Rhodiola rosea supplementation on sports performance: A systematic review of randomized controlled trials

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Abstract:

Rhodiola rosea (RR) is an herb that has been used for centuries for its various properties. The aim of this systematic review was to determine whether the supplementation with RR can have an effect on muscle damage and physical performance. The databases PubMed, Web of Science and Cochrane Library were used to find studies published until January 2022 that met the following inclusion criteria: randomized controlled trials, healthy participants, and no use of other supplements. Twelve studies were included with 251 participants, 186 men and 65 women between 18-65 years old. Two studies followed acute supplementation, 4 chronic, and 6 combined both. The results were heterogenous, having 10 studies with some positive effects while 2 studies show no effect in variables such as rating of perceive exertion, heart rate, antioxidant capacity, blood lactate, creatine kinase or C-reactive protein. Two limitations were found, firstly, the difference between supplementation and exercise protocols, and secondly, the existence of unclear or high risk of bias in most of the studies included. Acute supplementation with RR has a positive effect on endurance performance and rating of perceived exertion (RPE). Chronic supplementation has a positive effect on anaerobic exercise performance, but not endurance exercise performance. Chronic supplementation may positively impact muscle damage during exercise.

Keywords: roseroot, ergogenic aid, exercise, training

1. Introduction

When categorizing supplements for exercise performance, the Australian Institute of Sport considers four groups (A, B, C, D) based on scientific evidence (Australian Institute of Sport, 2021). Group A includes the supplements with strong scientific evidence to support their efficacy. Group B referrers to the substances with emerging scientific support and deserving further research. Group C are all those substances with no evidence of benefits, or without enough research undertaken to guide an informed opinion. Finally, Group D involves supplements prohibited, or at high risk of contamination with substances that could lead to a positive doping test. Supplements in group C, as is the case of *Rhodiola Rosea* (RR), should not be advocated for use by athletes (Australian Institute of Sport, 2021).

RR, commonly known as golden root or roseroot, is a perennial herb from the Crassulaceae family that grows in the mountainous and arctic territories of Asia, Europe, and North America. In traditional medicine, RR has been used to treat conditions such as fatigue, depression, anemia, and nervous system disorders, as well as used for its anti-inflammatory, anti-aging, and anti-tumor activity (Chiang et al., 2015; Kosanovic et al., 2013; Recio et al., 2016). Moreover, this herb has been employed to enhance physical endurance, labor productivity, longevity or resistance to high altitude sickness (Brown et al., 2002).

RR plants contain polyphenols such as flavonoids, proanthocyanidin, tyrosol and cinnamyl alcohol, as well as glycosides, organic acids, essential oils, sugars, fats, alcohols, and proteins. RR extract can be consumed in a variety of forms: capsules, tablets, powder, dried root extracts, spray bottles, dry roots, sliced roots formula, or syrup rice protein (Khanum et al., 2005). Rosavin, cinnamyl alcohol, salidroside and tyrosol are the major components (Ioset et al., 2011). Researchers have classified RR as an "adaptogen" because of its observed

ability to increase resistance to various chemical, biological, and physical stressors, and its performance enhancing effect in humans (Kelly, 2001). When administered continually, it seems to exert an anti-fatigue effect that may enhance mental performance, especially the ability to concentrate, and reduces cortisol awakening response in patients with burnout and fatigue syndrome (Olsson et al., 2009). These responses may be due to the influence of RR on levels and activity of monoamine and opioid peptides such as beta-endorphins (Kelly, 2001). Furthermore, RR possesses antioxidant capacities as shown by singlet oxygen scavenging, H_2O_2 scavenging, hypochlorite scavenging, ferric reducing, ferrous chelating, and protein thiol protective activities. It also inhibits the production of intracellular reactive oxygen species and increases the activity of antioxidant enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (Calcabrini et al., 2010).

Although several studies have attempted to determine the mechanisms by which RR may improve mental and physical performance, to date a specific mechanism has not been established (Hung et al., 2011; Sellami et al., 2018; Walker & Robergs, 2006). A systematic review concluded that the evidence regarding efficacy of RR and exercise performance was contradictory and inconclusive (Ishaque et al., 2012), however, numerous articles have been published after this review was written. Therefore, in this systematic review we examined whether acute or chronic supplementation with RR has beneficial effects on sports performance in athletes, physically active or inactive individuals.

2. Materials and methods

2.1. Eligibility criteria

The PICOS model eligibility criteria considered for study inclusion were population, intervention, comparators, outcome and study design (Pollock & Berge, 2018). The participants considered were healthy males and females between 18 to 65 years old who were untrained, active, or trained athletes. The interventions of the studies included chronic and/or acute supplementation of RR combined with physical exercise. The comparators were the differences observed with a placebo group. The outcomes reported were related with performance and muscle damage measurements. All the studies had to be randomized controlled trials (RCT), either single or double blind. The following studies were excluded: studies with a secondary design such as meta-analysis, systematic reviews, narrative reviews; animal studies; studies conducted in injured or ill participants; studies in which RR administered with other supplements or in multi-ingredient supplements; articles with no full-text available, opinion pieces, commentaries, and editorials.

2.2. Literature search

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was used to conduct and identify the studies to be included in the systematic review (Page et al., 2021). The databases used were PubMed, the Cochrane Library and Web of Science which includes other databases such as SciELO, MEDLINE, KJD, RSCI, CCC, DIIDW. The keywords used were ("Rhodiola rosea" OR "Rhodiola" OR "rosea, Rhodiola" OR "Roseroot" OR “Roseroots” OR “Rhodiola crenulate”) AND ("performance" OR "athletic performance" OR "sport performance") AND ("sport" OR "sports" OR "athletic"

OR "athletics" OR "exercise" OR "training" OR "physical"). All original full-text articles in English published until January 2022 were considered for the review.

2.3. Search strategy

Initially, all articles found in the mentioned databases and those included manually were assessed for duplicates. After all duplicates were removed, a meticulous screening process was performed for the selection of the studies. At first, all titles and abstracts were evaluated to identify the articles that met all the search and eligibility criteria. Then, the full articles chosen were carefully studied to confirm they met the optimal inclusion criteria to be included in the review.

2.4. Data extraction

Specific pieces of information were extracted from the selected studies such as authors and year of publication; experiment design (blinded, double-blind, randomized); subjects (participant characteristics: level of activity or sports discipline, number of subjects, age, gender, and health status); supplementation (the type, the dosage and the period of supplementation); exercise protocol (type of exercise performed); outcomes (the performance-related variables measured after intervention); and results.

2.5. Quality assessment and risk of bias

The level of quality for each of the selected studies was done following the Cochrane Collaboration Guidelines (Higgins et al., 2011). The Cochrane Risk of Bias tool for randomized clinical studies is based on seven domains: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias),

selective reporting (reporting bias) and other sources of bias (other bias). Risk of bias was categorized as low, high, or unclear.

3. Results

3.1. Study Selection

179 studies were initially identified through different databases. Additionally, one study was identified manually. Of these records, 68 were duplicates. Moreover, 94 were excluded after screening their title and abstract because they did not meet the eligibility criteria. 17 papers remained to be evaluated by full text to meet eligibility. From the 17 studies, three were removed according to the inclusion/exclusion criteria, one due to lack of full-text availability and one more because it was not available in English. Finally, the total number of studies included were 12. See Figure 1 for more details.

3.2. Characteristics of the studies

Twelve RCT were included in this systematic review, 11 of which were double-blind design, and 1 was a single-blind design. The total number of participants was 251, 65 were female, and 186 were men. Out of the 12 studies, ten had less than 26 participants, and only two had larger groups (n=48) (Shanely et al., 2014) and (n=36) (Abidov et al., 2004).

The level of physical activity varied among studies. Four studies worked with highly trained athletes of different sports (Parisi et al., 2010; Shanely et al., 2014; Skarpanska-Stejnborn et al., 2009; Walker et al., 2007). Seven studies used subjects with an active status or were recreationally trained (Ballmann et al., 2019; De Bock et al., 2004; Duncan & Clarke, 2014; Jówko et al., 2018; Noreen et al., 2013; Timpmann et al., 2018; Williams et al., 2021) and only one study used subjects that were physically untrained (Abidov et al., 2004). Most of

the studies included participants between 18 and 30 years old, with the exception of one study where the participants were between 38 and 45 years old (Shanely et al., 2014).

The RR supplementation designs between studies were then classified as acute, chronic or both acute and chronic. The studies that were both used a chronic supplementation period, but also ingested RR on the day of the physical test. Two studies followed an acute protocol, in which the supplementation dosage was taken 1 hour before exercise (Duncan & Clarke, 2014; Noreen et al., 2013). In addition, De Bock et al. (2004) divided the experiment in two phases, phase I being acute with supplementation consumed 1h before exercise. Three studies followed a chronic supplementation of 30 days (Abidov et al., 2004; Parisi et al., 2010; Skarpanska-Stejnborn et al., 2009) and one followed a chronic supplementation of 8 days (Timpmann et al., 2018). The remaining studies (Ballmann et al., 2019; De Bock et al., 2004; Jówko et al., 2018; Shanely et al., 2014; Walker et al., 2007; Williams et al., 2021) combined both acute and chronic supplementation. The dosage given in the studies had a variety of ranges, in the acute protocols, 200mg were given by De Bock et al. (2004) and 3mg/kg/day was the dosage used by Noreen et al. (2013) and Duncan & Clarke (2014). The chronic studies, used 340mg/day (Abidov et al., 2004), 432mg/day (Timpmann et al., 2018), 200mg/day (Skarpanska-Stejnborn et al., 2009) and 170mg/day (Parisi et al., 2010). Finally, the studies combining acute and chronic had the following dosage; De Bock et al. (2004) combined 200mg/day of RR for 30 days and 200mg 1 hour before exercise. Ballman et al. (2019) ingested 1500mg/day for 30 days and 500mg of RR 30 minutes before exercise. Jowko et at. (2018) used a dosage of 600mg/day for 27 days and on days 28 and 29 ingested 200mg of RR 1.5 hours before exercise. Following a similar dosage, Shanely et al. (2014) also used 600mg/day for 30 days, followed by the same dosage the day of the exercise and 7

days after. Lastly, Walker et al. (2007) opted for 1500mg/day for 3 days plus 1000mg the day of the test and Williams et al. (2021) used 1500mg/day during 3 days and the 500mg before exercise.

3.3 Composition of Rhodiola Rosea supplements

The RR extracts used in the included studies were mainly commercially available products (Table 1). Although the majority of the studies used a RR supplement that was standardized for a specified concentration of a marker compound, there was variation between the concentrations of the marker compounds used. RR is composed of many different phytochemicals, but it is commonly believed that the therapeutic benefit is derived from the rosavins and salidroside, which occur naturally in a roughly 3:1 ratio (Stojcheva & Quintela, 2022) . As a result, the majority of the studies that used a standardized extract were either standardized for 3% rosavins and 1% salidroside (Ballmann et al., 2019; De Bock et al., 2004; Noreen et al., 2013; Williams et al., 2021), or for 3% rosavins only (Jówko et al., 2018; Walker et al., 2007) . Of the included studies, only two independently tested the RR extract to ensure the supplement was of the correct concentration (Jówko et al., 2018; Walker et al., 2007). This raises the possibility that not all of the studies were using a RR extract that corresponded to the claimed concentrations since it has been shown that several commercial RR products failed to meet their claimed extract concentrations of marker compounds (Langeder & Grienke, 2021).

The dramatically different doses, dosing schedules, outcome measures and small number of total studies, precludes any real analysis of the impact of differing concentrations of RR on exercise performance. However, it is interesting to note that all of the studies that used a standardized extract of 3% rosavins and 1% salidroside showed a benefit on some measure

of exercise performance (Ballmann et al., 2019; de Bock et al., 2004; Noreen et al., 2013; Williams et al., 2021). Additionally, two studies that did not use a standardized extract of RR both failed to observe a positive effect of RR on exercise performance, although both did observe other positive effects (Parisi et al., 2010; Skarpanska-Stejnborn et al., 2009). It is important that future studies strive to use a standardized extract of RR to help ensure that any results can be better interpreted relative to the growing list of studies that have examined the effects of RR on exercise performance. Since RR naturally contains a ratio of 3:1 for rosavins and salidroside, it would logically make sense to use a RR extract standardized at this level. The review of the included studies suggests that this standardization appears to be effective, but significantly more studies are needed before any firm conclusions can be made.

3.4 Quality assessment and risk of bias

According to the quality assessment and risk bias table and graph, the following analysis was made. Out of 12 studies, all were categorized as unclear risk of bias in the "Random sequence generation" category. In the "Allocation concealment" category, eleven studies were considered unclear risk, and one study was considered as low risk. Regarding the "Performance bias", eleven studies were defined as unclear risk, and one study fell under the low risk. In the "Detection bias", nine studies fell under the unclear risk group, and three were low risk. For the category of "Incomplete outcome data", three studies were considered low risk, and nine fell under the unclear category. For "Selective outcome reporting", all studies were defined as unclear. Lastly, in "Other sources of bias" ten studies were considered unclear risk of bias, one study was defined as low risk, and one study was determined to have high risk of bias. All the information above is detailed in Table 2 and Figure 2.

3.5 Results of individual studies

The main results of the twelve selected studies are shown in Table 3.

3.5.1 Acute supplementation of Rhodiola rosea

De Bock et al. (2004) conducted a RCT, and double-blind study with 24 healthy and active subjects, 12 females and 12 males. The study encompassed two well defined phases: phase I, in which RR supplementation was provided acutely, and phase 2, in which subjects were given RR chronically and acutely. Following a cross-over design, Phase I consisted of two sessions (session 1 and 2) with two days each. Day one involved supplementation of 700mg of RR (200mg of RR + 500mg of starch) or placebo 1h before a speed of limb movement test, aural and visual reaction time test, and attention sustaining test. On day two, the same supplementation procedure was followed, and maximal isometric knee-extension torque and endurance exercise capacity were tested. The results showed significant difference in time to exhaustion (TTE), peak oxygen uptake (VO_{2peak}) and peak carbon dioxide uptake (VCO_{2peak}) ($p<0.05$ in all cases). In addition, RR had significant effect compared to the placebo group for submaximal heart rate (HR) at the 6-minute marker, where HR was significantly lower for the supplemented group ($p<0.05$). HR, pulmonary ventilation (PV), and blood lactate (BL) remained unchanged between groups ($p>0.05$ in all cases).

Noreen et al. (2013) conducted a RCT and double blind with cross-over study design with 18 recreationally active college women who ingested 3mg/kg of RR or placebo 1h before performing a 10 min warm up with 80% of the average watts produced during the familiarization time trial, followed by a 9656 m time trial in a Velotron bicycle ergometer. The results showed that the average HR during the warm-up was significantly lower for RR than placebo ($p<0.05$), and time to completion during the time trial was also significantly lower for RR treatment ($p<0.05$). In addition, the mean rate of perceived exertion (RPE) was

significantly lower for the RR group ($p<0.05$) during the time trial. However, no significant differences between groups were observed in the time trial for average power, average HR, average cadence, BL, fatigue, or confusion ($p>0.05$ in all cases).

Similarly, Duncan & Clarke (2014) examined the effects of 3 mg/kg of RR 1 h before a 30 min cycling test at 70% maximal oxygen uptake (VO_{2max}) in ten recreationally active males using a double-blind cross-over RCT. The results showed a lower RPE at 30 min of exercise ($p<0.01$) and higher vigor ($p<0.01$), perception of arousal ($p<0,05$) and pleasure ($p<0.001$) with RR supplementation. Nevertheless, no significant differences in HR, energy expenditure (kcal/min), carbohydrate and fat oxidation (g/min) and fatigue scale between groups were reported.

3.5.2 Chronic supplementation of Rhodiola rosea

Abidov et al. (2004) carried out a RCT, double blind, counterbalance, and parallel study with 36 healthy untrained subjects divided into 3 groups: the supplemented group received 680 mg/day for 30 days, ingesting 340mg in the morning and 340mg in the evening; the placebo group received 340mg of placebo for 30 days and 6 days post exercise, and the control group that only performed the exercise. The exercise test consisted of an incremental test to exhaustion on a bicyle ergometer. The results showed no significant difference in the creatine kinase (CK) levels between groups ($p>0.05$). However, C-reactive protein (CRP) was significantly lower both 5h post exercise, and 5 days post exercise, in the RR group compared with the control group and the placebo group ($p<0.05$).

Skarpanska-Stejnborn et al. (2009) performed a RCT, parallel and double blind study where chronic supplementation of 200mg of RR or placebo was used for 30 days in 22 Polish male rowers. The subjects performed a 2000m rowing time trial pre and post 30 days of RR

supplementation.. Following supplementation, plasma total antioxidant capacity (TAC) was significantly higher in the RR group ($p<0.05$) and the SOD levels in washed erythrocytes, were significantly lower than the placebo group ($p<0.05$). No significant differences were observed for BL, mean power output (MPO), time to completion, uric acid (UA), GPx, CK and thiobarbituric-acid-reactive substances (TBARS) ($p>0.05$ in all cases).

Parisi et al. (2010) completed a RCT, double-blind, cross-over study with 14 well-trained males that followed a chronic supplementation of 170mg per day of RR or placebo for 4-weeks followed by a cardiopulmonary exhaustion test (CPET) on a cycle ergometer. There were no significant differences in HR, rating of perceived exertion (Borg scale), $VO_{2max,}$ or time to exhaustion between groups ($p>0.05$ in all cases). However, there were significantly lower levels of BL and CK in RR group compared to placebo ($p<0.05$).

Timpmann et al. (2018) studied the effects of RR in the heat acclimation (HA) process of 20 male military college cadets in a RCT, double-blind and cross-over design. Their investigation consisted of two endurance capacity tests (H1 and H2), both involving walking at 6km/h until volitional exhaustion in a climate chamber. After H1 and before H2 an 8 days HA trial was performed, and it consisted of a treadmill run in the heat chamber until core temperature reached 38.5ºC, followed by three 30 min walking sessions separated by five-minute rest. The supplemented group ingested 432mg of RR 30 min before the daily HA session. HA significantly increased TTE ($p<0.001$) and decreased HR, core temperature (Tc), skin temperature (Tsk), stress hormones, as well as RPE, rate of perceived fatigue (RPF) and thermal sensation (TS) ($p<0.001$), but no significant changes were observed between RR and the placebo group ($p>0.05$).

3.5.3 Chronic and acute supplementation of Rhodiola rosea

De Bock et al. (2004) conducted both an acute (see above for details on Phase I), and a chronic RCT, double-blind, cross-over study with 24 healthy and active subjects (12 females and 12 males). In Phase II, the subjects underwent the same acute supplementation procedure and exercise protocol as Phase I (session 3 and session 4), however, they supplemented with 200mg per day of RR, 100mg at 9am and 100mg at 2pm, for 4 weeks after session 3 and before session 4. The results of the study in phase II showed all the variables measured, TTE, VO_{2peak}, peak carbon dioxide production (VCO_{2peak}), PV, BL, HR, maximal isometric muscle strength, speed of limb movement, and visual and aural reaction time did differ between groups ($p>0.05$ in all cases). However, BL values post supplementation and before starting the exercise protocol were significantly lower in subjects who had been taking RR ($p<0.05$).

Walker et al. (2007) conducted a RCT, double blind with a cross-over design study where 12 resistance-trained men ingested 1500mg of RR or placebo per day for three days and 1000mg of RR or placebo on test day before performing an incremental forearm wrist flexion exercise to volitional fatigue. The results indicated that RR failed to influence TTE, RPE, or muscle phosphate kinetics ($p>0.05$ in all cases). At resting, during exercise, and recovery, the levels of adenosine triphosphate (ATP) and phosphocreatine (PCr) did not differ between treatment groups ($p>0.05$).

Similarly, Williams et al. (2021) carried out a RCT, crossover and double-blinded study with ten resistance-trained males. Participants were supplemented with 1500 mg of RR for three days and 300 mg of RR 30 minutes before exercise, or placebo in two different trials separated by a week. On test day, participants completed 2 repetitions of bench press at 75% of one-repetition maximum (1RM) as explosively as possible. After 5 minutes of rest, participants performed 3 sets of repetitions to failure (RTF) at 75% of 1RM separated by 2

minutes of rest. It was shown that mean concentric velocity was significantly higher in RR than PLA, however, RR resulted in a lower RTF compared to PLA. BL immediately post exercise and norepinephrine levels pre-exercise were higher in RR compared to PLA ($p<0.05$; $p<0.01$). No significant differences between treatments were observed for epinephrine ($p>0.05$).

Shanely et al. (2014) performed the largest RCT, parallel and double-blind study included in this review, with 48 male and female runners who chronically ingested 600mg of RR or placebo for 30 days before a marathon, the day of the marathon and 7 days post marathon. They also performed a vertical jump (VJ) test the day before the marathon, 15 min and 1.5 h post marathon. Marathon race performance did not differ between groups ($p>0,05$), and VJ decreased post marathon in both groups ($p<0.001$), with no differences observed between groups ($p>0.05$). An increase was observed for delayed onset muscle soreness (DOMS), plasma cytokines, extracellular heat shock protein 72 (eHSP72), CK, or CRP; with no differences observed between groups ($p>0.05$ in all cases).

Jowko et al (2018) conducted a RCT, parallel and double-blind study with 26 male physical education students who completed an incremental cycle ergometer test to volitional fatigue (term I). The procedure started on day -1 where subjects performed a psychomotor test. On day 0, the incremental cycle ergometer test was performed. From day 1-27 students ingested 600mg per day of RR or placebo. On day 28, they consumed 200mg of RR or placebo 1.5h before the psychomotor test, and on day 29 they also supplemented with 200mg of RR 1.5h before performing another incremental cycle ergometer test (term II). Peak power obtained during the ergometer test (Pmax) declined significantly in the placebo group between the pre-test (Term I) and the post-test (Term II), and although Pmax increased in the RR group

following supplementation, this change was not significant. However, a significant interaction was observed, and although the pre to post-supplementation Pmax changes were small (-4.1% placebo and +5.7% RR), the difference over time was significantly different between the groups ($p>0.05$). Moreover, the chronic supplementation caused a significant decrease in resting BL in the RR group compared with placebo ($p<0.05$). Furthermore, in the RR group, resting plasma TAC increased significantly in Term II as compared to Term I ($p<0.05$), whereas no significant differences were observed in the placebo group ($p>0.05$). HR, power at lactate threshold, heart rate at lactate threshold, BL at rest (BL_{rest}) and max (BL_{max}), VO_{2peak}, TTE, SOD in erythrocytes and CK showed no significant differences between groups ($p>0.05$ in all cases).

Ballman et al. (2019) used 11 college-aged active female subjects in a RCT, single-blinded, cross-over counterbalanced study. The subjects were supplemented for 3 days with 1500mg of RR or placebo, followed the next day by the ingestion of 500mg of RR or placebo 30 min prior to a 3x15s Wingate anaerobic test, separated by 2 min active recovery period. Significant differences were found between the RR and the placebo groups for MPO (power output over the 15s), mean peak power, mean anaerobic capacity (mean power/kg body weight), mean anaerobic power (peak power/kg of body weight), as well as mean total work ($p<0.05$ in all cases). However, no significant differences were found for the mean fatigue index ($p>0.05$). This study also compared the anaerobic performance from consecutive tests and the results showed that even if there were some significant time differences between tests ($p<0.05$), there were no significant differences between groups in power output, peak power, anaerobic capacity, or anaerobic power ($p>0.05$ for all).

4. Discussion

4.1. Chronic supplementation with Rhodiola rosea

Four studies used chronic supplementation without any acute ingestion the day of the exercise (Abidov et al., 2004; Parisi et al., 2010; Skarpanska-Stejnborn et al., 2009; Timpmann et al., 2018). Five studies combined chronic supplementation with acute supplementation (Ballmann et al., 2019; De Bock et al., 2004; Jówko et al., 2018; Shanely et al., 2014; Walker et al., 2007). Two studies supplemented for 3 days plus the dosage on test day (Ballmann et al., 2019; Walker et al., 2007), and 3 supplemented for 30 days plus test day (De Bock et al., 2004; Jówko et al., 2018; Shanely et al., 2014). Each study used a different exercise protocol and different dosages, which makes it difficult to directly compare results. As a result, we have chosen to discuss variables measured and make comparisons between studies when appropriate.

4.1.1. Antioxidant biomarkers

Skarpanska-Stejnborn et al. (2009) studied the effects of rowing on antioxidant biomarkers with a chronic dose of 200mg/day of RR for 4 weeks. The results showed that SOD activity was significantly lower post-exercise and during recovery in the athletes supplemented with RR in comparison to the placebo group. In addition, there were significant effects of RR treatment and exercise on plasma TAC. TAC is an antioxidant system that protects cells and tissues against unnecessary amounts of reactive oxygen species (Kurutas, 2015). The significantly higher plasma TAC before and after exercise, and after a 24 h recovery in the RR supplemented group, could be due to the increased levels of UA. This is supported by the positive correlation seen between UA concentrations and TAC levels after supplementation.

UA, a final product of purine metabolism, is one of the most potent antioxidants in plasma (Kaur & Halliwell, 1990). On the contrary, no difference between groups was found for GPx or TBARS. This led Skarpanska-Stejnborn et al. (2009) to conclude that supplementation with RR increased antioxidant levels in the plasma of professional rowers without affecting the amount of oxidative damage caused by the intensive exercise. Contrary to this findings, Jówko et al. (2018) found no differences between groups for any antioxidant biomarkers, neither SOD nor TAC. Unfortunately, the different exercise protocols used (rowing vs cycle ergometer), and the different supplementation protocols used (200mg/day vs 600mg/day), as well as the different types of subjects used (professional rowers vs physically active students) prevents any clear conclusions to be drawn. More work is clearly needed in this area since it could have an important impact on athletes. For example, participation in a half-marathon was associated with increased markers of oxidative stress as reactive oxygen and nitrogen free radicals (RONS) (Withee et al., 2017). Since chronic supplementation with RR increases the total antioxidant capacity, it may have a positive effect on muscle damage (McGinley et al., 2009).

4.1.2. Muscle damage biomarkers

Vigorous physical exercise induces an inflammatory reaction demonstrated by the delayed increase in the blood of acute phase proteins such as CRP (Liesen et al., 1977). It has been established that there is a relationship between muscle damage and increased blood concentrations of CRP and CK (Mattusch et al., 2000), which means levels of CRP or CK can be used to evaluate muscle damage. Abidov et al. (2004) observed a decrease in CRP levels post-exercise at 5 hours and 5 days in the RR group compared to the placebo group.

In addition, the authors noted that even if the CK levels stayed the same between groups 5 h post exercise, 5 days later the results showed significant difference between groups, with decreased CK levels in the RR group compared to both the placebo and the control group. These results led them to conclude that long-term treatment of untrained, active subjects with RR inhibited the exhausting exercise-induced increase of blood levels of substances serving as inflammation markers. Similarly, Parisi et al. (2010) found a significant reduction of CK for the RR group at rest, peak and 30 min post-exercise, which suggested that chronic RR supplementation is able to reduce markers of skeletal muscle damage after an exhaustive exercise session. In contrast with these results, Skarpanska-Stejnborn et al. (2009) found no significant differences for CK levels between RR and placebo groups, following a 2000m rowing test in highly trained subjects. Similar to these findings, Shanely et al. (2014) observed that supplementation with 600mg/day of RR for 30 days before running a marathon did not alter the levels of CK and CRP between the supplemented and the placebo group, leading them to conclude that supplementation with RR did not attenuate the increase in muscle damage, DOMS, eHSP72, or plasma cytokines. Lastly, Shanely et al. (2014), and Jówko et al. (2018), found no significant differences in plasma CK levels post-exercise between RR and placebo. Evaluating these studies, it can be hypothesized that chronic RR supplementation may have an effect on muscle damage biomarkers, but significantly more work is needed since the effect was not observed in all studies.

4.1.3 Blood lactate

BL is one of the most frequently measured variables during exercise testing. The lactate threshold, the work rate beyond which BL increases exponentially, is a better predictor of

performance than VO_{2max} and a better indicator of exercise intensity than HR (Goodwin et al., 2007).

In strictly chronic protocols, three studies measured BL (Parisi et al., 2010; Skarpanska-Stejnborn et al., 2009; Timpmann et al., 2018) and they all found very different results. Parisi et al. (2010) found that RR supplementation of 85mg a day for 30 days significantly reduced BL after 3 min of recovery compared to the placebo. Skarpanska-Stejnborn et al. (2009) and Timpmann et al. (2018) both had higher dosage of RR, 200mg and 432mg respectively, and both found no effect of RR in BL. Timpmann et al. (2018) used a chronic protocol of only 8 days in comparison with the 30 days used in the other two studies (Parisi et al., 2010; Skarpanska-Stejnborn et al., 2009). It could be argued that a longer period of supplementation might be necessary since Timpmann et al. (2018) also performed an exercise protocol to exhaustion and did not see the same effect observed by Parisi et al. (2010). Studies that combined chronic and acute supplementation also showed equivicol results of RR effects on BL. De Bock et al. (2004) supplemented for 4 week with 200 mg/day and observed a reduction in BL for the RR group only during the pre-test period, with no differences during the exercise test. Jówko et al. (2018) supplemented for 30 days using a dosage of 600mg/day and 200mg on test day, and also observed a reduction in BL between RR and placebo groups only during the pre-test period. Williams et al. (2021) supplemented for three days with 1500 mg, and found that BL were significantly higher during exercise than the placebo group, but they were not different during the pre-test period. Looking at these studies collectively, it would be tempting to suggest that RR might reduce pre-test blood lactate values and that

longer periods of supplementation with lower doses of RR might decrease BL during exercise, but significantly more work needs to be done before any conclusions can be drawn.

4.1.4 Rate of perceived exertion

Only Parisi et al. (2010), Timpmann et al. (2018) and Walker et al. (2007) measured RPE and all found no significant differences between the RR supplemented and placebo groups. The studies performed very different exercise protocols and used different supplementation quantities making it difficult to draw conclusions, but these results could suggest that chronic supplementation of RR has no effect on RPE, which is interesting because acute supplementation appears to significantly lower RPE (see below).

4.1.5 Performance variables

Each of the studies in this review performed a different exercise performance test, which meant that depending on the test, different variables and outcomes were measured, making it difficult to compare each one of them independently. HR was a common variable in 3 of the studies (Jówko et al., 2018; Parisi et al., 2010; Timpmann et al., 2018), although none of them found any significant differences in RR groups compared with placebo. Several studies used some measure of TTE, with each failing to find a significant effect of RR (De Bock et al., 2004; Jówko et al., 2018; Parisi et al., 2010; Walker et al., 2007). It could be argued that since some significant effects were found on HR and TTE in acute protocols (see below) and no significant effects were found in chronic protocols, that there is no effect on HR or TTE when chronic supplementation is implemented.

Time to completion for a 2000m rowing TT was used by (Skarpanska-Stejnborn et al., 2009), with no significant differences observed between RR and the placebo group following supplementation.

Ballmann et al. (2019) supplemented with 1500mg of RR for three days, and they found significant differences for MPO, AnC, P_{peak}, and mean total work, leading to the conclusion that RR has an effect on certain anaerobic power variables. In line with this, Williams et al. (2021) found a significant increase in mean concentric velocity during a bench press of 75% of 1the 1 rep max following three days of 1500mg of RR.

Taken together, it appears that chronic supplementation of RR is more effective for anaerobic exercise performance, with little positive effects observed on aerobic endurance performance. However, significant differences in supplement dosage, duration and exercise performance tests between the studies makes it difficult to compare results and draw conclusions regarding RR and performance. For future studies, a more homogenized structure should be established in order to substantiate results and decide on the effects of RR.

4.2. Acute supplementation with *Rhodiola rosea*

Three studies followed a strictly acute protocol (De Bock et al., 2004; Duncan & Clarke, 2014; Noreen et al., 2013). Although there were differences between the studies, there were more consistencies between the acute studies than what was observed for the chronic supplementation studies, which makes direct comparison between the studies easier. For example, each study used a similar dose (~200mg) that was administered 1h prior to testing. Although the pharmacokinetics of RR ingestion in humans isn't fully established, 1h prior to

testing appears to be appropriate since the Tmax of ingested rosavins is roughly ½ h in rodents (Zhang et al., 2019).

4.2.1. Performance variables

De Bock et al. (2004) main finding was that an acute RR intake of 200mg increased endurance capacity during an incremental exercise test on a bicycle ergometer to volitional fatigue. TTE on average increased by ~3% and a similar increase was found in O_2 uptake and CO_2 output at peak exercise. In addition, an effect on submaximal HR was observed at the 6 min time point where RR significantly lowered HR compared to placebo. Similarily, Noreen et al. (2013) found a significant reduction in average HR during a standardized warm-up for the RR group compared to the placebo group. On the contrary, Duncan & Clarke (2014) found no significant effects for HR during a steady state exercise test at 75% of max. Duncan & Clarke (2014) used males for subjects, while De Bock et al. (2004) used males and females, and Noreen et al. (2013) used females. This raises the possibility that RR has more effect on HR for women than men, but more studies are needed to determine if a sex difference exists in response to RR supplementation.

Although Duncan & Clarke (2014) did not do an exercise performance test, both De Bock et al. (2004) and Noreen et al. (2013) observed an increase in endurance exercise performance following acute RR supplementation. However, neither group was able to fully identify the exact mechanism(s) that resulted in an improvement in exercise performance. It invites contemplation of the possible physiological mechanism by which acute ingestion of RR may have a beneficial effect on endurance exercise capacity. RR has a high content of phenylpropanoid rosavin and phenylethanol salidroside (Linh et al., 2000), which are

presumed to have the ability to stimulate the synthesis, transport and receptor activity of monoamines, and opioid receptors and peptides such as β-endorphins (Lishmanov et al., 1987) which can lead to a high tolerance for pain and discomfort (Kelly, 2001) both very important when performing exhausting exercise. This theory is at least partially supported by the effects of acute RR supplementation on RPE (see below).

4.2.2. Blood Lactate

De Bock et al. (2004) and Noreen et al. (2013) both failed to see any effect of RR on BL either before, or during the exercise test. However, De Bock et al. (2004) and others have observed a reduction in resting BL following chronic supplementation (see above), which suggests that there could be a difference between acute and chronic RR supplementation, although further research is required before any definitive conclusions can be made.

4.2.3 Rating of perceived exertion

Noreen et al. (2013) found a decreased RPE in the RR group compared to placebo during a TT test. In addition, the difference of RPE between treatments was even more pronounced when expressed as RPE relative to workload due to the small absolute increase in workload at all-time points after RR supplementation. For all trials, RPE was significantly correlated with the time to complete the trial, as well as with the change in time to complete the time trial after RR treatment. Duncan & Clarke (2014) used a slightly different protocol, but they also found a significant decrease of RPE in the RR group compared to the PLA group 30 min into a steady state exercise bout. It is interesting to note that both the acute studies that measured RPE found a significant effect of RR, but no chronic supplementation study did. This raises the possibility that whatever the mechanism is that is responsible for the acute

effect is somehow lost with chronic RR supplementation. However, the low number of both acute and chronic RR supplementation studies that have measured RPE during exercise makes it difficult to come to any clear conclusions.

4.3. Limitations

The main limitation is the difference between supplementation and exercise protocols, making it difficult to compare results and to draw clear conclusions.

On the other hand, there is a limitation regarding the risk of bias. Li et al. (2021) evaluated quality and risk of bias of studies with different species of *Rhodiola* though Cochran Collaboration Guidelines and Consolidated Standards of Reporting Trials (CONSORT). They obtained an unclear or high risk of bias in most of the studies included, which agrees with the bias analysis we have conducted in this review.

5. Conclusion

It is very hard to arrive at any firm conclusions based on the available datasets used in this review. Relatively few studies have been performed to date, and of those that have been done, significant differences in both the dose and duration of RR supplementation makes direct comparisons difficult. On top of this, the high risk of potential bias shown in the studies reviewed undermines the confidence in the results. Nevertheless, some trends have been identified in this systematic review. Acute RR supplementation appears to have a positive effect on endurance exercise performance and RPE, while chronic supplementation does not appear to be beneficial for either. However, chronic supplementation may have a positive effect on anaerobic power and exercise performance. Although chronic RR supplementation

does not seem to positively impact endurance exercise performance, it may have a positive effect on antioxidant status and muscle damage during exercise. Although this effect is still inconclusive, it could have important implications for athletes if future studies support this effect. Based on the information from this review, we can suggest that RR may have some effect on certain variables, although it is difficult to come to any final conclusions about the efficacy of RR on sports performance without further research using more standardized controls and measurement outcomes.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

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TABLES

Table 1. Description of Rhodiola Rosae supplements used.

Study	Brand of RR Supplement	Standardization of RR Supplement	Independently Tested
(De Bock et al., 2004)	Finzelberg GmbH, Andernach, Germany	3% rosavin, 1% salidroside	No
(Abidov et al., 2004)	Rhodax® by Bodyonics Ltd, Farmingdale, NY, USA	Standardized to provide 30 mg of each of the following 8 biomers: rosavin, rosarin, salidrosides, rosin, rhodalgin, acetylrhodalgin, rosaridin, and rosaridol	No
(Walker et al., 2007)	Bali Herbal, Singapore	3% rosavin	Yes

(Skarpanska-Stejnborn et al., 2009)	Rhodiolin® by CaliVita International, Rotterdam, NL	None	No
(Parisi et al., 2010)	Unspecified	None	No
(Noreen et al., 2013)	Bulknutrition.com, Northborough, MA, USA	3% rosavin, 1% salidroside	No
(Shanely et al., 2014)	PL Thomas & Co., Inc. Morristown New Jersey, USA	5% rosavin, 1.8% salidroside	No
(Duncan & Clarke, 2014)	Indigo Herbs, Glastonbury, UK	None	No
(Jówko et al., 2018)	Naturell, Akersberga, Sweden	3% rosavin	Yes
(Timpmann et al., 2018)	SHR-5® by Swedish Herbal Institute, Vallberga, Sweden	2.7% rosavin, 2.3% salidroside	No

(Ballmann et al., 2019)	NOW Food Inc., Bloomingdale, IL, USA	3% rosavin, 1% salidroside	No
(Williams et al., 2021)	NOW Food Inc., Bloomingdale, IL, USA	3% rosavin, 1% salidroside	No

Table 2. Risk of bias graph

Study	Sequences generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
(De Bock et al., 2004)	?	?	?	?	+	?	+
(Abidov et al., 2004)	?	?	?	?	?	?	?
(Walker et al., 2007)	?	?	?	+	+	?	-
(Skarpanska-Stejnborn et al., 2009)	?	?	?	?	?	?	?
(Parisi et al., 2010)	?	?	?	?	?	?	?
(Noreen et al., 2013)	?	?	?	?	?	?	?
(Shanely et al., 2014)	?	?	?	+	?	?	?
(Duncan & Clarke, 2014)	?	?	?	?	?	?	?
(Jówko et al., 2018)	?	?	?	?	+	?	?
(Timpmann et al., 2018)	?	?	?	?	?	?	?
(Ballmann et al., 2019)	?	?	?	?	?	?	?
(Williams et al., 2021)	?	+	+	+	?	?	?

[+] Low risk of bias; [?] Unclear risk of bias; [-] High risk of bias

Table 3. Results from individual studies

Study	Subjects	Supplementation	Exercise protocol	Variables	Results
(De Bock et al., 2004)	24 physically active females (*n* =12) 20.2 (0.3) years and males (*n* = 12) 21.8 (0.3) years SUP (*n* = 24) PLA (*n* = 24)	Phase I (Acute): 1h before test: SUP = 700mg RR (200mg of RR + 500mg of starch) Phase II (Chronic): 4-week SUP = 200mg/day RR and 700mg RR 1-h before exercise	Day I: Tapping test: Touch with preferred hand two 20cm apart discs alternatively, 25 cycles. 2 tests, 5min rest Reaction Time= 10 fastest tapping button responses measured for auditory (buzzer) & visual stimuli (white block) in computer screen Day II: Endurance exercise capacity= cycle-ergometer incremental test (60W for 6-min + increments of 20W/min until volitional exhaustion). Maximal isometric knee extension torque: 5 min warm up + 3 maximal isometric knee extensions of 3 s.	Endurance Capacity: TTE; VO_{2peak}, VCO_{2peak}; PV; BL; HR Muscle Strength: Maximal isometric muscle strength. Speed of Limb Movement Reaction Time: visual and aural reaction time.	Phase I TTE, VO_{2peak}, VCO_{2peak}: SUP > PLA Phase I HR, PV, BL: : SUP = PLA Phase II HR, PV, BL: SUP = PLA Phase II BL before exercise: SUP < PLA. Phase I and II: Muscle Strength: PLA = SUP Speed of Limb Movement: PLA = SUP Reaction Time: PLA = SUP

(Noreen et al., 2013)	18 active women 22.6 (3.3) years SUP (*n* = 18) PLA (*n* = 18)	Acute 3mg/kg RR 1h before test	2-7 days of familiarization (9656 m time trial). Test day: 9656 m time trail	Endurance capacity: RPE, Av HR, BL, fatigue, confusion Performance: trial time, cadence Muscle strength: AvP	RPE, AvHR (at warm-up), trial time: SUP < PLA Av cadence, BL, AvP, Fatigue, confusion: SUP = PLA
(Abidov et al., 2004)	36 untrained volunteers 21-26 years SUP (*n* = 12) PLA (*n* = 12) CG (*n* = 12)	Chronic 30 days before exercise and 6 days after. SUP = 680mg/day RHODAX (60mg/day RR) CG = only exercise	Incremental test in cycle–ergometer (20W +10W/min until exhaustion or 60 cycles/min)	Muscle damage biomarker: CK Inflammation biomarker: CRP	CK 5h after test: SUP = PLA = CG 5 days after test: SUP < (PLA = CG) CRP 5h after test: SUP < (PLA = CG) 5 days after test: SUP < (PLA = CG)
(Skarpanska-Stejnborn et al., 2009)	22 male rowers SUP (*n* = 11) 20.4 (1.2) years PLA (*n* = 11) 21.0 (0.9) years	Chronic 200mg/day RR during 4 weeks before exercise	2000m rowing	Oxidative stress biomarkers: TBARS Endurance capacity: BL Muscle damage biomarkers: CK Antioxidant biomarkers: SOD, GPx, TAC, UA Muscle strength: MPO	BL, MPO, Time, UA, GPx, CK, TBARS: PLA = SUP SOD, TAC: SUP > PLA

				Performance: Time	
(Parisi et al., 2010)	14 well-trained males 25 (5) years SUP (*n* = 14) PLA (*n* = 14)	Chronic 170 mg/day (85mg RR) during 4 weeks before exercise	Cycle-ergometer test until exhaustion (75% VO_{2max})	Endurance capacity: HR_{max}, VO_{2max}, BL, Borg scale. Performance: time Muscle damage biomarker: CK	HR, Borg, VO_{2Max}, Time: PLA = SUP BL, CK: SUP > PLA
(Timpmann et al., 2018)	20 male subjects 22.5 (3.0) years SUP (*n* = 10) PLA (*n* = 10)	Chronic 432mg RR during 8 days 30 min before each HA trail	Trial H1: Endurance capacity test in heat chamber until volitional exhaustion. (6km/h 10% grade) Heat Acclimation trial: 8 days Treadmill run in heat chamber until the core temperature (Tc) reached 38.5°C. Then, 3x30min walking sessions separated by 5-minute rest. Rest period: 1 day Trail H2: same test as H1	Endurance capacity: RPE, RPF, BL, HR Temperature markers: Tc, Tsk, TS	Tc, Tsk, HR, RPE, RPF, TS, BL: SUP = PLA

(Walker et al., 2007)	12 resistance trained males 29.92 (4.51) years SUP (*n* =12) PLA (*n* = 12)	Chronic 1500mg/day RR during 3 days before exercise and 1000mg RR test day	Incremental wrist flexion exercise to volitional fatigue	Endurance capacity: TTE, RPE ATP turnover: PCr	RPE, TTE, PCr: PLA = SUP
(Shanely et al., 2014)	48 trained runners females (*n* = 13) and males (*n* = 35) SUP (*n* = 24) 40.3 (1.44) years PLA (*n* = 24) 43.9 (1.23) years	Chronic: 600mg/day RR 30 days before marathon and 7 days after	Marathon	Muscle damage biomarker: CK, EIMD, DOMS Muscle function: VJ Inflammation biomarker: CRP, PCk Antioxidant biomarker: eHSP72	EIMD, VJ, DOMS, PCk, eHSP72, CK, CRP: SUP = PLA
(Duncan & Clarke, 2014)	10 recreationally active 26 (6) years	Acute 3mg/kg RR 1h before test	Cycling trial (30 min at 70% of VO_{2max})	Endurance capacity: HR Endurance capacity: RPE Mood state: feeling scale (pleasure and displeasure), arousal scale, fatigue and vigor scales Substrate oxidation: energy expenditure, carbohydrate, and fat oxidation rates	HR, substrate oxidation, fatigue scale SUP = PLA Feeling scale, arousal scale, vigor scale SUP > PLA RPE SUP < PLA
(Ballmann et al., 2019)	11 physically active females 19.4 (0.8) years	Chronic 1500mg/day RR during 3 before exercise and 500mg RR 30 min pre-exercise	Wingate Anaerobic Tests in electromagnetically braked cycle ergometer (3 × 15 s) pre and post supplementation	Muscle strength: MPO, Mean total work, P_{peak} Endurance capacity: AnC, Mean fatigue	MPO, Mean AnC, Mean P_{peak}, Mean total work: SUP > PLA

					Mean fatigue: SUP = PLA
(Jówko et al., 2018)	26 physically active male 20.9 (0.2) years SUP (*n* = 13) PLA (*n* = 13)	Chronic 4 600mg/day RR (day 1-27) and 200mg/day (day 28-29)	Incremental cycle-ergometer test to volitional fatigue pre and post supplementation	Antioxidant biomarkers: SOD, TAC Muscle damage biomarker: CK Endurance capacity: TTE, $VO_{2peak,}$ HR, HRLT, BL_{rest}, BL_{max} Muscle strength: PLT, P_{max}	P_{max}: SUP > PLA HR, PLT, HRLT, BL_{rest}, BL_{max}, VO_{2peak}, SOD, CK, TTE, TAC: SUP = PLA
(Williams et al., 2021)	10 resistance trained males 24.8 (5.6) years	Chronic 1500 mg/day RR during 3 days before exercise and 30 minutes prior to exercise	Warm up: 5 repetitions at 40% 1-RM + 3 repetitions at 60%RM of BP separated by 2 min rest 1-set x 2 repetitions of BP at 75% 1-RM with maximum explosive intent 5-min test 3 sets x RTF of BP at 75% 1-RM separated by 2 min rest	Resistance performance: total RTF, set-to-set RTF mean velocity Blood: BL, EPI, NE	Total RTF: SUP < PLA Mean velocity, BL (post-exercise), NE: SUP>PLA Set-to-set RTF, EPI: SUP=PLA

Average heart rate (AvHR), average power (AvP), bench press (BP), blood lactate (BL), concentration of phosphocreatine PCr, control group (CG), core temperature (Tc), C-reactive protein (CRP), creatine kinase (CK), delayed onset muscle soreness (DOMS), exercise-induced muscle damage (EIMD), extracellular Heat Shock protein 72 (eHSP72), epinephrine (EPI), Glutathione

peroxidase (GPx), heat acclimation (HA), heart rate (HR), heart rate at lactate threshold (HRLT), maximum blood lactate concentration (BLmax), maximum heart rate (HR Max), maximum power (P_{max}), mean anaerobic capacity (AnC), mean peak power (P_{peak}), mean power output (MPO), norepinephrine (NE), placebo group (PLA), plasma cytokines (PCk), one repetition to failure (1-RM), power at lactate threshold (PLT), profile of mood states test (POMS), pulmonary ventilation (PV), randomized controlled trial (RCT), rate of perceived exertion (RPE), rate of perceived fatigue (RPF), repetitions to failure (RTF), skin temperature (Tsk), Stroop incongruent word color test (SIWCT), Superoxide dismutase (SOD), supplemented group (SUP), thermal sensation (TS), thiobarbituric-acid-reactive substances (TBARS), time to exhaustion (TTE), total antioxidant capacity (TAC), uric acid (UA), vertical jump (VJ).