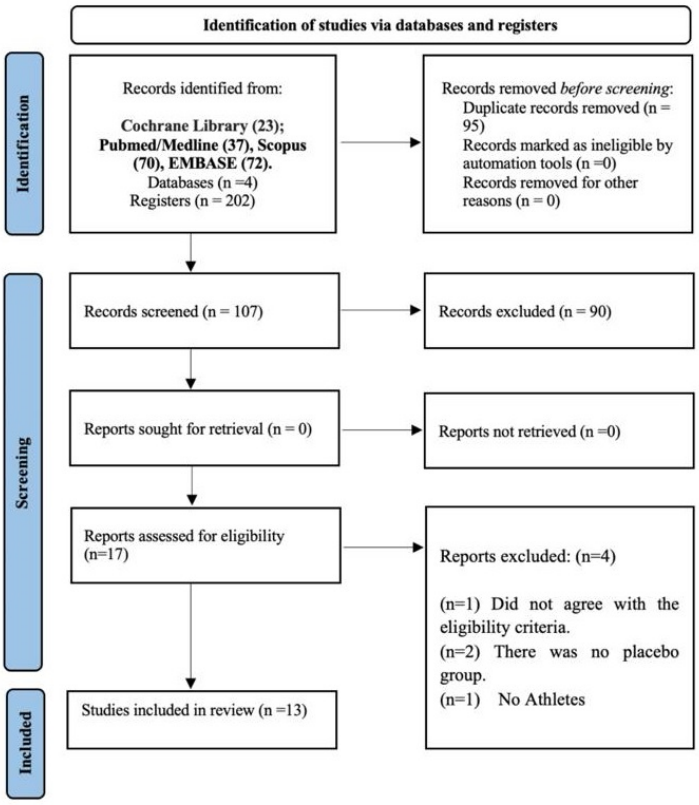

Fig. 1. Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for new systematic reviews which included searches of databases and registers only. EMBASE, Excerpta Medica Database.

of any species, comments, review publications, letters, duplicates, and missing data used in different studies were excluded.

Information Sources and Search Strategy

The search strategy was developed between December 2023 to February 2024. The following databases were used to select and include articles: Cochrane Library [https://www.cochranelibrary.com/advanced-search?cookiesEnabled], PubMed/Medline [https://pubmed.ncbi.nlm.nih.gov], Scopus [https://www.scopus.com/search/form.uri?display=basic#basic] and Excerpta Medica Database (EMBASE) [https://www.embase.com/search/quick], using the following search equation: (((((((("Athlete") OR ("Athletes")) OR ("Athlete, Professional")) OR ("Athletes, Professional")) OR ("Elite Athletes")) OR ("Elite Athlete")) OR ("College Athlete")) OR ("College Athletes")) AND ("Quercetin").

Selection and Data Collection Process

The screening of studies was performed by reading the title, abstract, and full text. The selection of studies was conducted by two independent researchers (MSSF and GCJS). Any discrepancies were resolved by a third reviewer. Data extracted was carried out independently by two researchers. All the selection process is described in Fig. 1.

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Table 2. Methodological quality assessment for non-randomized and randomized studies-Joanna Briggs Institute.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%
Abbey and Rankin (2011) [20]	Y	Y	Y	Y	N	N	Y	Y	75
Askari *et al.* (2012) [16]	Y	Y	Y	Y	N	N	Y	Y	75
Askari *et al.* (2012) [18]	Y	Y	Y	Y	N	N	Y	Y	75
Askari *et al.* (2013) [21]	Y	Y	Y	Y	N	N	Y	Y	75
Askari *et al.* (2013) [22]	Y	Y	Y	Y	N	N	Y	Y	75
Daneshvar *et al.* (2013) [23]	Y	Y	Y	Y	N	N	Y	Y	75
Darvishi *et al.* (2013) [19]	Y	Y	Y	Y	N	N	Y	Y	75
Dumke *et al.* (2009) [24]	Y	Y	Y	Y	N	N	Y	Y	75
Quindry *et al.* (2008) [27]	Y	Y	Y	Y	N	N	Y	Y	75
Konrad *et al.* (2011) [26]	Y	Y	Y	Y	N	N	Y	Y	75
McAnulty *et al.* (2008) [25]	Y	Y	Y	Y	N	N	Y	Y	75
Riva A *et al.* (2018) [15]	Y	Y	Y	Y	N	N	Y	Y	75
Utter *et al.* (2009) [28]	Y	Y	Y	Y	N	N	Y	Y	75

Y, YES; N, No; Q1: Were the inclusion criteria well defined? Q2: Have participants and context been described in detail? Q3: Were the measurements collected in a valid and reliable way? Q4: Were standardized and objective inclusion criteria used? Q5 Were any confounding variables found? Q6: Were strategies used to deal with confounding variables? Q7: Were the results measured validly and reliably? Q8: Was the statistical analysis used adequate?

Data Items

In the present review, information regarding the sample was extracted, including author and year, sample size, sex, sport modality, level of experience in the sport (amateur or professional/elite). Additionally, data on the quercetin supplementation protocol were collected, including dose, frequency, route of administration and duration (in days or weeks), as well as a description of the substance used by the control group. In addition, data on Inflammatory response markers were extracted such as: C-reactive protein (CRP); interferon gamma (IFN-γ); IL-1β; interleukin 2 (IL-2); interleukin 4 (IL-4); interleukin 6 (IL-6); interleukin 8 (IL-8); interleukin 10 (IL-10); tumor necrosis factor alpha (TNF-α). Biochemistry Parameters: Carbonyls; Creatine Kinase (CK); F2 isoprostane, 8-isoPGF2a; High Density Lipoprotein (HDL); Lactate Dehydrogenase (LDH), Trolox (Antioxidant Capacity), Xanthine Oxidase; Plasma Free Radical. Anthropometric/Body composition: Body Fat (%); Body Mass Index (BMI); Body Weight (BW); Lean Body Mass (kg). In addition, data related to Aerobic performance were extracted, such as Time to Exhaustion (sec); maximum oxygen consumption (VO_{2max}) (L.min); Distance (m); Sprint Time (sec); Cycling economy (W.min.L); Gross efficiency, Total energy expenditure, Training efficacy and post-run muscular pain (Visual Analog Score (VAS) score); and recovery time (hours). Finally, Physical Effort outcome was included such as Ratings of Perceived Exertion (RPE).

Methodological Quality Assessment

The Joanna Briggs Institute Critical Appraisal Checklist is used for analytical randomized controlled trial and non-randomized experimental studies was used to verify the methodological quality of the included articles. This tool consists of eight questions that assess the methodological quality. The questions were answered with "Yes", "No" or "Unclear". When the answer was "yes", a score was given, when the answer was "no" or "undefined", no score was given. The score for each article was calculated as a percentage and classified as high (80–100%), fair (50–79%), or low (50%). All studies were independently reviewed by two reviewers. Discrepancies between raters were resolved by consensus (Table 2, Ref. [15,16,18–28]).

Results

Search Results

A total of 202 studies were identified through searches in the databases [Cochrane Library (n = 23); PubMed/Medline (n = 37); Scopus (n = 70); and EMBASE (n = 72]. After removing duplicates (n = 95), 107 articles were screened for the inclusion process. Subsequently, 784 publications were excluded after reviewing the title/abstract, leaving 17 studies for full text evaluation. Finally, 13 studies were included in the present systematic review. The process of search, selection, and inclusion of studies was summarized in the flow diagram of the PRISMA statement (Fig. 1).

Methodological Quality Assessment

All included studies exhibited a fair quality level (75%). The identification and control of confounders were not assessed in all studies. However, criteria of inclusion,

Table 3. Sample description.

Author, year	*n*	Sex	Age (y)	Sport modality	Level	Country
Abbey and Rankin (2011) [20]	15	M	23.3 ± 2.6	Soccer and basketball	Amateur	Blacksburg, VA, USA
Askari *et al.* (2012) [16]	60	M	21.0 ± 1.6	Non-informed	Amateur	Isfahan, Iran
Askari *et al.* (2012) [18]	60	M	21.0 ± 1.6	Non-informed	Amateur	Isfahan, Iran
Askari *et al.* (2013) [21]	60	M	21.0 ± 1.6	Non-informed	Amateur	Isfahan, Iran
Askari *et al.* (2013) [22]	56	M	20.4 ± 1.1	Non-informed	Amateur	Isfahan, Iran
Daneshvar *et al.* (2013) [23]	26	M	17.5 ± 2.0	Badminton	Amateur	Isfahan, Iran
Darvishi *et al.* (2013) [19]	26	F	16.1 ± 2.5	Swimming	Amateur	Isfahan, Iran
Dumke *et al.* (2009) [24]	40	M	26.1 ± 1.8	Cycling	Amateur	Missoula, MT, USA
Quindry *et al.* (2008) [27]	63	F/M	44.2 ± 2.0	Ultramarathon	Elite	Nashville, TN, USA
Konrad *et al.* (2011) [26]	22	F/M	F (40.5 ± 3.0)/M (35.8 ± 2.7)	Running	Elite	Kannapolis, NC, USA
McAnulty *et al.* (2008) [25]	40	M	26.1 ± 1.8	Cyclists	Amateur	Boone, NC, USA
Riva A *et al.* (2018) [15]	48	F/M	33.0	Triathlon	Amateur	Genoa, Italy
Utter *et al.* (2009) [28]	63	F/M	44.2 ± 2.0	Ultramarathon	Elite	Boone, NC, USA

F, Female; M, Male; *n*, number of participants; USA, United States of America; y, years old.

description of participants context, utilization of reliable and valid measurements, and an appropriate statistical analysis process were considered (Table 2).

Characteristics of Included Studies

The studies included in this systematic review were published between 2008 and 2018 (Table 3, Ref. [15,16,18–28]). The number of participants varied between 15 and 63 athletes. Eight of the included studies focused solely on male athletes [16,18,20–25], while four studies included both sexes [15,26–28], and one study specifically included used female athletes [19]. The average age of participants ranges from 16.1 to 44.2 years. In terms of sports modalities, four studies exclusively involved runners [15,26–28], two studies focused on cyclists [24,25], one study included swimmers [19], another study involved badminton players [23] and one study included soccer and basketball athletes [20]. Finally, four studies mentioned using athletes without specifying their respective modalities [16,18,21,22]. Nine of the included studies focused solely amateur athletes [16,18–25], while four studies were conducted on elite athletes [15,26–28]. Regarding geographical distribution, six studies were conducted in the United States of America (USA) [20,24–28], six in Iran [16,18,19,21–23] and one in Italy [15].

Quercetin Supplementation Protocol

To establish the quercetin supplementation protocol, various parameters were considered, including the type of substance used in the control group, vehicle for ingestion, dose in milligrams, route of administration, and duration of supplementation in weeks. Among the thirteen included studies, only eight provided descriptions of the substances used in their control group. Two studies utilized only dextrose [19,23], one study used only 6% carbohydrates [20], one study used lactose [21] and another study used Tang® Powder (60093-2753, Kraft Foods Global, Northfield, Ill, USA) [24]. Conversely, two studies employed different substances to establish their control groups [27,28]. Regarding the ingestion vehicle, seven studies utilized capsules [16,18,19,21–23], while two included studies used chewable forms [26,27], and two studies used powder with an ingestion vehicle [24,25]. The dose of quercetin administered to athletes ranged from 250 mg to 1000 mg, with oral supplementation protocols being employed. Finally, the duration of quercetin supplementation protocols varied from 1 to 8 weeks (Table 4, Ref. [15,16,18–28]).

Impacts of Quercetin Supplementation on Biological Outcomes

Inflammatory Response

Four of the included studies assessed indicators related to inflammatory responses (CRP, IFN-γ, IL-1β, IL-2, IL-4; IL-6, IL-8, IL-10, TNF-α) in athletes following quercetin supplementation [16,20,25,26]. Three studies evaluated CRP levels, two studies did not observe significant differences between the groups [25,26], while one study reported a significant decrease after quercetin supplementation in athletes [16]. Two included studies assessed IL-6 levels after quercetin supplementation [16,20]. One study noted a significant increase in IL-6 following querentin supplementation in athletes [20], while the other study found no significant differences were observed between the groups [16]. One study evaluated the IFN-γ levels, with no significant differences observed between the groups [26]. The same study also evaluated the levels of IL-1β; IL-2; IL-8; IL-10; IL-12; TNF-α, all of which demonstrated a significant increase after quercetin supplementation in athletes. Based on these findings, it can be concluded that supplementation with this flavonoid was not effective in reducing the inflammatory response in athletes at different levels (Table 5, Ref. [15,16,18–28]).

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Table 4. Quercetin supplementation protocol.

Author, year	Control substance	Quercetin supplementation protocol		Route and time of administration
		Vehicle	Dose (mg/day)	
Abbey and Rankin (2011) [20]	6% carbohydrates	Dry Powder	500 mg quercetin-3-glucoside; (1000 mg)	OA, 1 wk
Askari *et al.* (2012) [16]	-	Capsules	500 mg quercetin	OA, 8 wks
Askari *et al.* (2012) [18]	-	Capsules	500 mg quercetin	OA, 8 wks
Askari *et al.* (2013) [21]	Lactose	Capsules	500 mg quercetin	OA, 8 wks
Askari *et al.* (2013) [22]	-	Capsules	500 mg quercetin	OA, 8 wks
Daneshvar *et al.* (2013) [23]	Dextrose	Capsules	1000 mg quercetin	OA, 8 wks
Darvishi *et al.* (2013) [19]	Dextrose	Capsules	1000 mg quercetin	OA, 8 wks
Dumke *et al.* (2009) [24]	Tang → Powder	Powder	1000 mg quercetin	OA, 3 wks
Quindry *et al.* (2008) [27]	Sugars, carnauba wax, and soy lecithin	Chewables	250 mg pure quercetin (1000 mg)	OA, 3 wks
Konrad *et al.* (2011) [26]	Brownrice syrup, evaporated cane juice, carnuba wax, natural flavors, gelatin, soy lecithin, palm oil, glycerin, xylitol, mono- and diglyceride, corn starch, carrageenan, sucralose with citric acid and FD&C yellow #5 and FD&C blue #1	Chewables	1000 mg quercetin	OA, 3 wks
McAnulty *et al.* (2008) [25]	-	Solid dispersion	250 mg querctin phytosome® (Indena S.p.A., Milan, Italy); (500 mg)	OA, 2 wks
Riva A *et al.* (2018) [15]	-	Powder	1000 mg quercetin	OA, 3 wks
Utter *et al.* (2009) [28]	Sugars in a carnauba wax, soy lecithin, corn starch, glycerin, and colored palm oil	Chewables	1000 mg quercetin	OA, 3 wks

mg, milligrams; wks, weeks; OA, Oral administration.

Biochemistry Parameters

Nine of the included studies investigated the effects of quercetin supplementation on various biochemical indicators in athletes (Table 5) [15,16,19–23,25,27]. Two studies assessed lactate levels, both of which did not observe significant differences after quercetin supplementation [19,23]. Similarly, two studies evaluated F2 isoprostane levels, with no differences between groups after supplementation in both studies [16,25]. One study examined CK levels after quercetin supplementation, but no significant differences were identified [18]. Another study assessed xanthine oxidase levels, noting a significant decrease in this marker after quercetin supplementation in athletes [20]. Additionally, one study evaluated HDL and Low Density Lipoprotein (LDL) levels following the quercetin supplementation protocol, with no significant differences observed between the groups [22]. Moreover, one study evaluated 8-isoPGF2a, carbonyls, and Trolox (antioxidant capacity), but found no significant differences after quercetin supplementation [27]. These findings indicate that quercetin supplementation was effective in reduce xanthine oxidase and plasma free radical levels in athletes.

Anthropometric and Body Composition

Five of the included studies included analyzed anthropometric variables (body weight and BMI) and body composition (body fat in percentage and lean body fat) following quercetin supplementation (Table 5). Regarding body weight, five studies evaluated athletes after the supplementation protocol, but no significant differences were observed between the groups [16,18,19,21,23]. Three studies assessed BMI after supplementation, with no significant differences were observed in athletes of different levels [16,18,22]. Furthermore, three studies examined the percentage of body fat in athletes after using quercetin as a supplement, and no significant differences were demonstrated between the groups [18,19,23]. Finally, only one included study evaluated lean body mass levels after quercetin supplementation in athletes. Following the supplementation protocol, a significant increase in lean body mass levels was observed [21]. These results suggest that quercetin supplementation was only able to increase lean body mass levels in athletes.

Table 5. Effects of quercetin supplementation on the inflammatory response, biochemical and anthropometric parameters, and body composition in athletes.

Author, year	Inflammatory response	Biochemistry parameters	Anthropometric/Body composition
Abbey and Rankin (2011) [20]	↔ IL-6	↔ Xanthine Oxidase	-
Askari *et al.* (2012) [16]	-	↔ HDL; ↔ LDH	-
Askari *et al.* (2012) [18]	-	↔ CK	↔ BW (kg); ↔ BMI; ↔ BF (%)
Askari *et al.* (2013) [21]	-	-	↔ BW (kg); ↔ BMI; ↔ LBM
Askari *et al.* (2013) [22]	↓ CRP; ↔ IL-6	↔ F2-isoprostane	↔ BW (kg); ↔ BMI
Daneshvar *et al.* (2013) [23]	-	↔ Lactate (mg/dL)	↔ BW (kg); ↔ BF (%)
Darvishi *et al.* (2013) [19]	-	↔ Lactate (mg/dL)	↔ BW; ↔ BF (%)
Dumke *et al.* (2009) [24]	-	-	-
Quindry *et al.* (2008) [27]	-	↔ F2-isoprostane; ↔ Carbonyls ↔ Ascorbate; ↔ FRAP; ↔ TEAC	-
Konrad *et al.* (2011) [26]	↔ CRP; ↔ IFN-γ; ↔ TNF-α; ↔ IL-1β; ↔ IL-2; ↔ IL-8; ↔ IL-10; ↔ IL-12	-	-
McAnulty *et al.* (2008) [25]	↔ CRP	↔ F2 isoprostane; ↔ Ascorbate; ↔ TEAC; ↔ Nitrite	-
Riva A *et al.* (2018) [15]	-	↓ Plasma Free radical	-
Utter *et al.* (2009) [28]	-	-	-

IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; HDL, High Density Lipoprotein; LDH, Lactate Dehydrogenase; BW, body weight; BMI, Body Mass Index; BF (%), body fat percentage; CK, Creatine Kinase; LBM, lean body mass; FFM, fat-free mass; IL-2, interleukin 2; IL-4, interleukin 4; IL-10, interleukin 10; IL-1β, interleukin-1 beta; IL-8, interleukin 8; CRP, C-reactive protein; TEAC, Trolox equivalent antioxidant capacity.

Performance Outcomes

Eight of the included studies assessed athletic performance parameters following quercetin supplementation (Table 6, Ref. [15,16,18–28]) [15,18–21,23,24,28]. Among them, seven studies evaluated parameters associated with aerobic performance [15,18–21,23,24]. Four studies evaluated VO_{2max} levels after the supplementation protocol, but no significant differences were observed [19,21,23,24]. Regarding time to exhaustion, two studies investigated this parameter; one study reported an increase after quercetin use [23], while the other found no significant differences [18]. Two studies evaluated total energy expenditure, both of which did not find significant differences between the groups [19,21]. One study assessed sprint time in seconds after quercetin supplementation, revealing a significant increase after the use of this substance in athletes [20]. Another study analyzed two variables related to aerobic performance-cycling economy (W.min.L-1), and gross efficiency- but neither showed significance differences after the supplementation protocol [24]. Finally, one study evaluated three essentials components of aerobic performance: Training efficacy, post-run muscle pain (VAS score), and recovery time (h). After quercetin, an increase in training efficacy and corresponding decreases in post-run muscle pain (VAS score) and recovery time (h) were observed, indicating promising impacts of this supplement on aerobic performance components [15]. Among the eight studies, four evaluated RPE levels after quercetin supplementation. However, none of these studies observe significant differences in athletes, suggesting that this supplement was not effective in altering RPE levels [20,23,24,28], (Fig. 2).

Discussion

Given quercetin's numerous pharmacological activities, its supplementation has demonstrated cytoprotective effects both in experimental and human studies. It is suggested that its anti-inflammatory and antioxidant effects may enhance biological function, including those involved in regular physical exercise. In this systematic review, we investigated the impacts of quercetin supplementation on biological and performance-related parameters in both amateurs and/or elite athletes.

Despite the therapeutic potential of quercetin, its application is limited due to its low solubility and poor gastrointestinal absorption. Therefore, the effectiveness of supplementation protocol (acute and/or chronic) should be evaluated/discussed in the research approach. To ad-

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Table 6. Quercetin supplementation on performance parameters.

Author, year	Performance parameters	Physical effort
Abbey and Rankin (2011) [20]	↔ Sprint time (s)	↔ RPE (A.U)
Askari *et al.* (2012) [16]	-	-
Askari *et al.* (2012) [18]	↔ Time to exhaustion	-
Askari *et al.* (2013) [21]	↔ Total energy expenditure; ↔ VO_{2max} ($L.min^{-1}$)	-
Askari *et al.* (2013) [22]	-	-
Daneshvar *et al.* (2013) [23]	↔ VO_{2max} ($L.min^{-1}$); ↑ Time to exhaustion	↔ RPE (A.U)
Darvishi *et al.* (2013) [19]	↔ VO_{2max} ($L.min^{-1}$); ↔ Total energy expenditure;	-
Dumke *et al.* (2009) [24]	↔ VO_{2max} ($L.min^{-1}$); ↔ Cycling economy ($W.min.L^{-1}$); ↔ Gross efficiency	↔ RPE (A.U)
Quindry *et al.* (2008) [27]	-	-
Konrad *et al.* (2011) [26]	-	-
McAnulty *et al.* (2008) [25]	-	-
Riva A *et al.* (2018) [15]	↑ Training efficacy and ↓ post-run muscular pain (VAS score); ↓ Recovery time (h)	-
Utter *et al.* (2009) [28]	-	↔ RPE (A.U)

L, Liters; Kg, Kilograms; ml, milliliter; min, minutes; VO_{2max}, maximum oxygen consumption; RPE (A.U), Ratings of Perceived Exertion (arbitrary units); s, seconds; W, Watts; VAS, Visual Analog Score; TNF-α, tumor necrosis factor alpha; IL, interleukin.

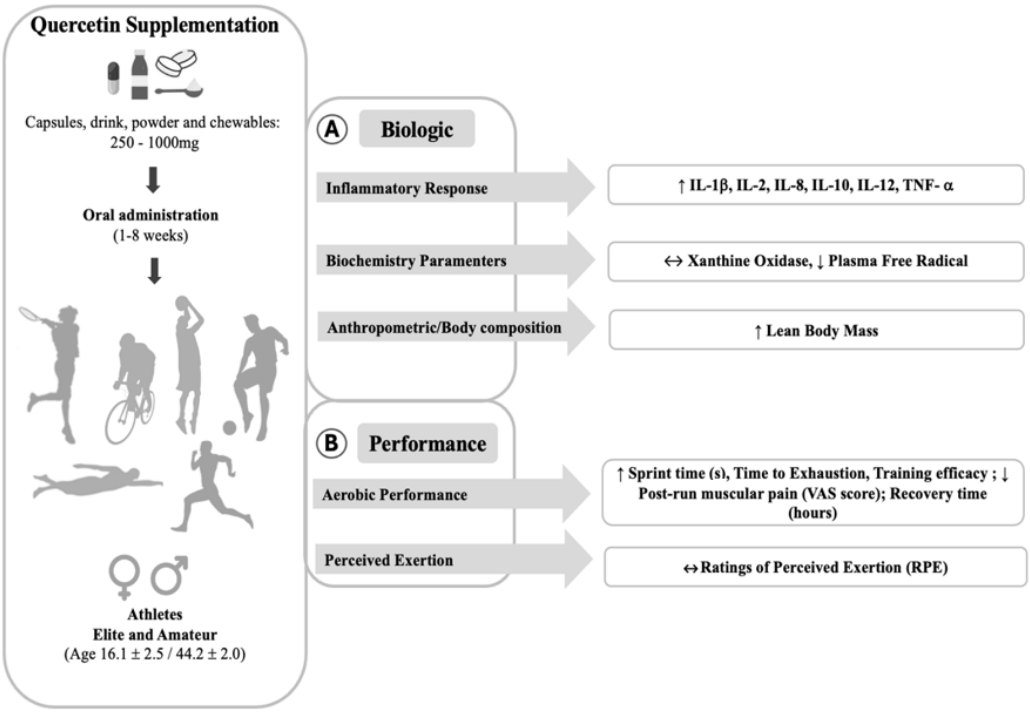

Fig. 2. Impacts of quercetin supplementation on biological and performance parameters in athletes.

dress the issue, it has been suggested that co-ingestion of quercetin with other food compounds such as flavonoids, sugar, and lipid-based systems can increase and prolong its bioactivity and bioavailability [29,30]. Among the studies included here, the main co-ingested elements were vitamin C, niacin, and carbohydrates, however, none of these strategies provide additional biological or athletic performance.

Plasma quercetin levels have been used to verify the effectiveness of quercetin absorption. According to Lai and Wong (2022) [31], exploring several approaches to optimize quercetin supplementation, taking 1000 mg of quercetin supplementation daily for three days leads to a cogent increase in its plasma concentration, see in detail. In this review, three studies assessed plasma quercetin levels, however, there were no differences in inflammatory or oxidative outcomes, even when quercetin levels were increased by over 500% compared to the placebo group. Interestingly, Quindry JC, *et al.* [27], evaluating athletes post a 160 km race, reported a general decrease in plasma quercetin concentration, wherein the supplemented

group experienced a compelled quercetin loss (~600 µg/L to ~100 µg/L) while the placebo group reduced its levels by 50%. As the unique difference found was the magnitude of quercetin reduction, assuming a tissue-specific distribution of quercetin and its metabolites is feasible [32]. Dabeek and Marra (2019) [33] highlighted that quercetin metabolism involves two metabolic stages in the liver, which generate metabolites for systemic circulation, wherein the kidney has an additional role by adding different conjugates to the quercetin structure. The absence of additional information on the contribution/importance of quercetin metabolites for the skeletal muscle, especially during exercise, limits further analysis while signaling the relevance of sport-related studies addressing this issue.

Regarding the inflammatory response, a single study observed the positive effects of quercetin. In this study, 2 months of oral quercetin supplementation (500 mg/day) alone resulted in decreased CRP levels [21]. CRP is commonly used for clinical purposes and is involved in the inflammatory response through its participating in the innate immune system. Although CRP levels increase rapidly after an inflammatory signal, it typically peaks only 36–50 hours after the onset of inflammation [34,35]. McAnulty SR, *et al*. [25] evaluating amateur cyclists across three days, demonstrated that CRP levels began to diverge from basal levels only on the second day (i.e., 24 hours later), without further influence over time. Therefore, it is crucial to consider the interval between the last exercise session (an environmental inflammatory stimulus) and blood sample collection to avoid misleading data.

Due to quercetin's antioxidant properties, one of the main outcomes of its supplementation is the maintenance of oxidative balance. However, only one study reported improvements in oxidative parameters by demonstrating that 250 mg quercetin phytosome®, taken twice a day, reduces plasma-free radicals [15]. The authors utilized the reactive oxygen metabolites Derivatives-Reactive Oxygen Metabolites (d-ROM) test, an indicator of reactive oxygen species/free radicals, instead of oxidative damage biomarkers used in other studies, indicating a reduction of almost 10% in Reactive oxygen species (ROS), possibly due to direct quercetin-related ROS quenching [16].

Related to the oxidative aspects, we have a few hypotheses that may explain some limitations in the results: (I) Quercetin's antioxidant activity includes the upregulation of antioxidant enzymes (e.g., SOD, Catalase (CAT) and Glutathione Peroxidase (GPx)) [5]; however, none of these enzymes have been evaluated; (II) It has been described that quercetin modulates GSH levels [5]; thus, the determination of GSH, redox status, and even sulfhydryl content would be suitable; (III) Most oxidative parameters evaluated reflect chronic outcomes from oxidative balance, thus the timing of the last exercise bout must be considered, except when an acute approach is used; (IV) As the studies were conducted in healthy and physically active subjects, the literature already supports a higher antioxidant capacity and lower susceptibility to oxidative stress in active subjects [36–38]. Therefore, quercetin may not exert additional benefits under normal conditions but perhaps in an overstressed event; (V) In the field of oxidative stress, both arms of the oxidative balance (i.e., prooxidant and antioxidant compounds) must be evaluated, especially in active/trained subjects.

Studies have suggested that quercetin supplementation may enhance exercise performance, especially the aerobic-exercise type [13,38]. The proposed mechanism relies on its ability to improve mitochondrial function by regulating proteins present in membrane, electron transport chain (ETC), as Krebs cycle [39]. This systematic review identified two studies that support this idea, although neither them demonstrated or evaluated classical aerobic/anaerobic parameters. Daneshvar P, *et al*. [23] described a slight increase in time to exhaustion, without changes in VO_2 values, while Riva A, *et al*. [15] described aspects of recovery training that may chronically enhance performance.

Although we were able to classify subjects' athletic levels, it is noteworthy that as exercise training progresses, the organic adaptability decreases. In the studies, however, there is scarce information about exercise/training aspects, wherein the unique parameter quoted was the volume training (km/week; three studies), which limits the outcome discussion. Besides, since dietary intake can affect the bioavailability of quercetin, the studies should have explored the subjects' nutritional status and dietary intake, done only by two studies. The absence of detailed data on these parameters can mislead interpretation, which difficult to draw clearer conclusions. Therefore, for long-term studies, it is recommended that studies considered and controlled quercetin bioavailability-related dietary intake, and properly address the influence of the training program (i.e. intensity, volume, frequency, and overload progress), as well as subjects' experience (time of practice) and sport-specific factors.

Conclusion

In summary, this systematic review suggests that quercetin supplementation does not improve exercise performance. However, it may have positive effects on training development, which could lead to improved performance as training progresses. Regarding inflammatory and oxidative-related parameters, only limited evidence suggests an improved biochemical profile, and the slight enhancement observed may not justify the costs of supplementation. Notwithstanding, longer-term studies and comparisons of supplementations protocol in similar subjects and biological parameters, would be beneficial for advancing the field.

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Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding author if needed.

Author Contributions

Conceptualization: MSdSF, JMdC, DJSF, GB, CJL; Data curation: MSdSF, DJSF, JMdC, CBGS, GCJS, RFdS; Formal analysis, Investigation: MSdSF, DJSF, GB, FHY, CJL; Methodology: MSdSF, DJSF, GCJS, CJL, FMC, RFdS, YA, JST; Project administration: MSdSF, GB, FHY, YA, JST, CJL, RFdS; Resources: MSdSF, GB, FHY, YA, JST, CJL, RFdS; Drafted this manuscript: MSdSF, GB, FHY, YA, JST, CJL, RFdS. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Georgian Badicu is serving as one of the Guest editors of this journal. We declare that Georgian Badicu had no involvement in the peer review of this article and has no access to information regarding its peer review.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20243807.430.

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